Omnibus Codes (for Pennsylvania Only)

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➲ Instructions for Use

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Related Policies
None

Application

This Medical Policy only applies to the state of Pennsylvania. Any requests for services that do not meet criteria set in the PARP will be evaluated on a case-by-case basis. Refer to Pennsylvania Exceptions, Pennsylvania Code, Title 55, Chapter 1101.

Definitions

Unproven Service(s): Services, including medications and devices, regardless of U.S. Food and Drug Administration (FDA) approval, that are not determined to be effective for treatment of the medical or behavioral health condition or not determined to have a beneficial effect on health outcomes due to insufficient and inadequate clinical evidence from well-designed randomized controlled trials or observational studies in the prevailing published peer-reviewed medical literature.

- Well-designed systematic reviews (with or without meta-analyses) of multiple well-designed randomized controlled trials.
- Individual well-designed randomized controlled trials.
- Well-designed observational studies with one or more concurrent comparison group(s) including cohort studies, case-control studies, cross-sectional studies, and systematic reviews (with or without meta-analyses) of such studies.

Coverage Summary

All CPT/HCPCS codes/services addressed in this policy are noted in the table below. Click the code link to be directed to the full coverage rationale and clinical evidence applicable to each of the listed procedures.

Note: Bracketed language following the unlisted code descriptions was added by UnitedHealthcare to indicate the intended use of the code within this policy.

Code	Description	Conclusion
0061U	Transcutaneous measurement of five biomarkers (tissue oxygenation [StO2], oxyhemoglobin [ctHbO2], deoxyhemoglobin [ctHbR], papillary and reticular dermal hemoglobin concentrations [ctHb1 and ctHb2]), using spatial frequency domain imaging (SFDI) and multi-spectral analysis	Unproven
0075T	Transcatheter placement of extracranial vertebral artery stent(s), including radiologic supervision and interpretation, open or percutaneous; initial vessel	Unproven

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Code	Description	Conclusion
0076T	Transcatheter placement of extracranial vertebral artery stent(s), including radiologic supervision and interpretation, open or percutaneous; each additional vessel (List separately in addition to code for primary procedure)	Unproven
0163U	Oncology (colorectal) screening, biochemical enzyme-linked immunosorbent assay (ELISA) of 3 plasma or serum proteins (teratocarcinoma derived growth factor-1 [TDGF-1, Cripto-1], carcinoembryonic antigen [CEA], extracellular matrix protein [ECM]), with demographic data (age, gender, CRC-screening compliance) using a proprietary algorithm and reported as likelihood of CRC or advanced adenomas	Unproven
0174T	Computer-aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed concurrent with primary interpretation (List separately in addition to code for primary procedure)	Unproven
0175T	Computer-aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed remote from primary interpretation	Unproven
0207T	Evacuation of meibomian glands, automated, using heat and intermittent pressure, unilateral	Unproven
0208T	Pure tone audiometry (threshold), automated; air only	Unproven
0209T	Pure tone audiometry (threshold), automated; air and bone	Unproven
0210T	Speech audiometry threshold, automated	Unproven
0211T	Speech audiometry threshold, automated; with speech recognition	Unproven
0212T	Comprehensive audiometry threshold evaluation and speech recognition (0209T, 0211T combined), automated	Unproven
0234T	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; renal artery	Unproven
0235T	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; visceral artery (except renal), each vessel	Unproven
0236T	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; abdominal aorta	Unproven
0237T	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; brachiocephalic trunk and branches, each vessel	Unproven
0247U	Obstetrics (preterm birth), insulin-like growth factor-binding protein 4 (IBP4), sex hormone-binding globulin (SHBG), quantitative measurement by LC-MS/MS, utilizing maternal serum, combined with clinical data, reported as predictive-risk stratification for spontaneous preterm birth	Unproven
0266T	Implantation or replacement of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed)	Unproven
0267T	Implantation or replacement of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)	Unproven
0268T	Implantation or replacement of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)	Unproven

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Code	Description	Conclusion
0269T	Revision or removal of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed)	Unproven
0270T	Revision or removal of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)	Unproven
0271T	Revision or removal of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)	Unproven
0272T	Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (e.g., battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day)	Unproven
0273T	Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (e.g., battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day); with programming	Unproven
0330T	Tear film imaging, unilateral or bilateral, with interpretation and report	Unproven
0331T	Myocardial sympathetic innervation imaging, planar qualitative and quantitative assessment	Unproven
0332T	Myocardial sympathetic innervation imaging, planar qualitative and quantitative assessment; with tomographic SPECT	Unproven
0333T	Visual evoked potential, screening of visual acuity, automated, with report	Unproven
0335T	Insertion of sinus tarsi implant	Unproven
0338T	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; unilateral	Unproven
0339T	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; bilateral	Unproven
0347T	Placement of interstitial device(s) in bone for radiostereometric analysis (RSA)	Unproven
0348T	Radiologic examination, radiostereometric analysis (RSA); spine, (includes cervical, thoracic and lumbosacral, when performed)	Unproven
0349T	Radiologic examination, radiostereometric analysis (RSA); upper extremity(ies), (includes shoulder, elbow, and wrist, when performed)	Unproven
0350T	Radiologic examination, radiostereometric analysis (RSA); lower extremity(ies), (includes hip, proximal femur, knee, and ankle, when performed)	Unproven
0358T	Bioelectrical impedance analysis whole body composition assessment, with interpretation and report	Unproven
0394T	High dose rate electronic brachytherapy, skin surface application, per fraction, includes basic dosimetry, when performed	Unproven

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Code	Description	Conclusion
0395T	High dose rate electronic brachytherapy, interstitial or intracavitary treatment, per fraction, includes basic dosimetry, when performed	Unproven
0397T	Endoscopic retrograde cholangiopancreatography (ERCP), with optical endomicroscopy (List separately in addition to code for primary procedure)	Unproven
0408T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator with transvenous electrodes	Unproven
0409T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator only	Unproven
0410T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; atrial electrode only	Unproven
0411T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; ventricular electrode only	Unproven
0412T	Removal of permanent cardiac contractility modulation system; pulse generator only	Unproven
0413T	Removal of permanent cardiac contractility modulation system; transvenous electrode (atrial or ventricular)	Unproven
0414T	Removal and replacement of permanent cardiac contractility modulation system pulse generator only	Unproven
0415T	Repositioning of previously implanted cardiac contractility modulation transvenous electrode, (atrial or ventricular lead)	Unproven
0416T	Relocation of skin pocket for implanted cardiac contractility modulation pulse generator	Unproven
0417T	Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, including review and report, implantable cardiac contractility modulation system	Unproven
0418T	Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording and disconnection per patient encounter, implantable cardiac contractility modulation system	Unproven
0440T	Ablation, percutaneous, cryoablation, includes imaging guidance; upper extremity distal/peripheral nerve	Unproven
0441T	Ablation, percutaneous, cryoablation, includes imaging guidance; lower extremity distal/peripheral nerve	Unproven
0442T	Ablation, percutaneous, cryoablation, includes imaging guidance; nerve plexus or other truncal nerve (e.g., brachial plexus, pudendal nerve)	Unproven
0444T	Initial placement of a drug-eluting ocular insert under one or more eyelids, including fitting, training, and insertion, unilateral or bilateral	Unproven
0445T	Subsequent placement of a drug-eluting ocular insert under one or more eyelids, including re-training, and removal of existing insert, unilateral or bilateral	Unproven
0485T	Optical coherence tomography (OCT) of middle ear, with interpretation and report; unilateral	Unproven
0486T	Optical coherence tomography (OCT) of middle ear, with interpretation and report; bilateral	Unproven
0506T	Macular pigment optical density measurement by heterochromatic flicker photometry, unilateral or bilateral, with interpretation and report	Unproven

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Code	Description	Conclusion
0507T	Near-infrared dual imaging (i.e., simultaneous reflective and trans-illuminated light) of meibomian glands, unilateral or bilateral, with interpretation and report	Unproven
0510T	Removal of sinus tarsi implant	Unproven
0511T	Removal and reinsertion of sinus tarsi implant	Unproven
0515T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; complete system (includes electrode and generator [transmitter and battery])	Unproven
0516T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; electrode only	Unproven
0517T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; both components of pulse generator (battery and transmitter) only	Unproven
0518T	Removal of pulse generator for wireless cardiac stimulator for left ventricular pacing; battery component only	Unproven
0519T	Removal and replacement of pulse generator for wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming; both components (battery and transmitter)	Unproven
0520T	Removal and replacement of pulse generator for wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming; battery component only	Unproven
0521T	Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording, and disconnection per patient encounter, wireless cardiac stimulator for left ventricular pacing	Unproven
0522T	Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, including review and report, wireless cardiac stimulator for left ventricular pacing	Unproven
0525T	Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging supervision and interpretation; complete system (electrode and implantable monitor)	Unproven
0526T	Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging supervision and interpretation; electrode only	Unproven
0527T	Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging supervision and interpretation; implantable monitor only	Unproven
0528T	Programming device evaluation (in person) of intracardiac ischemia monitoring system with iterative adjustment of programmed values, with analysis, review, and report	Unproven
0529T	Interrogation device evaluation (in person) of intracardiac ischemia monitoring system with analysis, review, and report	Unproven
0530T	Removal of intracardiac ischemia monitoring system, including all imaging supervision and interpretation; complete system (electrode and implantable monitor)	Unproven
0531T	Removal of intracardiac ischemia monitoring system, including all imaging supervision and interpretation; electrode only	Unproven

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Code	Description	Conclusion
0532T	Removal of intracardiac ischemia monitoring system, including all imaging supervision and interpretation; implantable monitor only	Unproven
0558U	Oncology (colorectal), quantitative enzyme-linked immunosorbent assay (ELISA) for secreted colorectal cancer protein marker (BF7 antigen), using serum, result reported as indicative of response/no response to therapy or disease progression/regression	Unproven
0559T	Anatomic model 3D-printed from image data set(s); first individually prepared and processed component of an anatomic structure	Unproven
0559U	Oncology (breast), quantitative enzyme-linked immunosorbent assay (ELISA) for secreted breast cancer protein marker (BF9 antigen), serum, result reported as indicative of response/no response to therapy or disease progression/regression	Unproven
0560T	Anatomic model 3D-printed from image data set(s); each additional individually prepared and processed component of an anatomic structure (List separately in addition to code for primary procedure)	Unproven
0561T	Anatomic guide 3D-printed and designed from image data set(s); first anatomic guide	Unproven
0562T	Anatomic guide 3D-printed and designed from image data set(s); each additional anatomic guide (List separately in addition to code for primary procedure)	Unproven
0563T	Evacuation of meibomian glands, using heat delivered through wearable, open-eye eyelid treatment devices and manual gland expression, bilateral	Unproven
0571T	Insertion or replacement of implantable cardioverter-defibrillator system with substernal electrode(s), including all imaging guidance and electrophysiological evaluation (includes defibrillation threshold evaluation, induction of arrhythmia, evaluation of sensing for arrhythmia termination, and programming or reprogramming of sensing or therapeutic parameters), when performed	Unproven
0572T	Insertion of substernal implantable defibrillator electrode	Unproven
0573T	Removal of substernal implantable defibrillator electrode	Unproven
0574T	Repositioning of previously implanted substernal implantable defibrillator-pacing electrode	Unproven
0575T	Programming device evaluation (in person) of implantable cardioverter-defibrillator system with substernal electrode, with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, review and report by a physician or other qualified health care professional	Unproven
0576T	Interrogation device evaluation (in person) of implantable cardioverter-defibrillator system with substernal electrode, with analysis, review and report by a physician or other qualified health care professional, includes connection, recording and disconnection per patient encounter	Unproven
0577T	Electrophysiologic evaluation of implantable cardioverter-defibrillator system with substernal electrode (includes defibrillation threshold evaluation, induction of arrhythmia, evaluation of sensing for arrhythmia termination, and programming or reprogramming of sensing or therapeutic parameters)	Unproven
0578T	Interrogation device evaluation(s) (remote), up to 90 days, substernal lead implantable cardioverter-defibrillator system with interim analysis, review(s) and report(s) by a physician or other qualified health care professional	Unproven
0579T	Interrogation device evaluation(s) (remote), up to 90 days, substernal lead implantable cardioverter-defibrillator system, remote data acquisition(s), receipt of transmissions and technician review, technical support and distribution of results	Unproven

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Code	Description	Conclusion
0580T	Removal of substernal implantable defibrillator pulse generator only	Unproven
0581T	Ablation, malignant breast tumor(s), percutaneous, cryotherapy, including imaging guidance when performed, unilateral	Unproven
0583T	Tympanostomy (requiring insertion of ventilating tube), using an automated tube delivery system, iontophoresis local anesthesia	Unproven
0594T	Osteotomy, humerus, with insertion of an externally controlled intramedullary lengthening device, including intraoperative imaging, initial and subsequent alignment assessments, computations of adjustment schedules, and management of the intramedullary lengthening device	Unproven
0600T	Ablation, irreversible electroporation; 1 or more tumors per organ, including imaging guidance, when performed, percutaneous	Unproven
0601T	Ablation, irreversible electroporation; 1 or more tumors, including fluoroscopic and ultrasound guidance, when performed, open	Unproven
0607T	Remote monitoring of an external continuous pulmonary fluid monitoring system, including measurement of radiofrequency-derived pulmonary fluid levels, heart rate, respiration rate, activity, posture, and cardiovascular rhythm (e.g., ECG data), transmitted to a remote 24-hour attended surveillance center; set-up and patient education on use of equipment	Unproven
0608T	Remote monitoring of an external continuous pulmonary fluid monitoring system, including measurement of radiofrequency-derived pulmonary fluid levels, heart rate, respiration rate, activity, posture, and cardiovascular rhythm (e.g., ECG data), transmitted to a remote 24-hour attended surveillance center; analysis of data received and transmission of reports to the physician or other qualified health care professional	Unproven
0614T	Removal and replacement of substernal implantable defibrillator pulse generator	Unproven
0615T	Automated analysis of binocular eye movements without spatial calibration, including disconjugacy, saccades, and pupillary dynamics for the assessment of concussion, with interpretation and report	Unproven
0631T	Transcutaneous visible light hyperspectral imaging measurement of oxyhemoglobin, deoxyhemoglobin, and tissue oxygenation, with interpretation and report, per extremity	Unproven
0640T	Noncontact near-infrared spectroscopy (e.g., for measurement of deoxyhemoglobin, oxyhemoglobin, and ratio of tissue oxygenation), other than for screening for peripheral arterial disease, image acquisition, interpretation, and report; first anatomic site	Unproven
0647T	Insertion of gastrostomy tube, percutaneous, with magnetic gastropexy, under ultrasound guidance, image documentation and report	Unproven
0651T	Magnetically controlled capsule endoscopy, esophagus through stomach, including intraprocedural positioning of capsule, with interpretation and report	Unproven
0658T	Electrical impedance spectroscopy of 1 or more skin lesions for automated melanoma risk score	Unproven
0659T	Transcatheter intracoronary infusion of supersaturated oxygen in conjunction with percutaneous coronary revascularization during acute myocardial infarction, including catheter placement, imaging guidance (e.g., fluoroscopy), angiography, and radiologic supervision and interpretation	Unproven
0664T	Donor hysterectomy (including cold preservation); open, from cadaver donor	Unproven
0665T	Donor hysterectomy (including cold preservation); open, from living donor	Unproven
0666T	Donor hysterectomy (including cold preservation); laparoscopic or robotic, from living donor	Unproven

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Code	Description	Conclusion
0667T	Donor hysterectomy (including cold preservation); recipient uterus allograft transplantation from cadaver or living donor	Unproven
0668T	Backbench standard preparation of cadaver or living donor uterine allograft prior to transplantation, including dissection and removal of surrounding soft tissues and preparation of uterine vein(s) and uterine artery(ies), as necessary	Unproven
0669T	Backbench reconstruction of cadaver or living donor uterus allograft prior to transplantation; venous anastomosis, each	Unproven
0670T	Backbench reconstruction of cadaver or living donor uterus allograft prior to transplantation; arterial anastomosis, each	Unproven
0672T	Endovaginal cryogen-cooled, monopolar radiofrequency remodeling of the tissues surrounding the female bladder neck and proximal urethra for urinary incontinence	Unproven
0686T	Histotripsy (i.e., non-thermal ablation via acoustic energy delivery) of malignant hepatocellular tissue, including image guidance	Unproven
0692T	Therapeutic ultrafiltration	Unproven
0694T	3-dimensional volumetric imaging and reconstruction of breast or axillary lymph node tissue, each excised specimen, 3-dimensional automatic specimen reorientation, interpretation and report, real-time intraoperative	Unproven
0695T	Body surface-activation mapping of pacemaker or pacing cardioverter-defibrillator lead(s) to optimize electrical synchrony, cardiac resynchronization therapy device, including connection, recording, disconnection, review, and report; at time of implant or replacement	Unproven
0696T	Body surface-activation mapping of pacemaker or pacing cardioverter-defibrillator lead(s) to optimize electrical synchrony, cardiac resynchronization therapy device, including connection, recording, disconnection, review, and report; at time of follow-up interrogation or programming device evaluation	Unproven
0735T	Preparation of tumor cavity, with placement of a radiation therapy applicator for intraoperative radiation therapy (IORT) concurrent with primary craniotomy (List separately in addition to code for primary procedure)	Unproven
0766T	Transcutaneous magnetic stimulation by focused low-frequency electromagnetic pulse, peripheral nerve, with identification and mapping of the treatment location, including noninvasive electroneurographic localization (nerve conduction localization), when performed; first nerve	Unproven
0767T	Transcutaneous magnetic stimulation by focused low-frequency electromagnetic pulse, peripheral nerve, with identification and mapping of the treatment location, including noninvasive electroneurographic localization (nerve conduction localization), when performed; each additional nerve (List separately in addition to code for primary procedure)	Unproven
0859T	Noncontact near-infrared spectroscopy (e.g., for measurement of deoxyhemoglobin, oxyhemoglobin, and ratio of tissue oxygenation), other than for screening for peripheral arterial disease, image acquisition, interpretation, and report; each additional anatomic site (List separately in addition to code for primary procedure)	Unproven
0861T	Removal of pulse generator for wireless cardiac stimulator for left ventricular pacing; both components (battery and transmitter)	Unproven
0862T	Relocation of pulse generator for wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming; battery component only	Unproven
0863T	Relocation of pulse generator for wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming; transmitter component only	Unproven

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Code	Description	Conclusion
0870T	Implantation of subcutaneous peritoneal ascites pump system, percutaneous, including pump-pocket creation, insertion of tunneled indwelling bladder and peritoneal catheters with pump connections, including all imaging and initial programming, when performed	Unproven
0871T	Replacement of a subcutaneous peritoneal ascites pump, including reconnection between pump and indwelling bladder and peritoneal catheters, including initial programming and imaging, when performed	Unproven
0872T	Replacement of indwelling bladder and peritoneal catheters, including tunneling of catheter(s) and connection with previously implanted peritoneal ascites pump, including imaging and programming, when performed	Unproven
0873T	Revision of a subcutaneously implanted peritoneal ascites pump system, any component (ascites pump, associated peritoneal catheter, associated bladder catheter), including imaging and programming, when performed	Unproven
0874T	Removal of a peritoneal ascites pump system, including implanted peritoneal ascites pump and indwelling bladder and peritoneal catheters	Unproven
0875T	Programming of subcutaneously implanted peritoneal ascites pump system by physician or other qualified health care professional	Unproven
0888T	Histotripsy (i.e., non-thermal ablation via acoustic energy delivery) of malignant renal tissue, including imaging guidance	Unproven
17999	Unlisted procedure, skin, mucous membrane and subcutaneous tissue [when used to report ablative laser treatment for wounds]	Unproven
19105	Ablation, cryosurgical, of fibroadenoma, including ultrasound guidance, each fibroadenoma	Unproven
19294	Preparation of tumor cavity, with placement of a radiation therapy applicator for intraoperative radiation therapy (IORT) concurrent with partial mastectomy (List separately in addition to code for primary procedure)	Unproven
33289	Transcatheter implantation of wireless pulmonary artery pressure sensor for long-term hemodynamic monitoring, including deployment and calibration of the sensor, right heart catheterization, selective pulmonary catheterization, radiological supervision and interpretation, and pulmonary artery angiography, when performed	Unproven
43206	Esophagoscopy, flexible, transoral; with optical endomicroscopy	Unproven
43252	Esophagogastroduodenoscopy, flexible, transoral; with optical endomicroscopy	Unproven
53451	Periurethral transperineal adjustable balloon continence device; bilateral insertion, including cystourethroscopy and imaging guidance	Unproven
53452	Periurethral transperineal adjustable balloon continence device; unilateral insertion, including cystourethroscopy and imaging guidance	Unproven
53453	Periurethral transperineal adjustable balloon continence device; removal, each balloon	Unproven
53454	Periurethral transperineal adjustable balloon continence device; percutaneous adjustment of balloon(s) fluid volume	Unproven
53860	Transurethral radiofrequency micro-remodeling of the female bladder neck and proximal urethra for stress urinary incontinence	Unproven
53899	Unlisted procedure, urinary system [when used to report Viveve system]	Unproven
55899	Unlisted procedure, male genital system [when used to report UroCuff]	Unproven
61715	Magnetic resonance image guided high intensity focused ultrasound (MRgFUS), stereotactic ablation of target, intracranial, including stereotactic navigation and frame placement, when performed	Unproven

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Code	Description	Conclusion
63268	Laminectomy for excision or evacuation of intraspinal lesion other than neoplasm, extradural; sacral	Proven in certain circumstances
64454	Injection(s), anesthetic agent(s) and/or steroid; genicular nerve branches, including imaging guidance, when performed	Unproven
64624	Destruction by neurolytic agent, genicular nerve branches including imaging guidance, when performed	Unproven
64999	Unlisted procedure, nervous system [when used to report any method of radiofrequency ablation]	Unproven
66683	Implantation of iris prosthesis, including suture fixation and repair or removal of iris, when performed	Unproven
77424	Intraoperative radiation treatment delivery, x-ray, single treatment session	Unproven
77425	Intraoperative radiation treatment delivery, electrons, single treatment session	Unproven
77469	Intraoperative radiation treatment management	Unproven
80145	Adalimumab	Unproven
80230	Infliximab	Unproven
80280	Vedolizumab	Unproven
81490	Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score	Unproven
81599	Unlisted multianalyte assay with algorithmic analysis [when used to report PreTrm]	Unproven
88375	Optical endomicroscopic image(s), interpretation and report, real-time or referred, each endoscopic session	Unproven
90999	Unlisted dialysis procedure, inpatient or outpatient [when used to report aquapheresis (ultrafiltration)]	Unproven
93264	Remote monitoring of a wireless pulmonary artery pressure sensor for up to 30 days, including at least weekly downloads of pulmonary artery pressure recordings, interpretation(s), trend analysis, and report(s) by a physician or other qualified health care professional	Covered in certain circumstances
93998	Unlisted noninvasive vascular diagnostic study [when used to report contact near-infrared spectroscopy studies of wounds]	Unproven
94011	Measurement of spirometric forced expiratory flows in an infant or child through 2 years of age	Unproven
94012	Measurement of spirometric forced expiratory flows, before and after bronchodilator, in an infant or child through 2 years of age	Unproven
94013	Measurement of lung volumes (i.e., functional residual capacity [FRC], forced vital capacity [FVC], and expiratory reserve volume [ERV]) in an infant or child through 2 years of age	Unproven
A4542	Supplies and accessories for external upper limb tremor stimulator of the peripheral nerves of the wrist	Unproven
C1839	Iris prosthesis	Unproven
C2624	Implantable wireless pulmonary artery pressure sensor with delivery catheter, including all system components	Unproven
E0734	External upper limb tremor stimulator of the peripheral nerves of the wrist	Unproven
E1399	Durable medical equipment, miscellaneous [when used to report non-invasive bimodal neuromodulation]	Unproven

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Code	Description	Conclusion
E1399	Durable medical equipment, miscellaneous [when used to report robotic lower body exoskeleton device]	Unproven
E2001	Suction pump, home model, portable or stationary, electric, any type, for use with external urine and/or fecal management system	Unproven
G0555	Provision of replacement patient electronics system (e.g., system pillow, handheld reader) for home pulmonary artery pressure monitoring	Covered in certain circumstances
K1007	Bilateral hip, knee, ankle, foot (HKAFO) device, powered, includes pelvic component, single or double upright(s), knee joints any type, with or without ankle joints any type, includes all components and accessories, motors, microprocessors, sensors	Unproven
K1030	External recharging system for battery (internal) for use with implanted cardiac contractility modulation generator, replacement only	Unproven
L8699	Prosthetic implant, not otherwise specified [when used to report three-dimensional (3-D) printed cranial implants]	Unproven
L8701	Powered upper extremity range of motion assist device, elbow, wrist, hand with single or double upright(s), includes microprocessor, sensors, all components and accessories, custom fabricated	Unproven
L8702	Powered upper extremity range of motion assist device, elbow, wrist, hand, finger, single or double upright(s), includes microprocessor, sensors, all components and accessories, custom fabricated	Unproven
P2031	Hair analysis (excluding arsenic)	Unproven
S2117	Arthroereisis, subtalar	Unproven

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Coverage Rationale/Clinical Evidence

Code	Description
0061U	Transcutaneous measurement of five biomarkers (tissue oxygenation [StO2], oxyhemoglobin [ctHbO2], deoxyhemoglobin [ctHbR], papillary and reticular dermal hemoglobin concentrations [ctHb1 and ctHb2]), using spatial frequency domain imaging (SFDI) and multi-spectral analysis

Transcutaneous measurement of biomarkers using spatial frequency domain imaging (SFDI) and multi-spectral analysis is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Spatial Frequency Domain Imaging (SFDI) technology is an optical technique used to quantitatively characterize turbid (multiple scattering) materials. The Clarifi® Imaging System (Modulated Imaging, Inc.) is a non-contact, noninvasive tissue oxygenation measurement system that reports an approximate value of oxygen saturation, oxy-hemoglobin, and deoxy-hemoglobin into 2D/3D visual presentations. It is indicated for use to determine oxygenation levels in superficial tissues for patients with potential circulatory compromise.

According to the manufacturer, the Clarifi® Imaging System itself does not provide any medical diagnosis or prescribe a medical course of treatment. It is intended to be part of a larger assessment battery and used in conjunction with other clinical assessment and diagnostic tests.

Jett et al. (2023) conducted an observational study evaluating microvascular disease (MVD) severity in the foot using SFDI. There were 299 limbs from 154 patients included in the study. The authors compared non-invasive vascular testing and SFDI in patients with no diabetes, diabetes, diabetes with neuropathy, and diabetes with neuropathy and retinopathy. Measurements included ankle brachial index (ABI), toe brachial index (TBI), vibratory sensory testing, and SFDI. For SFDI, the authors evaluated the papillary hemoglobin (HbT1) and tissue oxygen saturation (StO2). The authors noted no statistical significance between groups when evaluating for ABI and TBI. When evaluating SFDI, the authors noted a concomitant decrease in HbT1 with an increase in StO2 as MVD severity increased which was statistically significant in all

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groups except for the difference between the diabetes group and the diabetes with neuropathy group. The authors conclude that SFDI is a promising tool for evaluating MVD, however, prospective studies with wound-based outcomes are needed to further evaluate the role of MVD assessment in the clinical evaluation of patients at risk for lower extremity complications. Limitations of the study include lack of direct measurement of microvascular changes and lack of assessment of sensory neuropathy, autonomic neuropathy, retinal exams, and A1C history. Furthermore, the study does not address the clinical utility of the technology in improving patients' outcomes.

An ECRI clinical evidence assessment (2022) states that the evidence for SFDI is inconclusive as there are too few data on outcomes. SFDI may eventually be used to estimate foot ulcer risk, but the available data are insufficient to determine its efficacy compared to other diagnostic methods.

Weinkauf et al. (2019) analyzed 47 patients (94 limbs) with and without diabetes. The SFDI Reflect RS machine was used to collect maps showing StO2 and hemoglobin content within the papillary dermis or microcirculation (HbT1) and reticular dermis or macro - circulation (HbT2) of the plantar aspects of each foot. The authors evaluated the SFDI hemoglobin maps, which identified the total hemoglobin present in the papillary and reticular dermis in addition to the pedal Doppler waveforms; these were used as standards for estimating lower extremity blood supply. After review and analysis of the data, the authors concluded that the SFDI technology is a noninvasive technology that can be a tool to manage patients with peripheral arterial disease; however, further studies will need to be designed to fully evaluate the applicability of this new technology. Limitations of the study included small sample size, the absence of a "gold standard" for non-invasive imaging of lower extremity perfusion, and a design that did not allow assessment of whether the use of SFDI improves patient care or patient outcomes.

The U.S. Food and Drug Administration (FDA) cleared the Clarifi® Imaging System under its 510(k) premarket notification process as substantially equivalent to predicate devices. For additional information, refer to the following:

- https://www.accessdata.fda.gov/cdrh_docs/pdf18/K181623.pdf
- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K181623

(Accessed April 16, 2025)

For information on current clinical trials evaluating SFDI, go to www.clinicaltrials.gov. (Accessed April 16, 2025).

Reference(s)

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Jett S, Thompson MR, Awasthi S, et al. Stratification of microvascular disease severity in the foot using spatial frequency domain imaging. J Diabetes Sci Technol. 2023 Jan;17(1):25-34.

Modulin. https://modulim.com/solutions. Accessed April 16, 2025.

Weinkauf C, Mazhar A, Vaishnav K, et al. Near-instant noninvasive optical imaging of tissue perfusion for vascular assessment. *J Vasc Surg*. 2019;69(2):555–562.

Code	Description
0075T	Transcatheter placement of extracranial vertebral artery stent(s), including radiologic supervision and interpretation, open or percutaneous; initial vessel
0076T	Transcatheter placement of extracranial vertebral artery stent(s), including radiologic supervision and interpretation, open or percutaneous; each additional vessel (List separately in addition to code for primary procedure)

Transcatheter placement of extracranial vertebral artery stent(s) is considered unproven and not medically necessary due to insufficient evidence of efficacy.

Clinical Evidence

Li et al. (2025) conducted an observational registry-based study to examine the role of extracranial vertebral artery (VA) stenting for individuals with posterior circulation tandem lesion (PCTL) stroke undergoing endovascular treatment (EVT). To carry out the study, individual data was pooled from the BASILAR (EVT for Acute Basilar Artery Occlusion Study) and PERSIST (Posterior Circulation Ischemic Stroke) registries. Then, individuals with PCTLs who underwent EVT were divided into the stenting and non-stenting groups based on the placement of the extracranial VA stents. The main outcome measured was the modified ranking scale (mRS) measured at 90 days and 1 year. The cause of mortality at 90 days and 1-year post-surgery and 24-hour symptomatic intracranial hemorrhage (sICH) were included in the safety outcomes measured. The results of the study included 1320 individuals with posterior circulation artery occlusion. The

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stenting group consisted of 84 (38.7%) individuals, while the non-stenting group had 133 (61.3%). It was found that after adjustment for the potential confounders, extracranial VA stenting was associated with favorable shifts in mRS scores at both 90 days and 1 year, along with lower rate of mortality at both 90 days and 1 year, with no significant difference in sICH incidence. This observational registry-based study suggests supporting the safety and efficacy of EVT in individuals with PCTL-induced AIS caused by PCTL treated within 24 hours of the estimated occlusion time. The data collected also suggest that acute extracranial VA stenting during mechanical thrombectomy may enhance functional outcomes and reduce mortality rates for individuals with PCTL. Like anterior circulation tandem occlusions, randomized control trials investigating the best endovascular management in PCTL are warranted. The limitations of the study included the inherent potential for selection bias due to retrospective design and the absence of a control group. Furthermore, the BASILAR and PERSIST studies began in China in 2024 and 2015, respectively, during which some stroke centers had access to angiographic CT (ACT), while others did not. If a suspicious intracerebral hemorrhage was found through ACT, these factors may have influenced the proceduralist's decision to continue with the stenting. An analysis of the contralateral VA was not conducted due to the unavailability in some cases. There was no long-term follow up imaging, and patency rates of the stents were only assessed in 21 people. And lastly, the lack of generalization. It was concluded that currently, literature on the outcomes of individuals with EVT for PCTL is limited, predominantly from single-center studies.

The European Society for Vascular Surgery (ESVS) 2023 Clinical Practice Guidelines on the Management of Atherosclerotic Carotid and Vertebral Artery Disease state:

- Open or endovascular interventions are not recommended for individuals with asymptomatic vertebral artery atherosclerotic lesions.
- Routine stenting is not recommended for individuals presenting with a vertebrobasilar territory transient ischemic attack (TIA) or stroke and a 50-99% vertebral artery stenosis.
- Revascularization may be considered for individuals with recurrent vertebrobasilar territory symptoms (despite best medical therapy) and a 50-99% extracranial vertebral artery stenosis.
- Synchronous carotid and vertebral artery revascularization are not recommended for individuals with combined carotid and vertebral artery disease.
- For individuals undergoing vertebral artery stenting, drug-eluting stents should be considered in preference to bare metal stents.

Additionally, the clinical practice guidelines recommend that all those who have a stroke or TIA due to narrowing in their vertebral arteries will benefit from the same lifestyle advice, risk factor control, and medications (e.g., antiplatelet agents, medicines to lower blood pressure, statins to reduce cholesterol and careful management of diabetes) as described for individuals with symptoms due to carotid disease. Open operations are rarely performed for individuals symptomatic with narrowing in their vertebral arteries, and most are treated by medicines alone. The 2023 ESVS guidelines say that stenting of vertebral artery narrowing may be considered for individuals with recurrent TIA/stroke despite taking their medications (Naylor et al., 2023).

In 2022, Xu and associates assessed the safety and efficacy of percutaneous transluminal angioplasty, with or without stenting combined with medical treatment (MT), compared to MT alone, for individuals with episodes of cerebral ischemia due to vertebral artery stenosis. In the form of a systematic review, all randomized controlled trials that compared EVT with MT and MT alone were included. All types of ET modalities were included, and the MT included risk factor control, antiplatelet therapy, lipid-lowering therapy, and individualized management of those with hypertension or diabetes. The primary outcomes measured were death/stroke after 30 days of randomizations and fatal/non-fatal stroke after 30 days post-randomization to the completion of the follow-up. A total of 349 participants with symptomatic vertebral artery stenosis averaging 64.4 years were included. No significant difference in the 30-day post-randomization of deaths and strokes between the ET and MT and MT alone was seen [risk ratio (RR) 2.33, 95% confidence interval (CI) 0.77 to 7.07; 3 studies, 349 participants; low-certainty evidence]. There were no significant differences between ET plus MT and MT alone in fatal/non-fatal strokes in the territory of the treated vertebral artery stenosis after 30 days post-randomization to completion of follow-up (RR 0.51, 95% CI 0.26 to 1.01; 3 studies, 349 participants; moderate-certainty evidence), ischemic or hemorrhagic stroke during the entire follow-up period (RR 0.77, 95% CI 0.44 to 1.32; 3 studies, 349 participants; moderate-certainty evidence), death during the whole follow-up period (RR 0.78, 95% CI 0.37 to 1.62; 3 studies, 349 participants; low-certainty evidence), and stroke or TIA during the entire follow-up period (RR 0.65, 95% CI 0.39 to 1.06; 2 studies, 234 participants; moderate-certainty evidence). The authors concluded through this Cochrane review that low-to moderate-certainty of evidence suggests that there are no significant differences in the short- or long-term risks of stroke, death, or TIA for individuals with symptomatic vertebral artery stenosis while treated with either ET plus MT or those treated with MT alone.

Through a prospective, randomized, open, parallel, blinded end-point clinical trial, Markus et al. (2019) sought to compare the risks and benefits of vertebral angioplasty and stenting with the best medical treatment (BMT) alone for recently

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symptomatic vertebral artery stenosis. The Vertebral Artery Ischaemia Stenting Trial (VIST) took place in 14 hospitals in the UK, where individuals were followed up for at least one year. Participants had to have symptomatic vertebral stenosis of at least 50% manifested from presumed atheromatous disease to be included in the trial. The participants were assigned randomly (1:1) to either vertebral angioplasty/stenting plus BMT (n = 91) or BMT alone (n = 88), for a total of 179 contributing to the follow-up data and outcomes measured. The outcomes measured were the occurrence of fatal or non-fatal stroke in any arterial territory during follow-up. The trial results showed a median follow-up of 3.5 (interquartile range 2.1-4.7) years. Of the 61 participants who were stented, 48 (78.7%) had extracranial stenosis, and 13 (21.3%) had intracranial stenosis. No perioperative complications occurred with extracranial stenting; two strokes occurred during intracranial stenting. The primary end-point occurred in five people (including one fatal stroke) in the stent group and 12 participants (including two fatal strokes) in the medical group (giving a hazard ratio of 0.40, 95% CI 0.14 to 1.13; p = 0.08), with an absolute risk reduction of 25 strokes per 1000 person-years. The authors concluded that there was no difference in risk of the primary endpoint between the two points. The post hoc analysis suggests that stenting could be associated with a decrease in recurrent stroke risk for symptomatic vertebral arteries. Further studies are necessary to confirm the findings, especially with extracranial vertebral artery stenosis, as the complication rates with stenting were meager. The trial was limited by its failure to reach the target recruitment and the high rate of non-confirmation of stenosis in the stented group of the trial.

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Markus HS, Larsson SC, Dennis J, et al. Vertebral artery stenting to prevent recurrent stroke in symptomatic vertebral artery stenosis: the VIST RCT. Health Technol Assess. 2019 Aug;23(41):1-30.

Naylor R, Rantner B, Ancetti S, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2023 Clinical Practice Guidelines on the Management of Atherosclerotic Carotid and Vertebral Artery Disease. Eur J Vasc Endovasc Surg. 2023 Jan;65(1):7-111.

Xu R, Zhang X, Liu S, et al. Percutaneous transluminal angioplasty and stenting for vertebral artery stenosis. Cochrane Database Syst Rev. 2022 May 17;5(5):CD013692.

Code	Description
0163U	Oncology (colorectal) screening, biochemical enzyme-linked immunosorbent assay (ELISA) of 3 plasma or serum proteins (teratocarcinoma derived growth factor-1 [TDGF-1, Cripto-1], carcinoembryonic antigen [CEA], extracellular matrix protein [ECM]), with demographic data (age, gender, CRC-screening compliance) using a proprietary algorithm and reported as likelihood of CRC or advanced adenomas

The use of a biomarker panel based algorithmic analysis test [e.g., BeScreened™-CRC using three tumor proteins teratocarcinoma derived growth factor-1 (TDGF-1, Cripto-1), carcinoembryonic antigen (CEA), extracellular matrix protein (ECM)] to screen for colorectal cancer or advanced adenomas is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Blood-based biomarker panels are tests to assess the expression of genes to theoretically calculate a risk of having colorectal cancer (CRC). BeScreened™-CRC is manufactured by Beacon Medical Inc. and partnered with Sonora Quest Laboratories is an ELISA-based multiplexed, CLIA laboratory developed CRC screening test. It tests three plasma or serum cancer related proteins [carcinoembryonic antigen, extracellular matrix protein involved in early-stage tumor stroma changes, teratocarcinoma derived growth factor-1 (TGDF-1, Cripto-1)] to determine an algorithmic analysis reported as a positive or negative result. https://bescreened.com/. (Accessed March 31, 2025).

The 2021 United States Preventive Services Task Force (USPSTF) recommendation statement for colorectal cancer screening indicates that because of limited evidence, the USPSTF recommendations do not include “serum tests, urine tests, or capsule endoscopy for colorectal cancer screening.”

In a systematic review, Harlid et al. (2021) summarized the evidence from 53 studies (between 2011 and 2021) that used blood-based colorectal cancer biomarkers in pre-diagnostic, asymptomatic settings. The quality of the studies was mostly high, but very few possible biomarkers showed consistent results in more than one study. The most promising biomarkers was the anti-p53 antibodies which performed well with constant findings in one screening cohort and in the 3-4 years prior to diagnosis in two prospective cohort studies. Proteins were the most common type of biomarker assessed, particularly carcinoembryonic antigen (CEA) and C-reactive protein (CRP), with uncertain results. Other possible promising biomarkers included proteins, such as AREG, MIC-1/GDF15, LRG1 and FGF-21, metabolites and/or metabolite profiles, non-coding RNAs and DNA methylation, as well as re-purposed routine lab tests, such as ferritin and the triglyceride-

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glucose index. Biomarker panels generally achieved higher discriminatory performance than single markers. There were study limitations which included: general search topic in a many different exposures, lack of define criteria to differentiate the etiology verses the biomarkers between the studies and relevant studies before 2011 were not included which could have missed other biomarkers. In conclusion, this systematic review highlighted anti-p53 antibodies as a promising blood-based biomarker for use in colorectal screening panels, together with other specific proteins. Additional research is needed to evaluate these promising biomarkers in independent pre-diagnostic settings.

Voronova et al. 2020 in a pilot study evaluated the performance of 20 blood markers including tumor antigens, inflammatory markers, and apolipoproteins as well as their combinations in colorectal cancer screening programs. This study consisted of 203 healthy volunteers and 102 patients with CRC were enrolled into the study. Differences between healthy and cancer subjects were evaluated using Wilcoxon rank-sum test. Several classification algorithms were employed using information about different combinations of biomarkers altered in CRC patients as well as age and gender of the subjects; random sub-sampling cross-validation was done to overcome overfitting problem. Diagnostic performance of single biomarkers and the different classification models was evaluated by receiver operating characteristic (ROC) analysis. Of 20 biomarkers, 16 were significantly different between the groups; ApoA1, ApoA2 and ApoA4 levels were decreased, while levels of tumor antigens (e.g., carcinoembriogenic antigen) and inflammatory markers (e.g., C-reactive protein) were increased in CRC patients verses healthy subjects. Combination markers including information about all 16 significant analytes, age, and gender of patients, demonstrated better performance over single biomarkers with average accuracy on test datasets ≥ 95% and area under ROC curve ≥ 98%. The combination biomarkers showed more accurate discrimination between healthy subjects and CRC patients, compared to a univariate biomarker. Limitations included small sample size and variations in algorithms. Larger studies are necessary to confirm the clinical efficacy of biomarker and algorithm screening.

Bhardwaj et.al., (2020) used a two-stage design to measure 275 protein markers by proximity extension assay (PEA), first in plasma samples of a discovery set consisting of 98 newly diagnosed CRC cases and 100 age- and gender-matched controls free of neoplasm at screening colonoscopy. An algorithm predicting the presence of early- or late-stage CRC was derived by least absolute shrinkage and selection operator regression with .632 + bootstrap method, and the algorithms were then validated using PEA again in an independent validation set consisting of participants of screening colonoscopy with and without CRC (n = 56 and 102, respectively). Three different signatures for all-, early-, and late-stage CRC consisting of 9, 12, and 11 protein markers were obtained in the discovery set with areas under the curves (AUCs) after .632 + bootstrap adjustment of 0.92, 0.91, and 0.96, respectively. External validation among participants of screening colonoscopy yielded AUCs of 0.76 [95% confidence interval (95% CI), 0.67-0.84], 0.75 (95% CI, 0.62-0.87), and 0.80 (95% CI, 0.68-0.89) for all-, early-, and late-stage CRC, respectively. The authors concluded that although the identified protein markers are not competitive with the best available stool tests, the combination of identified protein markers with other informative blood-based markers could contribute to the development of a promising blood-based test for CRC screening. Additionally, this study is based on more biomarkers and a different algorithm from BeScreened™-CRC.

Gawel et. al., (2019) Screening programs for colorectal cancer (CRC) often rely on detection of blood in stools, which is unspecific and leads to a large number of colonoscopies of healthy subjects. Research has led to the identification of many different types of biomarkers, few of which are in general clinical use. Here, the authors searched for highly accurate combinations of biomarkers by meta-analyses of genome- and proteome-wide data from CRC tumors. They focused on secreted proteins identified by the Human Protein Atlas and used recently described algorithms to find optimal combinations of proteins. The authors identified nine proteins, three of which had been previously identified as potential biomarkers for CRC, namely CEACAM5, LCN2 and TRIM28. The remaining proteins were PLOD1, MAD1L1, P4HA1, GNS, C12orf10 and P3H1. They analyzed these proteins in plasma from 80 patients with newly diagnosed CRC and 80 healthy controls. A combination of four of these proteins, TRIM28, PLOD1, CEACAM5 and P4HA1, separated a training set consisting of 90% patients and 90% of the controls with high accuracy, which was verified in a test set consisting of the remaining 10%. Further studies are warranted to test algorithms and proteins for early CRC diagnosis. Additionally, this study is based on different biomarkers and a different algorithm from BeScreened™-CRC.

For use of liquid biopsy tests for colorectal cancer (CRC) screening to reduce CRC morbidity and mortality, evidence from 3 studies suggests that CRC screening-eligible adults, especially those who reject a colonoscopy screen, prefer a blood-based test for mSEPTIN9 to a standard stool-based test. However, evidence comparing new versus established screening test performance in an unselected, prospective screening population is insufficient to support conclusions. Similarly, evidence for other types of liquid biopsy CRC screening tests is lacking. (Hayes, 2020; updated 2023).

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Harlid S, Gunter MJ, Van Guelpen B. Risk-Predictive and diagnostic biomarkers for colorectal cancer; a systematic review of studies using pre-diagnostic blood samples collected in prospective cohorts and screening settings. Cancers (Basel). 2021 Aug 31;13(17):4406.

Hayes, Inc., Clinical Utility Evaluation. Liquid Biopsy Tests for Colorectal Cancer Screening Hayes Inc., March 26, 2020, updated March 30, 2023.

US Preventive Services Task Force; Davidson KW, Barry MJ, Mangione CM, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA. 2021 May 18;325(19):1965-1977.

Voronova V, Glybochko P, Svistunov A, et al. Diagnostic value of combinatorial markers in colorectal carcinoma. Front Oncol. 2020 May 22;10:832.

Code	Description
0174T	Computer-aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed concurrent with primary interpretation (List separately in addition to code for primary procedure)
0175T	Computer-aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed remote from primary interpretation

Computer aided detection (CAD) of chest radiographs is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Computer aided detection (CAD) systems are adjunctive tools used in assessing chest radiographs. CAD uses a computer algorithm to analyze features of a lesion to determine the level of suspicion and is intended to enhance the reader's diagnostic performance. CAD is thought to improve the accuracy and consistency of radiological diagnosis by reducing the time it takes to interpret images.

The published literature regarding CAD for chest radiographs consists primarily of the technical capabilities of CAD systems. There is presently inadequate evidence in the medical literature that population-based mass screening with CAD for chest radiographs will contribute substantially to the detection of smaller cancers, or decreases mortality. High-quality, randomized trials examining the effect of CAD systems for chest radiographs are necessary to determine the true impact of this technology on health outcomes.

A health technology evaluation (NICE, 2025) was conducted to assess AI-derived software, used with chest x-rays, for suspected lung cancer. This guideline states that more research is needed for this type of software, including but not limited to, its impact on clinical decision making, subsequent referrals for CT scans, effect on costs and resources, and diagnostic accuracy.

NCCN guidelines on lung cancer screening do not mention CAD for chest radiographs. They further state that chest radiographs are not currently recommended for lung cancer screening. (NCCN, 2024).

In a 2023 evidence analysis research brief, Hayes reviewed abstracts related to CAD systems, used with chest radiographs, in assessing pulmonary nodules or masses. The purpose of this review was to determine if there is adequate published peer-reviewed literature to evaluate this technology in the future. Their analysis included six abstracts: two cross-sectional studies, and four case-control studies. No position statements or guidelines were found. While they cannot make a determination on this topic from abstracts, they may conduct a full evidence-based report in the future. Hayes, 2023).

Kajuji et al. (2023) conducted a retrospective review of a cross-sectional active TB case finding study. "Of 1884 participants, 452 (24.0%) had a history of previous TB. Prevalence of microbiologically confirmed TB among those with and without history of previous TB was 12.4% and 16.9%, respectively. Using CAD4TB, sensitivity and specificity were 89.3% (95% CI: 78.1–96.0%) and 24.0% (19.9–28.5%) and 90.5% (86.1–93.3%) and 60.3% (57.4–63.0%) among those

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with and without previous TB, respectively. Using qXR, sensitivity and specificity were 94.6% (95% CI: 85.1–98.9%) and 22.2% (18.2–26.6%) and 89.7% (85.1–93.2%) and 61.8% (58.9–64.5%) among those with and without previous TB, respectively." The authors concluded that using CAD systems as a tool for TB triage was decreased among persons who had previously been treated for this disease.

In a randomized controlled trial, Hwang et al. (2023) compared conventional interpretation of chest radiographs (CR) versus CRs with artificial intelligence-assisted interpretation (AI-CAD), in individuals with acute respiratory symptoms. Individuals presenting to a single-center emergency department for these symptoms were randomly assigned to receive either CRs with assistance from AI-CAD interpretation (1761 in the intervention group), or CRs without AI-CAD assistance (1815 in the control group). "The sensitivity [67.2% (317/472) in the intervention group vs. 66.0% (324/491) in the control group; odds ratio, 1.02 (95% confidence interval, 0.70–1.49); p = 0.917] and false-positive rate [19.3% (249/1289) vs. 18.5% (245/1324); odds ratio, 1.00 (95% confidence interval, 0.79–1.26); p = 0.985] of CR interpretation by duty radiologists were not associated with the use of AI-CAD." The authors concluded that diagnosing acute thoracic disease in individuals with acute respiratory symptoms was not improved with AI-CAD; the computer assistance did not improve the sensitivity and false-positive rate (FPR) of the CR interpretation.

In a systematic review, Haber et al. (2020) aimed to identify whether there was an advantage to using Computer Aided Detection (CAD) to support CXR interpretation of pulmonary nodules; our findings were inconclusive. From the initial 290 articles retrieved; seven studies were included in the review following a systematic screening process. The average CAD sensitivity in these studies was 58.67% (range; 44.2%–71%) alongside a mean 2.22 (range; 0.19–3.9) FP rates per image. No correlation between CAD sensitivity and false positive rates was identified. The findings suggest that further work is needed with larger sample sizes to improve confidence in synthesized findings. While future studies to evaluate CAD in the detection of PNs could be recommended, the recent research related to the higher potential effectiveness of Artificial Intelligence (AI) systems to support CXR interpretation suggests that this may no longer be an appropriate recommendation. Future research in either CAD or AI should explore and evaluate the risk versus benefit of computer-assisted technologies, as well as the impact on the imaging workforce and workflow. These technologies offer huge potential for diagnosis at an earlier stage, with a focus on saving more lives and improving the quality of life for those diagnosed with disease.

In a small retrospective study, Dellios et al. (2017) applied two CAD systems, SoftView™ 2.4A and OnGuard™ 5.2, to 100 posteroanterior chest radiographs with pulmonary lesions larger than 5 mm. Of these initial 100 radiographs, 75 of them had been confirmed via CT scans and histologically as malignant prior to the application of the software. The number of detected lesions by observation in unprocessed images was compared to the number of CAD-detected lesions in bone-suppressed images. 20% of the true positive lesions were proven benign while 80% were malignant whereas the false negative lesions were 47% benign and 53% malignant. The false positive rate was 0.88/image, and the false negative rate was 0.35/image. The researchers concluded a "hybrid" approach of CAD implementation with a critical radiological reading is effective for the detection of lung nodules. They noted that it does increase the amount of time necessary to complete the radiograph readings.

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Code	Description
0207T	Evacuation of meibomian glands, automated, using heat and intermittent pressure, unilateral
0563T	Evacuation of meibomian glands, using heat delivered through wearable, open-eye eyelid treatment devices and manual gland expression, bilateral

Due to insufficient evidence of safety and/or efficacy, the following are unproven and not medically necessary for the evaluation or evacuation of meibomian glands:

- Thermal pulsation or automated evacuation using heat and intermittent pressure.
- Wearable, open-eye eyelid treatment devices used for application of localized heat.

Clinical Evidence

Eyelid Thermal Pulsation

The LipiFlow® Vectored Thermal Pulsation (VTP) System (Johnson & Johnson Vision) is an eyelid thermal pulsation device that uses heat and intermittent pressure to automatically evacuate the meibomian glands. The iLUX MGD Treatment System (Alcon) is a thermal pulsation device that simultaneously applies localized heat and compression to treat meibomian gland dysfunction (MGD). These devices are intended to treat individuals with dry eye disease and other conditions that cause MGD.

The American Academy of Ophthalmology Preferred Practice Pattern Guidelines on dry eye syndrome (Amescua et. al., 2024) lists thermal pulsation devices as a second-stage option for treatment of dry eye disease (DED).

The American Academy of Ophthalmology Preferred Practice Pattern Guidelines for Blepharitis (Lin et al., 2024) indicates that multiple industry-sponsored studies have demonstrated that a single vectored thermal pulsation (VTP) treatment can be effective at improving meibomian gland function and reducing dry eye symptoms for a year or more post procedure. However, there have been no independent, randomized, clinical trials confirming or refuting these industry-sponsored studies.

In a Cochrane review summary, Yim et al. (2025) evaluated the effectiveness of LipiFlow for treating DED signs and symptoms and the safety of LipiFlow compared with sham or other available treatments for MGD in adults. The authors searched several databases for randomized trials, including CENTRAL, MEDLINE Ovid, Embase.com, PubMed, LILACS, ClinicalTrials.gov, and WHO ICTRP on October 24, 2022. The studies involved adults (≥ 18 years) diagnosed with DED or MGD as defined by the investigators. This review included 13 trials with a total of 1,155 randomized participants (66% female; ages 19 to 86). Five trials compared LipiFlow with basic warm compresses, showing mixed results regarding symptom improvement after 4 weeks. There was no significant difference in meibomian gland expression, meibum quality, or tear breakup time between LipiFlow and warm compresses. Another five trials compared LipiFlow with thermostatic devices, revealing that thermostatic devices reduced Ocular Surface Disease Index (OSDI) scores by an average of 4.59 points compared to LipiFlow. The remaining three trials were not comparable. The overall evidence was of low or very low certainty, with most trials having a high risk of bias. No trial reported any vision-threatening adverse events related to the intervention. The authors note that there are limited long term studies evaluating the use of LipiFlow when in fact DED is a chronic lifelong condition. LipiFlow's performance is comparable to other DED treatments. Further research with better masking and standardized testing methods are needed to determine if and when LipiFlow should be used (Tauber 2020 is included in this review).

In a 2024 Cochrane review, Pucker et al. evaluated the effectiveness of LipiFlow for treating DED and the safety of this treatment compared to sham and/or other treatments for MGD. There were a total of 1155 participants (1720 eyes) with DED from 13 randomized trials from a database thru October 2022. The authors compared LipiFlow to other basic treatments such as warm compresses, various eyelid hygiene products or DED medications. There was no clear evidence indicating an improvement based on symptoms scores from participants questionnaires or in signs from surface eye tests. The authors indicated that LipiFlow compared to the more common basic treatments with conflicting and inconclusive findings. They did note that they found no evidence of indicating there were negative side effects or that this treatment was unsafe. Study limitations included a high level of bias therefore the authors confidence in the evidence was low to very low. Biases were related to the participants knowing the treatment they were receiving along with variations in testing regimens. Based on this review, it is difficult to evaluate the advantages and disadvantages of LipiFlow compared to other treatments. More robust studies are needed to include a control group who undergoes a sham LipiFlow treatment without thermal pulsation. (Hagen et. al., and Tauber et al., 2020 which were previously cited in this policy, are included in this systematic review).

A Hayes report for Thermal Pulsation System for Chronic Dry Eye Syndrome and Meibomian Gland Dysfunction (2019, updated 2023) indicates that there is low-quality evidence that thermal pulsation therapy has efficacy similar to or

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somewhat better than standard warm compress treatment. However, the durability of benefit is unclear due to inadequate follow-up times. There is limited evidence comparing thermal pulsation therapy with established medications to treat dry eye or MGD. The authors conclude that there is potential but unproven benefit of this technology (Blackie et al. 2018 and Tauber et al. 2020 are included in this review).

Tao et al. (2023) in an Ophthalmic Technology Assessment by the American Academy of Ophthalmology reviewed the literature to determine the efficacy and safety of thermal pulsation technologies in improving signs or symptoms of MGD and dry eye compared with no therapy, with conventional warm compress therapy or eyelid hygiene. There were 11 studies included, 8 rated at level I evidence and 3 with level II evidence. All studies evaluated a single 12-minute session using the LipiFlow automated thermal pulsation system (TearScience, Inc, or Johnson & Johnson). Improvements were detected in subjective and objective metrics of MGD or dry eye in patients within 1 to 12 months of thermal pulsation treatment compared with nontreatment. Most of the studies (9/11) reported greater efficacy with thermal pulsation than with standard warm compress therapy and eyelid hygiene. No serious adverse events were reported in any of the 11 studies. The authors indicate that a single thermal pulsation session may improve subjective or objective parameters of MGD and dry eye safely. Four of the studies were sponsored by the industry which could result in bias. The three level I studies that were not sponsored by the industry indicated that thermal pulsation treatment was not significantly different than general eyelid hygiene. Thermal pulsation appears to be safe and the authors note that it could be used when basic MGD and DED treatments are not available or desirable by the participant. Larger robust studies are needed to assess the long-term benefits of this treatment. (Blackie et al. 2016, 2018 below are included in this review).

Novo-Diez et al. (2022) conducted a prospective, single-center, open-label study to assess the prophylactic effect of LipiFlow treatment in MGD. There were two aims of the study: the first was to assess the efficacy of a single LipiFlow treatment in MGD individuals over a 12-month period under normal environmental conditions and the second was to evaluate the prophylactic benefits of LipiFlow in individuals with MGD undergoing an adverse environmental humidity exposure. patients with MGD were exposed to normal (23 °C; 50% relative humidity; 30 min) and adverse (23 °C; 10% relative humidity; 2 h) controlled environments consecutively during baseline and follow-up visits (3, 6, and 12 months) after a single LipiFlow treatment. Ocular Surface Disease Index (OSDI), lipid layer thickness (LLT), fluorescein tear break-up time (TBUT), corneal and conjunctival staining, change in dry eye symptoms questionnaire (CDES-Q), and meibomian gland yielding liquid secretion (MGYLS), were assessed. Linear mixed-effects and cumulative logit mixed models were fitted to assess the effect of the LipiFlow treatment over time and within the controlled environments. Seventeen females and 4 males (59.6 ±9.4 years) completed the study. LLT and TBUT did not vary significantly ($p > 0.05$) after LipiFlow treatment. OSDI, corneal and conjunctival staining, and MGYLS scores were improved ($p \leq 0.01$) 12 months after treatment. After the adverse exposure, corneal staining increased at all visits ($p = 0.01$), and there was no significant improvement in CDES-Q scores after LipiFlow treatment ($p \geq 0.07$). One LipiFlow treatment improved objective and subjective outcomes in MGD disease for at least one year. Further studies are needed to support that LipiFlow might also help as an adjuvant to avoid acute flares against an adverse environmental humidity. The study is limited by lack of a contemporary comparison group undergoing a different treatment.

Hu et al. (2022) conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to examine the efficacy and safety of a vectored thermal pulsation system (LipiFlow®) for the treatment of DED related to MGD. Subjective symptoms, objective tests of dry eye, meibomian gland function, and the incidence of adverse events were evaluated from RCTs thru January 2021. Results were based on ten qualified RCTs incorporating 761 participants with a range of comparison groups. Findings were stratified by whether the study analysis took into account the correlation between two eyes included per participants. In the comparison of LipiFlow® treatment and lid hygiene, the subgroup with inconsistent units of randomization and analysis (not taking into consideration correlation between the two eyes of study participants) showed that the LipiFlow® treatment brought slight improvement in corneal fluorescein staining [mean difference (MD), -0.42; 95% CI, -0.75 to -0.1], significant improvements in ocular surface disease index (OSDI) score (MD, -7.4; 95% CI, -11.06 to -3.74), Standard Patient Evaluation of Eye Dryness (SPEED) score (MD, -2.7; 95% CI, -3.95 to -1.45), meibomian glands yielding liquid secretion (MGYLS) (MD, 1.3; 95% CI, 0.78 to 1.82), and meibomian glands yielding secretion score (MGYSS) (MD, 4.09; 95% CI, 1.18 to 6.99). Significant improvements were detected in OSDI score, SPEED score, MGYLS, and MGYSS with individuals who received LipiFlow® treatment compared with those who received nontreatment. The adverse events were similar in the two control groups. Findings were not significant or less consistent among studies with data analysis strategies taking into account correlation between participants eyes. The authors also noted that no individual trial was assessed as having a low risk of bias for all domains. They however concluded that LipiFlow® treatment can improve the subjective and objective outcomes of MGD and does not increase the incidence of adverse events. Further well-designed, large-scale RCTs are essential to reach a stronger conclusion. (Tauber 2020 and Blackie 2018 included in this study).

Pang et al. (2019) conducted a systematic review and meta-analysis of RCTs that compared the efficacy of vectored thermal pulsation treatment (VTPT) and warm compress treatment (WCT) in treating DED. The primary outcome was the

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gland function. The analysis consisted of 4 trials with 385 individuals. Significantly greater improvement was observed in meibomian gland function, tear breakup time, and Standard Patient Evaluation for Eye Dryness at 2 to 4 weeks in the VTPT group than in the WCT group. A significantly greater decrease in Ocular Surface Disease Index was observed at 2 to 4 weeks and 3 months in the VTPT group than in the WCT group. The authors concluded that a single 12-minute VTPT was more efficacious than traditional WCT in treating DED either in objective or subjective measurements. There were several study limitations. All four included trials that were considered at high risk of overall bias. All participants belonged to an age group (45-65 years) therefore the results may not apply to the younger population. The authors also notes that it was not known if the WCT group was treated per the protocol. Lastly the included trials were limited to three-months follow-up. These findings require confirmation in RCTS with larger patient populations, confirmed treatment protocols and long-term follow-up. (Blackie et al. 2016 included in this review).

In a prospective randomized, multi-center clinical trial, Blackie et al. (2018) evaluated the effect of a single VTP treatment in contact lens wearers with (MGD) and dry eye symptoms. The trial included 55 soft contact lens (SCL) wearers with MGD and evaporative dry eye. Subjects were randomized to the single VTP treatment group or an untreated control. The controls received a crossover VTP treatment at 3 months (crossover treatment group). Primary effectiveness measures were meibomian gland secretion (MGS) score and Standard Patient Evaluation of Eye Dryness (SPEED) that were evaluated at baseline, at 1 and 3 months post-VTP treatment, and at 1-month post-VTP treatment in the crossover treatment group. Exploratory variables included fluorescein tear break-up time (TBUT), lid wiper epitheliopathy (LWE), lid parallel conjunctival folds (LIPCOF), ocular surface staining, frequency of over the counter (OTC) drop use, and hours of comfortable contact lens wear. At 3 months, the treatment group showed significantly greater mean change from baseline in MGS, SPEED and significantly greater improvement in exploratory variables (TBUT, LWE, and frequency of OTC drop use) relative to the controls. Mean comfortable contact lens wearing time increased by 4.0 ±3.9 hours at 1 month. This was sustained for 3 months with no change in the control group. The crossover treatment group demonstrated similar results to the treatment group at 1-month post-VTP. The authors concluded that in SCL wearers with MGD, a single VTP treatment significantly improved mean meibomian gland function and significantly reduced dry eye signs and symptoms compared to an untreated control. This was a small study intended to assess the value of performing a larger clinical study in contact lens wearing individuals with MGD. The authors indicated that they cannot rule out investigator bias or the placebo effect, especially in the context of an open-label trial. Furthermore, this study was funded by the manufacturer of LipiFlow (TearScience, Inc) and lack comparison to established treatments.

The Tear Film and Ocular Surface Society (TFOS) recommends LipiFlow as a second-line option for treatment of DED (Craig et al., 2017).

Blackie et al. (2016) evaluated the sustained effect (up to 1 year) of a single, 12-minute VTP treatment in improving MGD and dry eye symptoms in individuals with MGD and evaporative dry eye. The prospective, multicenter, open-label clinical trial included 200 subjects (400 eyes) who were randomized to a single VTP treatment (treatment group) or twice-daily, 3-month, conventional warm compress and eyelid hygiene therapy (control group). Control group subjects received crossover VTP treatment at 3 months (crossover group). Effectiveness measures of MGS and dry eye symptoms were evaluated at baseline and 1, 3, 6, 9, and 12 months. Subjects with inadequate symptom relief could receive additional MGD therapy after 3 (treatment group) and 6 months (crossover group). At 3 months, the treatment group had greater mean improvement in MGS and dry eye symptoms, compared to controls. At 12 months, 86% of the treatment group had received only one VTP treatment, and sustained a mean improvement in MGS from 6.4 ±3.7 (baseline) to 17.3 ±9.1 and dry eye symptoms from 44.1 ±20.4 to 21.6 ±21.3; 89% of the crossover group had received only one VTP treatment with sustained mean improvement in MGS from 6.3 ±3.6 to 18.4 ±11.1 and dry eye symptoms from 49.1 ±21.0 to 24.0 ±23.2. The authors concluded that a single VTP treatment can deliver a sustained mean improvement in meibomian gland function and mean reduction in dry eye symptoms, over 12 months. A single VTP treatment provides significantly greater mean improvement in meibomian gland function and dry eye symptoms as compared to a conventional, twice-daily, 3-month regimen. According to the authors, a significant limitation of this study is that the investigators were not masked, which could have introduced a bias in the findings. This study was funded by the manufacturer of Lipiflow (TearScience, Inc) and the lead authors are affiliated with TearScience, Inc.

Wearable, Open-Eye Eyelid Treatment Devices Used for Application of Localized Heat

TearCare® (Sight Sciences) is a software-controlled, wearable eyelid technology that provides targeted and adjustable heat energy to the tarsal plates and underlying meibomian glands. It is intended to treat eye conditions such as MGD, dry eye, and blepharitis.

The American Academy of Ophthalmology Preferred Practice Pattern Guidelines on Blepharitis (Lin et al., 2024) or dry eye syndrome (Amescua et al., 2024) do not address wearable, open-eye eyelid treatment devices.

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In a Clinical Evidence assessment published by ECRI (2024), the evidence indicated that TearCare for the treatment of dry eyes is favorable based on the evidence from three RCTs and four before and after studies. TearCare was compared with cyclosporine eyedrops in one RCT, additional RCTs are needed to support firm conclusions. This ECRI review has several limitations. The pilot RCT is biased due to its single-center focus and small sample size. Participants in the TearCare group had more severe MGD at baseline, potentially favoring the control condition. Larger, multicenter RCTs did not blind participants to the treatment performed, leading to high bias risk, especially in comparisons with cyclosporine ophthalmic emulsion and LipiFlow. Before-and-after studies also faced high bias risk due to single-center focus, retrospective design, and lack of an independent control group. In one study, participants needing retreatment for DED were excluded from results, though this would have been a relevant outcome. There are significant evidence gaps in comparative effectiveness, highlighting the need for further studies to confirm the findings. In addition, all studies in this review were also funded by the manufacturer.

The SAHARA trial, led by Ayres et al. (2023), is a manufacturer-funded randomized controlled trial. Phase 1 of this trial evaluated the effectiveness of TearCare versus Restasis (cyclosporine ophthalmic emulsion 0.05%) for treating DED associated with MGD. Phase 1 included 345 subjects randomized to either TearCare or Restasis. TearCare showed superior improvements in tear film break-up time (TBUT) at all measured time points (one week, one month, and six months) compared to Restasis. In 2024, Ayres reported Phase 2 results from 163 patients who switched from Restasis to TearCare at the six-month mark. These patients experienced further improvements in TBUT and dry eye symptoms, which persisted through 12 months. The trial demonstrated TearCare's effectiveness both as a primary and secondary treatment for DED. In Phase 2, signs assessments were not assessor-masked as they were in Phase 1, so assessor bias could not be ruled out. Based on prior studies, the assessor knew that the effects of TearCare began to diminish by six months, indicating that the results reported at 12 months likely underestimated the maximum benefit. As the SAHARA RCT continues into Phase 3, it will provide long-term, two-year data of the TearCare trial in an attempt to validate TearCare's effectiveness and safety for treating DED. The findings are limited by lack of masking of participants or use of sham procedures. Additional robust long-term studies are needed to support these findings. (Ayres 2023, 2024 included in the above ECRI report).

Gupta et al. (2022) in a masked RCT evaluated the safety and effectiveness of a single TearCare procedure compared with a single LipiFlow procedure in the treatment of DED associated with MGD. 135 subjects received a single TearCare (TC) treatment (n = 67) or a single LipiFlow (LF) treatment (n = 68) at baseline and were followed for 1 month posttreatment. Tear film breakup time, meibomian gland function, and corneal and conjunctival staining scores were assessed as dry eye signs at baseline, 2 weeks, and 1 month; dry eye symptoms were assessed using the Ocular Surface Disease Index, Symptom Assessment in Dry Eye, and eye dryness questionnaires at baseline and 1 month. At 1 month posttreatment, both groups demonstrated significant improvements ($p < 0.0001$) in mean tear film breakup time and meibomian gland secretion score to 3.0 ±4.4 and 11.2 ±11.1 in the TC group and 2.6 ±3.3 and 11.0 ±10.4 in the LF group, respectively. The mean eye dryness, Symptom Assessment in Dry Eye, and Ocular Surface Disease Index scores were significantly reduced ($p < 0.0001$) by 35.4 ±34.1, 38.2 ±31.0, and 27.9 ±20.5 in the TC group and 34.9 ±26.9, 38.0 ±25.9, and 23.4 ±17.7 in the LF group, respectively. The groups showed no statistically significant differences for any one result. The TC group demonstrated numerically greater improvements consistently in all signs and symptoms. Device-related ocular adverse events were reported in 3 participants in the TC group (superficial punctate keratitis, chalazion, and blepharitis) and 4 participants in the LF group (blepharitis, 2 cases of foreign body sensation, and severe eye dryness). Study limitations included outcomes were subjective, interpretation of results from the examiner even though masked, and lack of long-term follow-up. The authors concluded that a single TearCare treatment alleviates the signs and symptoms of DED in individuals with MGD and is equivalent in its safety and effectiveness profile to LipiFlow treatment as shown in this 1-month follow-up study. Due to study limitations, further well-controlled studies that includes long-term efficacy are needed.

Karpecki et al. (2020) conducted a prospective exploratory single-arm interventional study to evaluate the safety and effectiveness of the TearCare® System to treat adults with signs and symptoms of DED. A total of fifty-eight eyes (29 subjects) received a single TearCare procedure and were assessed at baseline, post-procedure 1-week and 1-month. Effectiveness was assessed as mean change from baseline in tear break-up time (TBUT), Ocular Surface Disease Index (OSDI), total Meibomian Gland Secretion Score (MGSS), and corneal/conjunctival staining. Adverse events (AE) and changes in visual acuity were used to assess safety. The baseline TBUT of 3.7 ±1.1 seconds was improved by 2.6 ±1.6 (70%) seconds at 1-week and by 3.1 ±2.2 (84%) seconds at 1-month ($p < 0.0001$). Mean baseline OSDI of 54.9 ±20.2 improved by 17.9 ±20.9 at 1-week and 25.8 ±24.3 at 1-month ($p < 0.001$). A clinically meaningful improvement was seen in 83% of subjects as per the Miller-Plugfelder definition and 66% of subjects improved by at least 1 OSDI category. The baseline MGSS of 5.6 ±4.0 improved by 9.3 ±4.0 at 1-week and 8.8 ±5.8 at 1-month ($p < 0.0001$). Corneal and conjunctival staining improved by 1.4 ±2.8 and 1.2 ±2.9 from a mean baseline of 4.8 ±2.5 and 5.9 ±3.2, respectively. Similar lines of improvement were also observed for subgroups of subjects ranked by severity. Subjects with more severe gland obstruction at baseline had greater improvements in TBUT and staining compared to the less severe subgroup. No

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device-related adverse events or significant changes in visual acuity were observed. Study limitations included the possibility of subjective grading of endpoints by investigators even though they underwent thorough training in an attempt to adhere to standardization. Another limitation is the sample size did not allow for hypothesis testing and statistical analysis. Significant improvements were seen in all subjects (100%) in all signs and symptoms of DED within 1-week of treatment and 83% of subjects experienced symptom relief. In addition, TearCare seems to be effective in treating DED associated with all levels of meibomian gland obstruction. Authors indicate that these promising preliminary results related to safety and effectiveness will support future robust RCTs. The findings of this study are limited by lack of comparison group.

Badawi (2019) evaluated the safety and effectiveness of TearCare retreatment in adults with clinically significant DED that was an extension of an initial 6-month, prospective, single-center, randomized, parallel-group pilot study (Badawi, 2018). In the case series, subjects were evaluated for the clinical signs and symptoms of DED prior to retreatment in the extension study that would measure the safety, effectiveness, and durability of a TearCare retreatment for another 6 months through a 12-month end point. The TearCare retreatment procedure consisted of 12 minutes of thermal eyelid treatment immediately followed by manual meibomian gland clearance. The primary effectiveness end point was the change in tear break-up time TBUT from baseline to 1-month follow-up. Twelve subjects participated in the 6-month extension study. At a 1-month clinic visit following retreatment, a significant improvement from baseline in mean (±SD) TBUT of 12.4 (±3.3) seconds was observed. Significant improvements in the mean change from baseline in meibomian gland scores, corneal and conjunctival staining scores, and symptoms of DED were also observed following retreatment. The second treatment was well tolerated. The investigator concluded that the findings of the extension study through 12 months suggest that a second TearCare treatment after 6 months provides additional improvement in the signs and symptoms of DED. According to the investigator, there are some limitations to this study. This was a single-treatment, single-investigator study so it was not possible to mask subjects or the investigator. Also, the study population was small. This and the original studies were funded by the manufacturer of the device and the author disclosed that he is an employee of the manufacturer. Independent confirmation of these findings would be helpful.

Badawi (2018) evaluated the safety and effectiveness of the TearCare System in adult patients with clinically significant DED in a prospective, single-center, randomized, parallel-group, clinical trial. Subjects with DED were randomized to either a single TearCare treatment conducted at the clinic or 4 weeks of daily warm compress (WC) therapy. The TearCare procedure consisted of 12 minutes of thermal eyelid treatment immediately followed by manual expression of the meibomian glands. WC therapy consisted of once daily application of the compresses to the eyelids for 5 minutes. Subjects were followed until 6 months post-treatment. The primary effectiveness end point was defined as change from baseline to 4 weeks for TBUT. Twenty-four subjects were enrolled, and all subjects completed 6 months follow-up. At the 1-month follow-up, TearCare subjects demonstrated an improvement from baseline in mean (±SD) TBUT of 11.7 ±2.6 seconds compared with an average worsening of -0.3 ±1.1 seconds for subjects in the WC group. Significantly greater improvements in the change from baseline in meibomian gland scores, as well as corneal and conjunctival staining scores, were observed in the TearCare group. Subjects in the TearCare group also showed significantly greater improvement in dry eye symptoms as measured by 3 questionnaires. Both treatments were well-tolerated. The investigator concluded that the findings of this pilot study suggest that the TearCare System is an effective treatment option for individuals with DED, with the effects on the signs and symptoms of DED persisting for at least 6 months. This study was limited by lack of masking to the intervention. A larger number of subjects enrolled at different centers is needed to enhance the evidence base for this technology.

The American Academy of Ophthalmology Preferred Practice Pattern Guidelines on Blepharitis (2018a) or dry eye syndrome (2018b) do not address wearable, open-eye eyelid treatment devices.

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Code	Description
0208T	Pure tone audiometry (threshold), automated; air only
0209T	Pure tone audiometry (threshold), automated; air and bone
0210T	Speech audiometry threshold, automated;
0211T	Speech audiometry threshold, automated; with speech recognition
0212T	Comprehensive audiometry threshold evaluation and speech recognition (0209T, 0211T combined), automated

Automated speech audiometry that is either self-administered or administrated by non-audiologists is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

While automated audiometry that is either self-administered or administrated by non-audiologists has been studied, its efficacy has not been adequately validated to be equivalent to audiometry performed by an audiologist. Further studies are needed to support its routine use.

Swords et al. (2024) conducted a prospective multicenter study to assess the validity and feasibility of to self-assess hearing thresholds at home, with comparison to pure tone audiometry (PTA). Participants eligible for the study were adults over 18 who visited ENT or audiology clinics for ear or hearing assessments and owned an iOS or Android smartphone. Only those needing PTA as part of their standard care, as determined by an independent clinician, were recruited. One hundred thirty-nine participants submitted data. The results of two at-home automated smartphone apps correlated strongly/very strongly with PTA average and their frequency-specific median was within ±10 dB accuracy. Smartphone audiometry performed in sound-treated and home conditions were very strongly correlated. The apps were rated as easy/very easy to use by 90% of participants and 90% would be happy/very happy to use an app to monitor their hearing. The authors selected four freely available apps across common smartphone operating systems, prioritizing feasibility and participant data security without requiring identifiable data. The widely validated uHear app was excluded as it was not available in the UK, and other apps may vary in performance. Although the study included a broad age range, children were not tested, potentially impacting results. Smartphones cannot fully replicate PTA due to the lack of bone conduction

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and masking, which is crucial for monitoring unilateral hearing loss. Results were more accurate at home. Future studies should compare app accuracy at home versus sound-treated rooms, ensuring participants practice multiple times before data collection. Participants were limited to one hospital test to reduce time burden and due to room availability. The authors concluded that home-based, patient-conducted audiometry is becoming more desirable with the shift toward remote care, possibly improving accessibility. Two of the four apps (iOS-1 and Android-2) demonstrated clinically acceptable accuracy (strong correlation and median within ±10 dB), making them appropriate for clinical use. However, these apps cannot replace PTA, since they often overestimate hearing thresholds. Providers should be cautious about recommending unvalidated apps. Additional research is needed regarding these self-administered hearing tests.

Oremule et al. (2023) conducted a systematic review aimed to identify mobile audiometry (MA) options available to health providers, to assess their accuracy in measuring hearing thresholds, and examine factors that might influence their accuracy. A meta-analysis was completed to look at the difference between thresholds measured with MA and conventional audiometry (CA) in dB HL. Participants included adults and children, with and without diagnosis of hearing impairment. After systematic review, 17 out of 858 articles were included with a total of 1032 participants analyzed. The most used software application was Shoebox™ (6/17) followed by Hearing Test™ (3/17), then HearTest™ (2/17). Tablet computers were used in ten studies, smartphones in six, and a computer in one. The mean difference between MA and CA thresholds was 1.36 dB (95% CI, 0.07-2.66, p = 0.04). Significant differences between MA and conventional audiometry CA thresholds were observed in thresholds measured at 500Hz, in children, when MA was conducted in a sound booth, and when MA was self-administered. However, these differences did not exceed the clinically significant threshold of 10 dB. Limitations included elevated levels of heterogeneity with a high risk of bias, although there were low concerns regarding applicability. The authors indicate that MA shows promising results to be used as a tool for hearing assessment, there are limitations in detecting mixed and conductive hearing loss and there is the possibility that it overestimates hearing loss in children compared to CA. The authors indicate that MA may provide a reliable testing method in areas where CA is not available. Additional research is needed to further evaluate the use of MA to improve its reliability and efficacy.

Wasman et al. (2022) conducted a systematic review of the current status of automation and machine learning approaches in hearing assessment using validated pure-tone audiometry with possible indicators of accuracy, reliability, and efficiency of these approaches. These automated methods are being developed for self-administered digital hearing assessments without the direct administration by professionals. This review is an extension of a 2013 systematic review (Mahomed, 2013). Fifty-six reports from 2012 to June 2021 were included. There were 27 select automated approaches that were identified. The authors noted the following. Machine learning approaches require fewer trials than conventional threshold-seeking approaches, and personal digital devices make assessments more accessible. Validity can be improved using digital technologies for quality surveillance, including noise monitoring, and detecting inconclusive results. In the past 10 years, an increasing number of automated approaches have reported similar accuracy, reliability, and time efficiency as manual hearing assessments. Limitations included commercialized automated approaches may have been developed without peer-reviewed reports, no gold standard for reporting audiometry validation studies, which confines a consistent comparison among methods and early users could lead to more optimistic findings. New developments, including machine learning approaches, offer features and versatility beyond manual audiometry. Additional peer-reviewed studies are needed to support their use in the future while taking the limitations into consideration. (Colsman et al., 2020 which was previously cited in this policy, is included in this systematic review).

Chen et al. (2021) conducted a systematic review and meta-analysis to summarize the factors that influence the diagnostic accuracy of smartphone-based hearing assessments for hearing loss. Their aim was to provide more standard evidence of the benefit of smartphone audiometry in clinical application in the future**.** A total of 4470 individuals from twenty-five studies were included in the meta-analysis. The overall sensitivity, specificity, and area under the receiver operating characteristic curve for smartphone-based audiometry were 89% (95% CI 83%-93%), 93% (95% CI 87%-97%), and 0.96 (95% CI 0.93-0.97), respectively; the corresponding values for the smartphone-based speech recognition test were 91% (95% CI 86%-94%), 88% (95% CI 75%-94%), and 0.93 (95% CI 0.90-0.95), respectively. Meta-regression analysis revealed that patient age (accuracy was lower in elderly and children), equipment used, and the presence of soundproof booths were significantly related to diagnostic accuracy. Limitations included a different threshold among the studies leading to a threshold effect and heterogeneity regarding the study designs, test protocols, and reference PTA thresholds which may have biased the results when combining them into the meta-analyses. The author's indicated that smartphone-based audiometry could be equal to that of the standard PTA for assessing hearing loss where there are limited resources available. Future studies should focus on adjusting the potential factors that may affect smartphone-based audiometry diagnostic accuracy. (Saliba 2017 included below).

Brennan-Jones et al. (2018) conducted a study to compare remote interpretation of manual and automated audiometry. The results from 42 participants who underwent manual and automatic audiograms were interpreted by five audiologists. Audiograms were randomized and audiologists were blinded as to whether they were interpreting a manual or automated

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audiogram. Cohen's Kappa and Krippendorff's Alpha were used to calculate and quantify the intra- and inter-observer agreement, respectively, and McNemar's test was used to assess the audiologist-rated accuracy of audiograms. Audiologists were 2.8 times more likely to question the accuracy of an automated audiogram to a manual audiogram. The authors noted that there is a lack of agreement between audiologists when interpreting audiograms, whether recorded with automated or manual audiometry.

Pereira et al. (2018) examined the validity and efficiency of automated audiometry in school-aged children. Hearing thresholds for 0.5, 1, 2, 4, 6, and 8 kHz were collected in 32 children ages 6-12 years using standard audiometry and tablet-based automated audiometry in a soundproof booth. Results revealed that the majority (67%) of threshold differences between automated and standard were within the clinically acceptable range (10 dB). The threshold difference between the two tests showed that automated audiometry thresholds were higher by 12 dB in 6-year-olds, 7 dB in 7- to 9-year-olds, and 3 dB in 10- to 12-year-olds. Results suggest that the clinical use of at least some types of tablet-based automated audiometry may not be feasible in children 6 years of age but support the use of tablet-based automated audiometry in children from ages 7-12 years. Further study is needed to determine the long-term safety and efficacy of tablet-based automated audiometry in children.

Saliba et al. (2017) in a prospective study compared the accuracy of 2 previously validated mobile-based hearing tests in determining pure tone thresholds and screening for hearing loss to determine the accuracy of mobile audiometry in noisy environments through noise reduction strategies. A total of 33 adults with or without hearing loss were tested (mean age of 49.7 years; women, 42.4%). Air conduction thresholds measured as pure tone average and at individual frequencies were assessed by conventional audiogram and by 2 audiometric applications (consumer and professional) on a tablet device. Mobile audiometry was performed in a quiet sound booth and in a noisy sound booth (50 dB of background noise) through active and passive noise reduction strategies. On average, 91.1% (95% CI: 89.1% to 93.2%) and 95.8% (95% CI: 93.5% to 97.1%) of the threshold values obtained in a quiet sound booth with the consumer and professional applications, respectively, were within 10 dB of the corresponding audiogram thresholds, as compared with 86.5% (95% CI: 82.6% to 88.5%) and 91.3% (95% CI: 88.5% to 92.8%) in a noisy sound booth through noise cancellation. When screening for at least moderate hearing loss (pure tone average greater than 40 dB HL), the consumer application showed a sensitivity and specificity of 87.5% and 95.9%, respectively, and the professional application, 100% and 95.9%. Overall, individuals preferred mobile audiometry over conventional audiograms. The authors concluded that mobile audiometry could correctly estimate pure tone thresholds and screen for moderate hearing loss. Adding noise reduction strategies in mobile audiometry could provide a portable effective solution for hearing assessments outside clinical settings where noise is a factor. Study limitations include the following: small sample size, the number of adults with audiometric hearing loss was limited which per the author could have affected sensitivity and specificity, each ear was counted separately which could have inflated sample size, also the earbuds used in mobile testing is different than commercial testing. Additional studies with larger samples are needed to validate the efficacy of mobile-based hearing.

Brennan-Jones et al. (2016) evaluated automated audiometry in adults with a variety of different characteristics using the KUDU wave automated audiometer. Comparative manual audiometry was performed in a sound-treated room. Automated audiometry was not performed in a sound treated room. A total of 42 adults were recruited. Absolute mean differences ranged between 5.12 to 9.68 dB (air-conduction) and 8.26 to 15 dB (bone-conduction). A total of 86.5% of manual and automated 4FAs were within 10 dB (i.e., ±5 dB); 94.8% were within 15 dB. There were significant ($p < 0.05$) differences between automated and manual audiometry at 250, 500, 1,000, and 2,000 Hz (air-conduction) and 500 and 1,000 Hz (bone-conduction). The effect of age (greater than or equal to 55 years) on accuracy ($p = 0.014$) was not significant on linear regression ($p > 0.05$; $R (2) = 0.11$). The presence of a hearing loss (better ear greater than or equal to 26 dB) did not significantly affect accuracy ($p = 0.604$; air-conduction), ($p = 0.218$; bone-conduction). The authors concluded that the findings provided clinical validation of the automated audiometry using KUDOwave, however variations in study design were significant and future research is recommended.

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Code	Description
0234T	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; renal artery
0235T	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; visceral artery (except renal), each vessel
0236T	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; abdominal aorta
0237T	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; brachiocephalic trunk and branches, each vessel

Transluminal peripheral atherectomy of visceral, renal, abdominal, or brachiocephalic arteries is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Atherectomy is the endovascular removal of atheromatous plaque by cutting drilling, shaving, pulverizing, lasing, or sanding. The result is improved compliance of the vessel wall and enlargement of the treated lumen. Atherectomy devices are categorized by their mode of action and include directional, rotational, orbital intravascular lithotripsy, excimer laser and a peripheral chronic total occlusion (CTO) recanalization system the Crosser™ (Bard Peripheral Vascular, Inc.) (Chowdhury et al., 2022).

The published evidence on the safety and efficacy of atherectomy devices for treatment of the visceral, renal, abdominal, and brachiocephalic arteries is limited to case reports. The effectiveness, safety and superiority to standard established treatments cannot be established.

There are multiple case reports for this technology, including but not limited to, Simonte et al., 2023, (Chowdhury et al., 2022; Diaz et al., 2020; Genet et al., 2019; Naganuma et al., 2018; Richard et al., 2016; Manunga et al., 2012).

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Code	Description
0247U	Obstetrics (preterm birth), insulin-like growth factor-binding protein 4 (IBP4), sex hormone-binding globulin (SHBG), quantitative measurement by LC-MS/MS, utilizing maternal serum, combined with clinical data, reported as predictive-risk stratification for spontaneous preterm birth
81599	Unlisted multianalyte assay with algorithmic analysis (when used to report PreTrm)

The use of a serum-based proteomic biomarker based algorithmic analysis test (PreTRM®) for screening pregnant individuals to predict the risk of preterm labor is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

PreTRM it is a blood test to predict spontaneous preterm birth (sPTB) risk by measuring two proteins, insulin-like growth factor-binding protein 4 and sex hormone-binding globulins (IBP4 and SHGB) that are relatively over- or under-expressed and are predictive of premature birth (or delivery) (Sera Prognostics website). There is insufficient evidence to support the use of serum-based proteomic testing to predict the risk of preterm delivery in asymptomatic pregnant women.

In 2023, Branch et al. published the results of a prospective, randomized intervention trail aimed to determine if serum proteomics screening of women at low risk for spontaneous preterm birth (sPTB) and the use of a PTB risk-reduction protocol in those whose results indicated an increased risk would reduce the likelihood of sPTB. The primary outcome of the study was the proportion of participants experiencing sPTB at less than 37 weeks gestation due to preterm labor or preterm premature rupture of membranes in the absence of clinically evident infection, placental abruption, or other indications for preterm delivery. The original secondary outcomes were the proportion of any PTB, total length of neonatal hospital stay for sPTB, and any PT.-After the initiation of the study, these were changed to gestational age (GA) at delivery, total length of neonatal stay, and neonatal intensive care unit (NICU) length of stay (LOS) among all neonates admitted to the NICU to allow sufficient power for the primary outcome. The study enrolled 1181 women whose pregnancies were prior to 19 to 20 weeks gestation, with no current or historical risk factors for sPTB. Individuals were randomly assigned 1:1 to have screening with the PreTRM test, or no test and standard obstetric care. A positive screen for sPTB was ≥ 14%. The results showed that in the group that underwent screening, 33.3% (198) were screen positive and were offered the sPTB risk-reduction protocol. Among these, 65.7% attended the first, and 64.1% attended the second prematurity prevention clinic. Spontaneous pre term birth occurred in 16 of the screened women and 21 of the unscreened women. Of the 196 women that screened positive, four had sPTB, but none were before 35 weeks. There were five sPTBs < 34 weeks in the entire study population, one in the screened group, and four in the unscreened group. No differences were found with regard to compliance with the PTB risk-reduction protocol. There were no significant differences between the screened and unscreened groups in the median GA at delivery, the median NICU LOS, or total neonatal length of stay. The authors also compared the severe neonatal composite morbidity and mortality and found among sPTB infants; a larger proportion of the screened group had lower, less morbid scores of 0 to 2 following sPTB compared with the unscreened group. Due to a lower rate than projected of sPTB, and inadequate funding, the trial was stopped before achieving the prespecified sample size for statistical power. Despite this, the authors concluded that serum proteomic screening of a low risk population coupled with a sPTB risk-reduction protocol in screen positive patients did not result in a significantly lower rate of sPTB < 37 weeks. Further independent research is needed to validate these findings.

A Hayes precision medicine research brief concluded that there are insufficient peer reviewed studies to perform a full technology assessment or provide evidence for the impact of the PreTRM test on outcomes (Hayes, 2022).

In its preterm labor and birth guideline, the National Institute of Health and Care Excellence (NICE, 2022), does not include testing of insulin-like growth factor-binding protein 4 (IBP4) as a screening strategy for diagnosing women with suspected, established, or risk for preterm labor.

Burchard et al. (2021) replicated a second independent study to validate the findings of the Multicenter Assessment of a spontaneous Preterm Birth Risk Predictor (TREETOP) (Markenson et al.) and the Proteomic Assessment of Preterm Risk (PAPR) (Saade, et al.) studies mentioned below which assessed the ability of the ratio of IBP4 to SHBG to risk stratify preterm delivery and associated adverse outcomes. The authors assessed an actionable threshold learned in one study and applied to the second in a critical and rigorous manner to show that not only the likelihood of spontaneous preterm delivery is similarly significantly predicted, but also the associated and clinically adverse end points are well predicted and similarly elevated at or above the threshold. Both studies of the IBP4/SHBG proteomic biomarker showed the ratio's potential to predict the majority of preterm birth based on tested populations in excess of 1000 subjects, and for predicting associated newborn complications of prematurity as well. The primary objective of this research was to demonstrate that statistically significant thresholds of prediction of adverse pregnancy outcomes in PAPR are also significant in the

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independent TREETOP population. The authors indicated that an additional strength of this comparison of the PAPR and TREETOP studies is that while the subpopulations analyzed are both the same in the intended use population for the proteomic biomarker, they are notably different on several demographic and baseline characteristics (maternal age, BMI, education, race, prior sPTB, etc.). Also, the eligible PAPR and TREETOP subjects for this study were enrolled at 10 and 14 clinical sites, respectively. All of these factors would provide further confidence that despite these demographic differences and diversity in site enrollment, the same proteomic biomarker threshold identified pregnancies of increased risk of sPTB and associated adverse outcomes. The authors concluded that this comparison demonstrated consistency and accordance of the proteomic biomarker in two large studies for predicting preterm delivery in a large diverse segment of low-risk pregnant women tested at a time in the second trimester when most women are seen for their anatomic ultrasound. The authors noted that this provides confidence that pregnancies can be robustly risk-stratified by the proteomic biomarker.

The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin #234, Prediction and Prevention of Spontaneous Preterm Birth, describes the risk factors, screening methods, and treatments for preventing spontaneous preterm birth in a review of the evidence supporting their roles in clinical practice. Several Level A and B recommendations are included. The bulletin does not provide recommendations on maternal serum analysis as several ongoing studies are evaluating the use of serum biomarkers for preterm birth risk assessment. (August 2021).

The multicenter, prospective TREETOP (The Multicenter Assessment of a Spontaneous Preterm Birth Risk Predictor) study investigated the performance of PreTRM in predicting preterm births occurring before the 32nd week of gestation (< 320/7). The study also assessed negative outcomes associated with these births, such as length of neonatal hospital stay and neonatal morbidity and mortality. The multicenter study enrolled 5,011 women across 18 sites, with a preplanned analysis performed on a randomly selected subgroup of 847 women. Results of the remaining study participants were blinded for future validation studies. In the subgroup, there were nine preterm births and 838 non-cases at ≥ 320/7 weeks' gestation. The IBP4/SHBG ratio was predictive of birth < 320/7 weeks among all 847 women. Additionally, the test predicted increased length of neonatal hospital stay and increased severity of adverse neonatal outcomes. This study is limited by lack of control group and incomplete results. Further results are expected from the second phase of the study (Markenson et al., 2020). NCT02787213.

In its guideline for biomarker tests to help diagnose preterm labor, the National Institute of Health and Care Excellence (NICE, 2018), does not mention testing of insulin-like growth factor-binding protein 4 (IBP4) to help diagnose preterm labor in women with intact membranes.

Saade et al. (2016) conducted the prospective Proteomic Assessment of Preterm Risk study to discover, verify and validate biomarkers for preterm birth. A total of 5,500 pregnant women between 17-28 weeks gestation were followed from 2011-2014 at 11 clinical sites in the United States. Of those, 5,235 remained in the study until their delivery and 4,825 were analyzed (410 were excluded due to being on progesterone therapy for preventing preterm birth). Of those 4,825 women, 4,292 carried their babies to term while 248 experienced spontaneous preterm birth (285 had medically indicated preterm births and were excluded.) Of these 248 sPTB subjects, 31 were excluded for pre analytic reasons, leaving 217, 86 of which were used in discovery, 50 in verification, and 81 in validation. The discovery and verification process identified 2 serum proteins, insulin-like growth factor binding protein 4 (IBP4) and sex hormone-binding globulin (SHBG), as predictors of spontaneous preterm delivery. The study found that the test was able to predict whether a woman would deliver before 37 weeks with 75 percent sensitivity and 74 percent specificity, and an area under the receiver operating curve of .75. It was able to predict delivery before 35 weeks with 100 percent sensitivity and 83 percent specificity and an AUC of .93. These biomarkers may predict risk for preterm sPTB. However, the study had several limitations including small sample size and had insufficient number of women with prior preterm delivery, and less than one-third of participants had transvaginal ultrasound cervical length performed. Further studies are needed to determine the clinical application of this test and how it relates to the current techniques used to identify high risk for preterm labor.

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Code	Description
0266T	Implantation or replacement of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed)
0267T	Implantation or replacement of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)
0268T	Implantation or replacement of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)
0269T	Revision or removal of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed)
0270T	Revision or removal of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)
0271T	Revision or removal of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)
0272T	Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (e.g., battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day)
0273T	Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (e.g., battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day); with programming

Chronic baroreceptor stimulation of the carotid sinus is unproven and not medically necessary for treating hypertension, heart failure, or other cardiovascular conditions due to insufficient evidence of safety and/or efficacy.

The Barostim neo® Legacy System (CVRx, Inc.) received U.S. Food & Drug Administration (FDA) humanitarian device exemption on December 12, 2014 (H130007) for patients with resistant hypertension who were previously determined to be responders in the Rheos® pivotal clinical study. Additional information (using product code DSR) is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm. (Accessed May 20, 2025)

The BAROSTIM NEO® System (CVRx, Inc.) received FDA premarket approval on August 16, 2019 (P180050) for the treatment of heart failure. Additional information (using product code DSR) is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm. (Accessed May 20, 2025)

Coverage for revision or removal of carotid sinus baroreflex activation devices may be addressed in the complication section of the benefit document. Refer to federal, state, or contractual requirements for coverage.

Clinical Evidence

Carotid sinus baroreflex activation devices stimulate baroreceptors (pressure sensors) in the neck. Baroreflex activation therapy (BAT) is intended to reduce blood pressure and improve heart failure symptoms. These devices consist of a pacemaker-like implantable pulse generator and a lead connected to a carotid sinus electrode (Hayes, 2022; Annual Review: 2024).

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Hypertension

Wallbach et al. (2023) conducted a prospective single-arm observational study to evaluate whether nighttime intensification of baroreflex activation therapy (BAT) improved nocturnal blood pressure (BP). The study included 24 participants with resistant hypertension and a non- or inverted dipping pattern. Participants were previously treated with BAT for a median of 44 months [interquartile range (IQR) 25-52]. Nighttime intensification of BAT was individually titrated at baseline and at week 6. Twenty-four hour ambulatory blood pressure monitoring (ABPM) was measured at inclusion and after 3 months. The study results revealed an increase in systolic dipping (2 ±6 to 6 ±8%; p = 0.03) and dipping pattern (p = 0.02) after BAT programming. Day and nighttime 24-hour ABPM readings were unchanged. The authors concluded that nighttime intensification of BAT improved the dipping profile. However, overall, 24-hour ABPM readings did not change. Whether nighttime intensification of BAT reduced the elevated cardiovascular risks associated with inadequate nocturnal BP reduction was not determined. Limitations of the study include small sample size, lack of comparison group or randomization, no assessment of antihypertensive medication adherence, and no measures of sympathetic activity, such as urinary catecholamines. Larger randomized trials that include more parameters are needed to confirm these results.

ECRI (2020) completed a product brief regarding the Barostim Neo™ System for treating resistant hypertension and determined the evidence was inconclusive. The brief included one systematic review and three comparative studies of more than 101 individuals. The evidence was limited by small study sizes, single-center participation, and lack of randomization, blinding, and parallel control groups.

Wallbach et al. (2020) reported on a prospective, observational study regarding the long-term effects of the BAT Neo device on 24-hour ABPM. Office and 24-hour ABPM were measured on 60 participants with resistant hypertension who were previously treated with the BAT Neo device. Baseline characteristics included office BP 172 ±25/90 ±17 mm Hg, 24-hour ABPM 150 ±16/80 ±12 mm Hg, and a median of seven antihypertensive drugs (IQR 6-8). BP measurements were performed before BAT implantation, and at 6,12, and 24 months after implantation. The study results revealed that after 24 months, there was a significant reduction of -25 ±33/-9 ±18 mm Hg (n = 50, both p < 0.01) in office BP and -8 ±23/-5 ±13 mm Hg (n = 46, both p = 0.02) in 24-hour ABPM. Antihypertensive medications were reduced to a median of five (4-6) drugs (p < 0.01). Participants with isolated systolic hypertension (ISH) experienced a BP-lowering effect in office BP, but not in ABPM at month 24. Using unadjusted BP values, BAT seemed to be more effective in combined hypertension (CH) than in ISH. After adjustment for baseline BP values, there was no significant difference observed in BP reduction between participants with ISH and CH. Baseline ambulatory systolic blood pressure (SBP) was the only independent predictor of BP response at 24 months. The authors concluded that BAT reduced office BP and improved relevant parameters of ABPM. However, after adjustment for baseline BP, the reduction was not different for participants with CH when compared to participants with ISH. Randomized controlled trials (RCTs) are needed to confirm these results. This study is limited by lack of a comparison group undergoing a different approach to resistant hypertension.

American College of Cardiology/American Heart Association guidelines for the prevention, detection, evaluation, and management of high BP in adults' states: "Several studies have investigated devices that interrupt sympathetic nerve activity (carotid baroreceptor pacing and catheter ablation of renal sympathetic nerves); however, these studies have not provided sufficient evidence to recommend the use of these device in managing resistant hypertension" (Whelton et al., 2018).

de Leeuw et al. (2017) assessed the long-term safety and efficacy of BAT by analyzing data from participants included in one of three trials that focused on treatment-resistant hypertension using the first-generation Rheos system. Collectively, 383 participants from the US Rheos Feasibility Trial, Device-Based Therapy in Hypertension Trial, and Rheos Pivotal Trial were available for analysis: Five years of follow-up was completed by 143 participants six years of follow up was completed by 48 participants. In the entire cohort, SBP fell from 179 ±24 mm Hg to 144 ±28 mm Hg, diastolic pressure dropped from 103 ±16 mm Hg to 85 ±18 mm Hg and heart rate fell from 74 ±15 beats per minute to 71 ±13 beats per minute. The effect of BAT was greater than average in participants with signs of heart failure and less than average in participants with isolated systolic hypertension. In 27% of participants, it was possible to reduce the number of medications from a median of six to a median of three. After a follow-up of 6 years, the authors concluded that BAT maintains its efficacy for persistent reduction of BP in participants with resistant hypertension without major safety issues. Limitations of this study include, lack of randomization in two of three studies and lack of a control group during long-term follow-up.

Wallbach et al. (2016) conducted a prospective case series of 44 participants treated with the Barostim neo™ for uncontrolled resistant hypertension. ABPM was performed before BAT implantation and at six months after the initiation of therapy. After 6 months, 24-hour ambulatory systolic (from 148 ±17 mm Hg to 140 ±23 mm Hg), diastolic (from 82 ±13 mm Hg to 77 ±15 mm Hg), and day- and night-time systolic and diastolic blood pressure (DBP) significantly decreased. Heart rate and pulse pressure remained unchanged. The authors concluded this was the first study demonstrating a

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significant BP reduction in ABPM for participants undergoing chronic stimulation of the carotid sinus using the Barostim neo™ device and that BAT might be considered as a new therapeutic option to reduce cardiovascular risk in resistant hypertension. However, RCTs are needed to evaluate the effects of accurately. The findings of this study are limited by a lack of comparison group.

A National Institute for Health and Care Excellence (NICE) guideline concluded that current evidence on the safety and efficacy of implanting a baroreceptor stimulation device for resistant hypertension is inadequate. NICE recommended the procedure only be used in the context of research (NICE, 2015).

After completion of the randomized Rheos® Pivotal Trial, Bakris et al. (2012) conducted an open-label, nonrandomized follow-up study to assess the long-term safety and efficacy of BAT. Clinically significant responder status was assessed according to FDA-mandated criteria. Of 322 individuals implanted, 76% (n = 245) qualified were clinically significant responders. An additional 10% were indeterminate. Among long-term responders receiving BAT, the mean BP drop was 35/16 mm Hg. Medication use was reduced by the end of the randomized phase and remained lower through the follow-up period. Among responders, 55% achieved targeted BP reduction goals sustained through 22 to 53 months of follow-up. Limitations of this study include lack of a control group during long-term follow-up.

The Rheos Pivotal Trial evaluated BAT for resistant hypertension in a double-blind, randomized, multicenter, placebo-controlled phase III clinical trial. Two hundred and sixty-five participants with resistant hypertension were implanted and subsequently randomized (2:1) 1 month after implantation. Participants received either BAT (Group A) for the first 6 months or delayed BAT initiation following the 6-month visit (Group B). The five primary endpoints were: (1) acute systolic blood pressure (SBP) responder rate at 6 months; (2) sustained responder rate at 12 months; (3) procedure safety; (4) BAT safety; and (5) device safety. The trial showed significant benefit for the endpoints of sustained efficacy, BAT safety and device safety. However, the endpoints for acute responders or procedural safety were not met. The authors concluded that the weight of the overall evidence suggested that over the long-term, BAT safely reduced SBP in participants with resistant hypertension. The authors also noted future clinical trials will address the limitations of this study, including the presence of some confounding factors associated with excess variability, and further define the therapeutic benefit of BAT (Bisognano et al., 2011).

Heart Failure

Abraham et al. (2025) used claims data to study the association between BAT implantation and subsequent survival and hospitalization. The study included 306 patients (mean age: 66 ±12 years), the majority of whom (90%) underwent implantation and follow-up between 2021 to 2023. The duration of post-implant follow-up was 1.92 ±1.87 years, representing a total of 586 patient-years. The study results revealed a mortality rate of 6.3% at one year and 12.3% at two years. When compared with the 12-month period prior to BAT implantation, an 85% post-implant rate reduction was observed for all-cause hospitalizations ($p < 0.001$). A rate reduction of 81%, 88%, and 71% was observed for cardiovascular, non-cardiovascular, and heart failure (HF) hospitalizations, respectively. An 86% post-implant rate reduction was also observed for all-cause hospital visits (defined as hospitalizations and emergency department encounters) ($p < 0.0001$). A rate reduction of 84%, 87%, and 85% was observed for cardiovascular, non-cardiovascular, and HF hospital visits, respectively. A reduction in post-implant hospitalization length of stay (LOS) was also observed. The authors concluded that BAT implantation in this population, using real-world data, was associated with reductions in all-cause, cardiovascular, non-cardiovascular, and HF hospital visits and hospitalization LOS. However, a larger, real-world dataset or prospective study with controls would provide a more accurate assessment. The authors noted several limitations of using claims data including the lack of controls, inability to fully characterize HF severity, and lack of information regarding changes in disease management. The COVID-19 pandemic may have also impacted health care utilization during the study.

ECRI conducted a clinical evidence assessment regarding the Barostim System for treating HF. The assessment included two systematic reviews, one multicenter RCT, and one single-center, nonrandomized study. ECRI concluded that BAT with the Barostim safely and effectively reduced symptoms and improved function and quality of life (QOL) for individuals with heart failure with reduced ejection fraction (HFrEF). However, it was unclear whether BAT reduced mortality and hospitalizations. The included studies reported too few or mixed findings. The studies were also determined to be at a significant risk of bias. None of the studies reported on long-term outcomes. ECRI noted that large, multicenter studies with a longer follow-up would be beneficial to support broader and stronger conclusions (ECRI, 2020; Revised 2024).

Shi et al. (2024) performed a systematic review and meta-analysis to study the effects of BAT in participants with HFrEF and to provide references for future clinical management. The systematic review included four RCTs and 343 participants with left ventricular ejection fraction (LVEF) < 40% and New York Heart Association (NYHA) class III HF. The primary outcome measures included LVEF, Minnesota Living with Heart Failure Questionnaire (MLHFQ), 6-minute walking test (6MWT), and left ventricular end-diastolic volume (LVEDV). The secondary outcome measures were estimated glomerular

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filtration rate (eGFR), DBP, and SBP. The study results revealed BAT enhanced LVEF [mean deviation (MD): 2.97, 95% confidence interval (CI): 0.53 to 5.41], MLHFQ (MD: -14.81, 95% CI: -19.57 to -10.06), and 6MWT (MD: 68.18, 95% CI: 51.62 to 84.74). BAT also reduced LVEDV (MD: -15.79, 95% CI: -32.96 to 1.37) and DBP (MD: -2.43, 95% CI: -4.18 to -0.68). Improvements in eGFR and SBP were determined to be non-statistically significant. The author's concluded BAT was an efficient treatment option for participants with HFrEF. However, additional multicenter RCTs and large sample sizes are needed to validate these findings. The authors noted the sample size for the included studies was limited, potentially effecting clinical heterogeneity. Three studies did not report allocation concealment, potentially influencing a preference for the outcome. Additionally, the systematic review was HFrEF focused and the result may not be generalizable to other types of HF. (This study is included in the clinical evidence assessment by ECRI, 2020; Revised 2024 and evolving evidence review by Hayes, 2022; Annual Review: 2024.) (Gronda et al. 2016, which was previously cited in this policy, is included in this systematic review.)

Zile et al. (2024) presented long-term outcomes from the Baroreflex Activation Therapy for Heart Failure (BeAT-HF) RCT (described by Zile et al., 2020 below). The study included 323 participants with HFrEF, 264 from the pre-market phase and an additional 59 randomized during the post-market phase. The primary endpoint was a composite of cardiovascular mortality and HF morbidity. Other pre-specified endpoints included durability of safety, QOL, 6MWT, NYHA class, hierarchical composite win ratio, freedom from all-cause death, left ventricular assist device (LVAD) implantation, and heart transplant. The median follow-up was 3.6 years/patient. The study results revealed that both the primary endpoint (rate ratio 0.94, 95% CI 0.57 to 1.57; p = 0.82) and components of the primary endpoints were not significantly different between BAT and control. With regards to durability of safety, the major adverse neurological or cardiovascular system or procedure-related event-free rate (MANCE) remained at 97% (nominal $p < 0.001$) throughout the trial. Symptom improvements in QOL, 6MWT, and NYHA class for the BAT group were durable in time and sustainable in extent (nominal $p < 0.001$). The win ratio (1.26, 95% CI 1.02 to 1.58) and freedom from all-cause death, LVAD implantation, and heart transplant (hazard ratio 0.66, 95% CI 0.43 to 1.01) favored the BAT group, but without statistical significance. The authors concluded that BAT did not result in a significant difference in the composite primary endpoint, mortality and HF morbidity, or the individual components of the primary endpoints compared with control. However, BAT did provide safe, effective, and sustainable improvements in functional status, 6MWT, and QOL for participants with HFrEF. The authors noted several limitations of BeAT-HF including the lack of blinding, non-implanted control, and a sample size likely to be underpowered for at least the cardiovascular mortality endpoint of the composite endpoint. (This study is included in the clinical evidence assessment by ECRI, 2020; Revised 2024 and evolving evidence review by Hayes, 2022; Annual Review: 2024.)

Coats et al. (2022) conducted an individual patient data (IPD) meta-analysis of two RCTs (described by Zile et al., 2020 and Abraham et al., 2015 below) to evaluate the effect of BAT on HF symptoms, QOL and NT-proBNP in participants with HFrEF. The meta-analysis included 554 participants from the BeAT-HF and Hope for Heart Failure (HOPE4HF) trials who were randomized to BAT + guideline-directed medical therapy (GDMT) or GDMT alone (open label). Endpoints included 6-month changes in 6MWT, MLHFQ QOL score, NT-proBNP, and NYHA class. The study results revealed that in the total population, BAT provided a significant improvement in 6MWT distance of 49 m (95% CI 33, 64), MLWHF QOL of -13 points (95% CI -17, -10), and 3.4 higher odds of improving at least one NYHA class (95% CI 2.3, 4.9) when compared from baseline to 6 months. These improvements were similar, or better, in participants who had baseline NT-proBNP < 1600 pg/ml, regardless of cardiac resynchronization therapy (CRT) indication status. The authors concluded that the IPD meta-analysis suggested BAT improved exercise capacity, NYHA class, and QOL in participants with HFrEF receiving GDMT. These improvements were clinically meaningful and consistent across the range of participants studied. BAT was also associated with an improvement in NT-proBNP for participants with a lower baseline NT-proBNP. The authors noted several limitations of the meta-analysis including a small sample size of only two RCTs and a limited number of participants restricting the ability to see subtle differences in responses between some cohorts of interest. Both RCTs were also open-label, which may result in bias in the more subjective endpoints. The lack of a systematic review also increases the potential for bias. (This study is included in the evolving evidence review by Hayes, 2022; Annual Review: 2024.)

American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines for HF management state: "Autonomic nervous system modulation is intriguing as a treatment for HFrEF because of the heightened sympathetic response and decreased parasympathetic response in HF. Trials of device stimulation of the vagus nerve, spinal cord, and baroreceptors have had mixed responses. An implantable device that electrically stimulates the baroreceptors of the carotid artery has been approved by the FDA for the improvement of symptoms in patients with advanced HF who are unsuited for treatment with other HF devices including CRT. In a prospective, multicenter, RCT with a total of 408 patients with current or recent NYHA class III HF, LVEF ≤ 35%, baroreceptor stimulation was associated with improvements in QOL, exercise capacity, and NT-proBNP levels. To date, there are no mortality or hospitalization rates results available with this device" (Heidenreich, et al., 2022).

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Zile et al. (2020) evaluated the safety and effectiveness of BAT for participants with HFrEF in the BeAT-HF RCT. The multicenter trial included 408 participants randomized 1:1 to receive either BAT plus optimal medical management (BAT group) or optimal medical management alone (control group). The study design also included four cohorts. Cohort D, consisting of 245 participants (120 in the BAT group and 125 in the control group) represented the intended population that reflected the FDA-approved instructions for use. Effectiveness endpoints were measured at baseline and at 6 months using 6MWT, MLHFQ QOL, and NT-proBNP. The safety endpoint was MANCE. The study results revealed that in the BAT group versus the control group, QOL score decreased (Δ = -14.1; 95% CI -19 to -9; p < 0.001), 6MWT increased (Δ = 60 m; 95% CI 40 to 80 m; p < 0.001), and NT-proBNP decreased (Δ = -25%; 95% CI -38% to -9%; p = 0.004). The MANCE-free rate was 97% (95% CI 93% to 100%; p < 0.001). The authors concluded that BAT was safe and significantly improved QOL, exercise capacity, and NT-proBNP. However, the authors also noted several study limitations including not examining morbidity and mortality or change in cardiovascular structure or function, the lack of blinding, and possibility of placebo effects. Further studies are needed to examine the impact of BAT on hospitalization frequency and mortality and identify the HFrEF population most likely to benefit. (This study is included in the evolving evidence review by Hayes, 2022; Annual Review: 2024, systematic review by Shi et al., 2024, and meta-analysis by Coats et al., 2022.)

In a pooled analysis of two multicenter RCTs, Abraham et al. (2015) assessed the safety and efficacy of BAT in advanced HF. The analysis included 146 participants from the HOPE4HF and Barostim Neo System in the Treatment of Heart Failure trials. Participants with NYHA class III HF and EFs ≤ 35% on chronic stable GDMT were randomly assigned to receive ongoing GDMT alone (n = 70) or ongoing GDMT plus BAT (n = 76) for 6 months. The MANCE-free rate was 97.2%. Participants assigned to BAT, compared with control group participants, experienced improvements in functional status, exercise capacity, QOL score and NT-proBNP. The treatment was also associated with a trend toward fewer hospitalizations for HF. (This study is included in the systematic review by Shi et al., 2024 and meta-analysis by Coats et al., 2022.) Zile et al. (2015) performed a subgroup analysis on the same study population as Abraham et al. (2015). The study focused on BAT in participants with and without CRT. The authors' findings demonstrated significant improvement in EF and a reduction in HF hospitalizations. Changes in efficacy endpoints for the CRT group favored BAT. However, the improvements were less than in the no-CRT group and not statistically different from control. (This study is included in the evolving evidence review by Hayes, 2022; Annual Review: 2024.) Weaver et al. (2016) described the intraoperative outcomes, as well as the long-term safety and efficacy of the second-generation Barostim neo using the same study population as Abraham et al. (2015). The authors' findings indicated that the procedure was safe, with a short-learning curve. Additionally, the therapeutic benefits of BAT in participants with HFrEF were significant and maintained for at least 1 year. Halbach et al. (2018) performed a post-hoc subgroup analysis of BAT efficacy and safety in participants with and without coronary artery disease (CAD) in same study population as Abraham et al. (2015). The authors' subgroup analysis did not reveal significant differences in BAT treatment effects or safety in participants with and without CAD. Positive effects of BAT in participants with ischemic and nonischemic cardiomyopathy included improvements in exercise capacity, QOL, and NT-proBNP. However, larger studies are needed to address potential minor differences in BAT therapeutic response. (This study is included in the evolving evidence review by Hayes, 2022; Annual Review: 2024.)

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Code	Description
0330T	Tear film imaging, unilateral or bilateral, with interpretation and report

Tear film imaging to monitor or assess tear film disorders is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Techniques that gather information from the tear film by processing reflected light or images from the tear are being investigated as representing the true state of the ocular surface. This includes techniques such as interferometry, meniscometry, high speed video topography, and optical coherence tomography (Dry Eye Workshop 2007). These tear film imaging techniques are being investigated to assist in better differentiating dry eye disorders and developing dry eye treatments.

The American Academy of Ophthalmology Preferred Practice Pattern Guidelines on dry eye syndrome (Amescua et.al., 2023) does not address tear film imaging.

Singh et al. (2022) assessed the repeatability, reproducibility, and agreement between three diagnostic imaging platforms for tear film evaluation. The study included fifteen consecutive subjects (n = 30 eyes), with a mean age of 43 years, diagnosed with dry eye disease (DED) at a single site. The study also included thirty subjects (n = 60 eyes), with a mean age of 31 years, without DED as a control group. The study evaluated the LipiView® II Ocular Surface Interferometer, the IDRA Ocular Surface Analyzer (IDRA-OSA), and the Oculus® keratograph 5 M (K5M). Two investigators operated the diagnostic imaging platforms, and a single measurement was performed when determined acceptable by the instrument. One investigator repeated the measurements in all subjects. No two readings on the same subject were separated by more than a week. The lipid layer thickness (LLT) measurements with the IDRA-OSA and Lipiview did not show significant intraobserver differences between the control and DED groups. The coefficient of variation (CoV) was more in the DED group when compared to the control group. However, both groups demonstrated low repeatability. The IDRA-OSA showed better repeatability compared to the Lipiview. A Bland-Altman analysis also showed poor reproducibility and limits of agreement between two devices. The mean tear meniscus height (TMH) measured with the IDRA-OSA and K5M revealed high CoV in both the control and DED groups. While statistically insignificant for the K5M, the repeatability was poor for both diagnostic imaging platforms. A Bland-Altman analysis showed good reproducibility of both the IDRA-OSA and K5M. However, there was poor agreement between IDRA-OSA and K5M. The average non-invasive tear break-up time (NIBUT) values obtained using IDRA-OSA and K5M had lesser CoV in the control group when compared to the DED group. The intraobserver values did not show a significant difference. A Bland-Altman analysis showed good reproducibility of both the IDRA-OSA and K5M, but poor agreement between them. Between the three diagnostic imaging

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platforms, LLT, TMH, and NIBUT were significantly different for same observer. Limitations of this study include the number of eyes examined, uneven number of subjects between groups, and the different proportions of gender and age between groups. The study authors concluded the IDRA-OSA, K5M, and Lipiview cannot be used interchangeably; and tear film imaging should be interpreted considering the variability of these diagnostic imaging platforms and the variability in tear film irrespective of the device used.

The American Academy of Ophthalmology Summary Benchmarks on cornea/external disease (2022) recommend slit-lamp biomicroscopy to monitor or assess blepharitis and dry eye syndrome.

Lee et al. (2020) evaluated the clinical accuracy and utility of the Antares topographer in the diagnosis of dry eye disease (DED). Thirty-three consecutive patients underwent analyses of their non-invasive first tear-film break-up time (NIF-BUT), tear meniscus height (TMH) and meibography with the Antares topographer. The meibography with the LipiView scan was conducted. Slit-lamp examinations were done for assessments of meibomian glands (MG) and fluorescein tear-film break-up time (FBUT). Schirmer 1 test was done. The Ocular Surface Disease Index (OSDI) scores were graded. Thirty-three eyes of 33 patients (mean age 61.5 ±10.6 years, range 37.5-76.4 years, 27.3% males) completed the study. According to the Antares measurements, the NIF-BUT of the patient population was 5.0 ±3.4 seconds on average (1.1-15.0 seconds), and the TMH was 0.2 ±0.1 mm at center (0.1-0.5 mm). The average OSDI score was 22.4 ±16.6 points (0.0-79.5 points). When correlations were calculated, significant correlations were found between the NIF-BUT from the Antares topographer and FBUT ($r = 0.538$, $p = .001$), and between MG dropout from the Antares topographer and that from the LipiView interferometer ($r = 0.446$, $p = .009$). Antares NIF BUT and FBUT were in agreement with one another [95% limits of agreement (LOA) -5.04 ±6.37, $p = .198$] as were the infrared images from the Antares topographer and those from the LipiView interferometer (95% LOA -0.25 ±0.35, $p = .073$). The authors concluded that the Antares topographer is useful in the diagnosis of DED. Among its outputs, the NIF-BUT and MG dropout most closely correlated with currently accepted modes of diagnosis. The authors indicated that concurrent clinical examinations are recommended for clinical follow-up. While this study reports correlations, it does not assess diagnostic performance or clinical utility of tear film imaging.

Lee et al. (2019) compared the lipid layer thickness (LLT) using the LipiView ocular surface interferometer between the eye treated with glaucoma medication and untreated normal eye in the unilateral glaucoma patients and evaluated the effect of topical glaucoma medication on the LLT parameters in glaucoma eyes. The 30 participants in this cross-sectional comparative study were unilateral glaucoma patients treated with topical glaucoma medications for more than 12 months. Three LLT parameters (average, minimum, and maximum) obtained by the LipiView were compared between the glaucomatous eye and normal eye. The factors associated with LLT parameters in the eyes treated with glaucoma medication were investigated with multiple regression analysis. Lipid layer average, minimum, and maximum were 64.83 ±16.50, 51.63 ±16.73, and 82.53 ±20.62 in glaucomatous eyes, 77.26 ±17.81, 62.83 ±20.99, and 86.13 ±15.42 in normal eyes. Lipid layer average and minimum were significantly thinner than those in normal eyes ($p < 0.001$, $p < 0.001$, respectively). Longer duration of glaucoma eye drops and a greater number of glaucoma medications were associated with the lower LLT average ($\beta = -0.456$, $p < 0.001$, $\beta = -8.517$, $p = 0.003$, respectively), and increasing glaucoma medications have a significant correlation with lower LLT minimum in glaucoma eyes ($\beta = -8.814$, $p = 0.026$). The authors concluded that patients with long-term glaucoma medications need to be assessed for LLT parameters to objectively evaluate their ocular surface health. According to the authors, the findings of this study are subject to the following limitations. First, the sample size of patients with unilateral glaucoma was relatively small because the prevalence of unilateral glaucoma treated with topical glaucoma medication in the affected eye only is much less than the prevalence of bilateral glaucoma. Also, the present study did not compare the parameters in the LipiView interferometer with other measurements including tear break-up time, ocular surface disease index, or tear osmolarity for OSDI. According to the authors, further study is needed for evaluating the correlations between conventional measurements in OSDI and LipiView interferometers.

Ji et al. (2017) investigated the clinical utility of automated values obtained by the Keratograph and LipiView when evaluating non-Sjögren dry eye syndrome (NSDES) with meibomian gland dysfunction (MGD). Sixty-four patients (64 eyes) diagnosed with NSDES with MGD were enrolled. All eyes were evaluated using the Ocular Surface Disease Index (OSDI), fluorescence staining score, tear film breakup time (TBUT), Schirmer test, and MGD grade. Noninvasive Keratograph average tear film breakup time (NIKBUTav), tear meniscus height (TMHk), meibomian gland (MG) dropout grade, and lipid layer thickness (LLT) using interferometry were measured. Among automated indexes, NIKBUTav and the MG dropout grade significantly correlated with the OSDI, as did all conventional indicators, except the Schirmer score. TMHk had significant correlation with the Schirmer score, the staining score, TBUT, and NIKBUTav, but not any MGD indicator, even the MG dropout grade. NIKBUTav showed significant correlations with all clinical parameters and other automated values, except the Schirmer score and LLT. The MG dropout grade highly correlated with all indexes except TMHk. LLT was significantly associated with TBUT, MGD grade, and MG dropout grade, although it was not related to patient symptoms. The authors concluded that automated noninvasive measurements using an advanced corneal topographer and LLT measured with an ocular surface interferometer can be alternatives to conventional methods to

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evaluate tear conditions on the ocular surface; the former device can provide information about conformational MG changes in NSDES with MGD. According to the authors, a limitation of this study was that they included dry eye limited to NSDES with MGD. Therefore, caution should be exercised when applying the present results to the general patient population with dry eyes. While the study reports correlations, it does not specifically assess diagnostic performance or clinical utility of tear film imaging.

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Code	Description
0331T	Myocardial sympathetic innervation imaging, planar qualitative and quantitative assessment
0332T	Myocardial sympathetic innervation imaging, planar qualitative and quantitative assessment; with tomographic SPECT

Myocardial sympathetic innervation imaging with 123 Iodine meta-iodobenzylguanidine (^{123}I-MIBG) is unproven and not medically necessary as a prognostic marker in patients with heart failure due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

While myocardial sympathetic innervation imaging has been studied, the evidence is insufficient to support its routine use as proven in clinical practice.

In a prospective study, da Silva et al. (2024) aimed to evaluate cardiac sympathetic activity using ^{123}iodine-meta-iodobenzylguanidine (^{123}I-MIBG) scintigraphy in patients with heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). The study included 61 participants with symptomatic heart failure (33 with HFpEF and 28 with HFrEF) and 20 healthy controls. The authors concluded that cardiac sympathetic function, as assessed by the delayed heart-to-mediastinum (H/M) ratio from ^{123}I-MIBG images, was abnormal in participants with both HFrEF and HFpEF compared to controls. Reported limitations include the single-center design, involving a relatively small number of participants from a tertiary heart failure clinic, the inability to achieve similar age profiles among participants, the imaging techniques not being routinely recommended or performed in all heart failure patients, and the limited sample size providing mostly hypothesis-generating insights that require broader clinical validation in a larger and more diverse patient cohort.

Pontico et al. (2022) conducted a systematic review to assess the predictive capability of ^{123}I-mIBG SPECT myocardial imaging in heart failure (HF) patients, investigating whether semi-quantitative SPECT scores could aid in precise risk assessment for arrhythmic events (AE) and sudden cardiac death (SCD). The review included 16 studies revealing that 123I-mIBG SPECT scores, such as summed defect score (SDS), regional wash-out (rWO), and regional myocardial tracer uptake, could exhibit promising predictive value for patients with HF, as indicated by the analysis. The authors noted evidence from this systematic review implies patients affected by chronic HF, including those receiving an implantable cardioverter-defibrillator (ICD), with a high SPECT SDS, and increased rWO or, reduced tracer uptake in specific segments of the myocardium, face elevated odds of experiencing AEs or SCD, indicating a poorer prognosis compared to patients with low SDS. Additionally, the authors concluded that while the obtained results are promising, there is a need for more standardized and reproducible method for analysis, along with further studies involving larger cohorts, to establish ^{123}I-mIBG SPECT myocardial imaging as a reliable and widely accepted alternative to conventional ^{123}I-mIBG planar myocardial imaging. Limitations of this study include the small sample size.

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Tamaki et al. (2022) analyzed participants who were enrolled in an ongoing, single-center, prospective cohort study, the Osaka Prefectural Trial: Acute Heart Failure Syndrome Registry (OPAR). The study included 407 consecutive participants who were admitted for acute decompensated heart failure (ADHF) and who survived to discharge. The study authors sought to validate a recently developed two-year cardiac mortality risk model and to compare its prognostic value with that of the Acute Decompensated Heart Failure National Registry (ADHERE) and Get With The Guidelines-Heart Failure (GWTG-HF) risk scores. The 2-year cardiac mortality risk model was calculated using four parameters: age, left ventricular ejection fraction, New York Heart Association functional class, and cardiac iodine-123 meta-iodobenzylguanidine (MIBG) heart-to-mediastinum ratio. ADHERE and GWTG-HF risk scores were calculated on admission. Cardiac MIBG imaging and echocardiography were performed just before discharge, after stabilization of HF symptoms. Participants were stratified into three groups based on their two-year cardiac mortality risk: low-risk, intermediate-risk, or high-risk. The primary endpoint was cardiac death, including pump failure death, sudden cardiac death, and death due to acute myocardial infarction. The secondary endpoints were all-cause death, unplanned hospitalization for worsening HF (WHF), a composite of cardiac death and WHF, and a composite of all-cause mortality and WHF. Over a median follow-up period of 1,039 days, 135 participants died. Of those participants, 61 died from cardiac causes and 74 died from non-cardiac causes. WHF occurred in 120 patients. The median two-year cardiac mortality rates estimated by the MIBG-based risk model were almost the same as those actually observed in each risk group: 3% versus 4% for the low-risk group, 7% versus 9% for the intermediate-risk group, and 20% versus 23% for the high-risk group. A receiver operating characteristic curve analysis of the two-year follow-up period revealed that the two-year MIBG-based risk model had higher predictive values, not only for cardiac death but also for all secondary endpoints, than the ADHERE and GWTG-HF risk scores. The authors concluded the two-year MIBG-based cardiac mortality risk model was useful for predicting post-discharge clinical outcomes in patients with ADHF, but larger multicenter studies were needed to further evaluate its usefulness. The authors identified several limitations of the single-center study including the small sample size and that the ADHERE and GWTG-HF risk scores were developed for patients admitted with ADHF to predict in-hospital mortality, but not long-term prognosis.

Seo et al. (2022) also utilized the data from Osaka Prefectural Trial: Acute Heart Failure Syndrome Registry (OPAR); a prospective, single-center, observational prospective cohort to study 148 individuals admitted with acute decompensated heart failure (ADHF) and nonischemic preserved left ventricular ejection fraction (HFpEF) who underwent ^{123}I-MIBG imaging at discharge. The author's goal was to uncover the prognostic value of cardiac sympathetic nerve dysfunction using ^{123}I-MIBG single-photon emission computed tomography (SPECT) imaging in those individuals with HFpEF. Methods utilized for the study include the cardiac ^{123}I-MIBG H/M, which calculated the delayed planar image (late H/M), and SPECT analysis of the delayed image conducted, with the tracer uptake in all 17 regions on the polar map, scored with a five-point scale. Calculating the total defect score (TDS) was accomplished by adding the score of each of the 17 segments, with the primary endpoint being the association between TDS and cardiac events. The authors concluded that from a mean follow-up period of 2.4 +/- 1.6 years, 61 individuals suffered cardiac events. TDS and cardiac events were significantly associated following the multivariate Cox adjustment ($p < 0.0001$). Those individuals with high TDS levels exhibited substantially greater risk for cardiac events than those with average or low TDS levels (63% vs 40% vs 20%, respectively; $p < 0.0001$; HR: 4.69; 95% CI: 2.29 to 9.61; and HR: 2.46; 95% CI: 1.14 to 5.29). C-statistic of TDS was 0.730 (95% CI: 0.651 to 0.799), which was considerably higher than previous H/M (0.607; 95% CI: 0.524 to 0.686; $p = 0.0228$). The authors conclude that cardiac ^{123}I-MIBG SPECT imaging offered valuable prognostic information for individuals with nonischemic ADHF with HFpEF. The study has several limitations that limit the technology applicability to larger populations. The study was a single-center cohort with a small sample size and short follow-up period.

Seo et al. (2021) conducted a prospective study in OPAR to determine the prognostic significance of cardiac ^{123}I-MIBG imaging in individuals with reduced, mid-range and preserved left ventricular ejection fraction admitted for ADHF. The study participants were 349 individuals admitted for ADHF who received cardiac ^{123}I-MIBG imaging, echocardiography, and venous sampling before discharge. After the isotope injection, the ^{123}I-MIBG late H/M was measured on the anterior chest view images. The study's endpoint was cardiac events, defined as unplanned HF hospital admissions and cardiac death, which was measured during a follow-up period of 2.1 +/- 1.4 years. During the follow-up period, 128 individuals experienced cardiac events. Multivariable Cox analysis revealed significant association of late H/M with cardiac events in the overall cohort ($p = 0.0038$); and in the subgroup analysis of each LVEF subgroup ($p = 0.0235$ in HFrEF, $p = 0.0119$ in HFmEF and $p = 0.0311$ in HFpEF). Utilizing Kaplan-Meier analysis, outcomes indicated that individuals with low late H/M had greater risk of cardiac events in the overall cohort (49% vs. 25% $p < 0.0001$) and in each LVEF subgroup (HFrEF: 48% vs. 23% $p = 0.0061$, HFmrEF: 51% vs. 21% $p = 0.0068$ and HFmrEF: 50% vs. 26% $p = 0.0026$). The authors concluded that cardiac sympathetic nerve dysfunction was associated with poor outcomes in ADHF patients regardless of HFrEF, HFmrEF, or HFpEF. Limitations of the study consist of a single-center cohort study with small sample size and a short follow-up period. Additionally, ^{123}I-MIBG uptake may have been affected by medication at discharge or during the follow-up period. Although the authors conveyed that serial ^{123}I-MIBG scintigraphy studies can be valuable for foreseeing cardiac events in HFrEF patients, the prognostic value of serial change of cardiac ^{123}I-MIBG studies remain to be clarified.

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In follow up of the AdreView Myocardial Imaging for Risk Evaluation in Heart Failure study (ADMIRE-HF), Agostini et al. (2019) published an evaluation of whether planar ^{123}I-MIBG myocardial scintigraphy was accurate in predicting risk of death in heart failure (HF) patients up to five years (median 62.7 months) after initial imaging. Using the heart/mediastinum (H/M) ratio on planar ^{123}I-MIBG scintigraphic images obtained at baseline (< 1.60 vs ≥ 1.60), 964 subjects were stratified according to their results. In subjects with H/M < 1.60, all-cause mortality was 38.4% compared to 20.9% in subjects with H/M ≥ 1.60. Cardiac mortality was 16.8% in subjects with H/M < 1.60 compared to 4.5% in subjects with H/M ≥ 1.60. Risk of arrhythmic events, sudden cardiac death, potentially life-threatening arrhythmias, all cause and cardiac death was substantially lower in subjects showing preserved sympathetic innervation of the myocardium (H/M ≥ 1.60). Within LVEF strata, trend toward a higher mortality, reaching significance only for LVEF 25 to ≤ 35%, for subjects with H/M < 1.60, was observed. The authors concluded that during this median follow-up of 62.7 months, patients with H/M ≥ 1.60 were at significantly lower risk of death and arrhythmic events independent of LVEF values. However, no clinical decisions were based on the ^{123}I-MIBG imaging results, therefore ADMIRE-HF and its follow up studies do not evaluate benefit derived from the ^{123}I-MIBG imaging stratification in terms of such key outcomes as mortality.

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Code	Description
0333T	Visual evoked potential, screening of visual acuity, automated, with report

The use of automated visual evoked potentials (VEPs) for visual acuity screening is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy.

Clinical Evidence

Hutchinson, et al. (2023) published an American Academy of Ophthalmology's (AAO) Pediatric Eye Evaluations Preferred Practice Pattern. While this guideline addresses instrument-based screening techniques, such as photoscreening and autorefraction as being useful for assessing amblyopia and reduced-vision risk factors for children ages one to five years, and instrument-based screening as useful for older children who are unable to participate in optotype-based screening, there is no mention of using VEP screening in this preferred practice pattern for either population.

In their 2022 vision screening recommendations, the American Association for Pediatric Ophthalmology (AAPOS) and Strabismus does not specifically mention the use of automated VEPs.

Data from 55 infants with severe cerebral visual impairment (CVI) were retrospectively reviewed by Howes et al. (2022) to see if pattern reversal visual evoked potentials (PRVEPs) would predict visual acuity. Behavioral visual acuity and VEPs were compared from the infants' initial ophthalmology visit at median age of 14 months, to their final visit at late preschool/early school age (an approximate four-year follow-up). Median age was 14 months at T1 (range: six-44 months) and 63 months at T2 (range: 29- 150months). The presence of a PRVEP produced by a check width of 50' (minutes of arc) or smaller (T1) predicted (p = 0.05) the presence of measurable preferential looking acuity at T2. The presence of PRVEP to check widths of 25' or smaller (T1) predicted (p = 0.02) better preferential looking acuity [logarithm of minimum angle of resolution (logMAR)-equivalent] scores at T2. The latter association was independent of presenting acuity at T1. The authors concluded that VEPs may have prognostic value regarding future visual acuity in young children with CVI. This study is limited by small sample size. Additionally, the severity of CVI in the study's participants does not allow generalizing these results to the entire CVI population and the implication of these findings for routine screening are unclear.

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In a systematic review, Hamilton et al. (2021) described the VEP limit in humans, and evaluated the accuracy and preciseness of VEP spatial frequency (SF) limits on visual acuity. A total of 155 studies were included in this review. The difference between VEP SF limit and behavioral acuity is variable and strongly dependent on the VEP stimulus and choice of acuity test. VEP SF limits mature rapidly, from 1.5 to nine cycles per degree (cpd) by the end of the first month of life to 12–20 cpd by eight–12 months, with slower improvement to 20–40 cpd by three to5 years. VEP SF limits are much better than behavioral thresholds in the youngest, typically developing infants. This difference lessens with age and reaches equivalence between one and two years; from around three to five years, behavioral acuity was better than the VEP SF limit, as for adults. Healthy, artificially blurred adults had slightly better behavioral acuity than VEP SF limits across a wide range of acuities, while adults with heterogeneous ophthalmic or neurological pathologies causing reduced acuity showed a much wider and less consistent relationship. For refractive error, ocular media opacity or pathology primarily affecting the retina, VEP SF limits and behavioral acuity had a fairly consistent relationship across a wide range of acuity. This relationship was much less consistent or close for primarily macular, optic nerve or neurological conditions such as amblyopia. VEP SF limits were almost always normal in patients with non-organic visual acuity loss. Especially in pre-verbal children, or individuals with motor or learning impairments, the authors concluded that the VEP SF limit has great use as an objective acuity estimator. The authors further stated that VEP SF diagnostic power depends heavily on adequate, age-stratified, reference data, age-stratified empirical calibration with behavioral acuity, and interpretation in the light of other electrophysiological and clinical findings. Future developments could encompass faster, more objective and robust techniques such as real-time, adaptive control.

In their recommendation statement for vision screening in children ages six months to five years, the U.S. Preventive Services Task Force (USPSTF, 2017), has not recommended vision screening for infants and young children. The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of vision screening for children less than 3 years of age. There is no mention of screening with automated VEPs in this recommendation. The evidence summary was based on a systematic review of the literature performed by Jonas et al., 2017.

Donahue et al. 2016b (reaffirmed in 2021) developed a policy statement for the American Academy of Pediatrics (AAP) co-authored by the AAO, AAPOS, and the American Association of Certified Orthoptists (AACO). The policy statement notes that evaluation of the visual system should commence in infancy and be conducted at regular intervals throughout childhood and adolescence. Furthermore, regular screenings of the visual system, utilizing validated techniques, offer an effective method for detecting potential visual system disorders which may facilitate timely referrals for further assessment and intervention. The AAP released an accompanying clinical report for evaluation of visual systems used by pediatricians as a supplement to the combined policy statement above. The report states that instrument-based devices that incorporate technologies such as VEPs and retinal birefringence are currently being developed and are expected to offer new and enhanced methods for assessing visual acuity and ocular health in young children (Donahue et al., 2016a).

A practice guideline with recommendations for screening of children aged 36 to younger than 72 months with eye and visual system disorders was developed by the National Expert Panel to the National Center for Children's Vision and Eye Health, sponsored by Prevent Blindness, and funded by the Maternal and Child Health Bureau of the Health Resources and Services Administration, United States Department of Health and Human Services. According to the guideline, there were two recommended vision screening methods: monocular visual acuity testing using single HOTV letters or LEA Symbols with crowding bars at a five-foot distance, where the child responds by matching or naming the symbols, and instrument-based testing using either the Retinomax autorefractor or the SureSight Vision Screener equipped with the Vision in Preschoolers Study data software. The authors noted there was insufficient evidence to recommend VEPs for screening children aged 36 to younger than 72 months over visual acuity testing or acceptable instrument-based methods of vision screening (Cotter et al. 2015).

A study to assess visual acuity in 190 children, by determining the value of pattern visual evoked potentials (PVEP) to five consecutive check size patterns was undertaken by Gundogan et al. (2010). Eventually, eighty-five children in the study group and 74 children in the control group who cooperated well with PVEP testing were included. Results of this study showed normal values for latency, amplitude, and normalized interocular amplitude/latency difference in each check size were defined in the control group. PVEP-estimated visual acuity (PVEP-VA) in the amblyopic eye was defined by the normal PVEP responses to the smallest check size associated with normal interocular difference from the non-amblyopic eye and was considered predictive if it is within +/- one Snellen line (one decimal) discrepancy with best corrected visual acuity (BCVA) in that eye. Mean age was 9.7 +/- 1.9 and 9.9 +/- 2.2 years in the study and the control groups, respectively. LogMAR Snellen acuity was well correlated with the logMAR PVEP-VA ($r = 0.525$, $p < 0.001$) in the study group. The Snellen line discrepancy between BCVA and PVEP-VA was within +/- 1 Snellen line in 57.6% of the eyes. The authors concluded that PVEP to five consecutive check sizes may predict objective visual acuity in amblyopic children.

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Simon et al. (2004) studied a new child-friendly VEP system for use in vision screening. Visual evoked potentials were compared to standard ophthalmology examination in one hundred and twenty-two children, ages six months to five years, with the test being completed by 94% of the study group. A statistical program analyzed VEP differences between fellow eyes to determine a "pass" or "fail" for each child. For verbal individuals, clinical amblyopia was defined as an interocular difference of two or more lines in best-corrected visual acuity. For preverbal individuals, clinical amblyopia was defined by the clinician's decision to treat with occlusion or atropine penalization. Preverbal children with significant refractive errors or structural eye pathology were also considered clinically abnormal. The authors concluded that this test shows promise as a screening tool to detect amblyopia and other visual deficits in young children, as this new system overcame technical difficulties associated with older VEP techniques due to its easy electrode placement and rapid attractive stimulus.

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Code	Description
0335T	Insertion of sinus tarsi implant
0510T	Removal of sinus tarsi implant
0511T	Removal and reinsertion of sinus tarsi implant
S2117	Arthroereisis, subtalar

The use of a sinus tarsi implant is unproven and not medically necessary for any indication due to insufficient clinical evidence of safety and/or efficacy.

Clinical Evidence

Sinus tarsi is the area between the ankle and heel bone that has the subtalar joint allowing for rotation of the foot. An injury can cause sinus tarsi syndrome by damage the interosseus and/or cervical ligaments.

Flexible flatfoot (Flexible Pes Planovalgus, Pes Planus) is the result of the loss of the medial longitudinal arch, abduction of the forefoot and subtalar aversion. It is common in children, and in adults may be due to trauma, overuse and inflammatory disorders. It may be asymptomatic, or become painful and require intervention. Non-surgical interventions

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include rest, physical therapy, orthotics and anti-inflammatory medications. Surgery may be indicated when conservative treatment is not successful.

Subtalar arthroereisis (SA) is a surgical procedure designed to correct the excessive movement of the joint by placing an implant in the sinus tarsi, or adjacent to it. The implants are commonly made of titanium or a resorbable poly-L-lactic acid (PLLA).

In a 2025 health technology review, the Canadian Agency for Drugs and Technologies in Health conducted a review to summarize the evidence regarding the clinical effectiveness and cost effectiveness of subtalar joint arthroereisis for adults with pes planus. Eight studies were identified, one systematic review and seven nonrandomized studies. Two studies for other foot conditions, reducible talotarsal joint dislocation and partial talotarsal joint instability were identified. The results showed that pain was a complication post-procedure and a common reason for implant removal. Rates of implant removal varied across studies, ranging from 0% to 48.1%. Other adverse events reported include the need for device revision, surgical infection, stress fracture, insufficient deformity correction, reoccurrence of foot deformity, wound healing issues, and muscle and tendon complications. Overall, these suggest that subtalar joint arthroereisis improves overall foot and ankle condition, health-related quality of life, and ability to perform activities of daily living in adults with pes planus. All studies were poor quality due to the absence of established methods of treatment, detailed reporting of processes, and consideration of risk of bias in reporting results. Furthermore, there was little, if any consideration given to confounders such as obesity which is known to affect post-procedure outcomes. The authors concluded that the true impact of subtalar joint arthroereisis remains unclear without accounting for confounding factors that may have influenced results.

Szesz et al. (2023) conducted a prospective non-controlled follow up study of 41 feet in 32 children aged 6-16 years with symptomatic, idiopathic flexible flatfoot, who received subtalar titanium screw arthroereisis after failure of conservative treatment. Clinical and standing radiological assessments, static and dynamic pedobarography, as well as podoscopy, were performed before surgery and at follow-up which ranged from 6-12 months with a mean of 8 months. The subjective results reported by a survey designed for this study showed that during the follow up period, 28 children reported mild to no pain during the last week, and two reported moderate pain. Twenty six children reported no pain during activities, and eleven reported pain during everyday activities, long walks, sports activities, walking on uneven surfaces and walking on stairs. Only two reported a poor level of wellbeing regarding the surgery. No other complications were reported. Objective results showed the mean level of correction of heel valgus after surgery ranged from 8° to 25°, and tarsal valgus < 10° was achieved in 83%. Tarsal valgus exceeded 10° after surgery in 13% of children and no overcorrection of heel valgus was noted in any of the children. Radiographs showed a statistically significant change in all tested parameters after the procedure, however not all children achieved normative values for all measurements. The greatest change was observed for the TMT 1 angle on dorso-planar and lateral view, and the talar declination angle. Dynamic pedobarography showed a significant prolongation of double support/swing and forefoot contact phase (FFCP). In addition, a significant increase was also noted in the load on the lateral edge of the foot, as well as reduced medial loading. Static pedobarography showed a significant increase in loading in the lateral midfoot area, and a decrease in the medial forefoot. The podoscopy examination revealed a significant improvement in all parameters. The authors concluded that subtalar arthroereisis corrects flatfoot by fixing the subluxation of the ankle and is an effective method of surgical treatment for symptomatic, idiopathic, flexible flatfoot. This study is limited by the lack of a control group and randomization and a short follow up time. Further research with longer follow up is needed to validate that these findings are due to surgery or natural improvement over time.

Garcia Bistolfi et al. (2022) conducted a retrospective cross-sectional study to evaluate the clinical/functional and radiographic outcomes of percutaneous subtalar arthroereisis in children with painful and disabling Flexible Flat Foot (FFF) for a minimum period of 6 months, and refractory to conservative treatment. Fourteen children (19 feet) aged 8-14 and followed for at least 24 months met the inclusion criteria. The results showed that all radiographic angles measured improved significantly, and only the talar declination angle and Kite's angle reached normal values. No signs of subtalar osteoarthritis were found in any of the children with follow-up longer than five years, and no implants were removed due to breakage, migration or pain. The American Orthopedic Foot and Ankle Scale (AOFAS) score showed significant improvement in all children. These results, however, should be interpreted with caution, as this score has not been validated for children, and answers given by children may be influenced by parents or interviewer. The authors concluded that subtalar arthroereisis is effective for improving clinical-functional and radiographic parameters in painful moderate pediatric FFF in children aged eight-14 as younger children may undergo spontaneous resolution of their flat feet, and those over 14 have little remaining growth and limited remodeling capacity. This study is limited by its small number of participants, retrospective design and lack of a control group.

Smolle et al. (2022) conducted a systematic review of the published literature up to July 2021 on the clinical and radiographic outcomes in children aged 6-11 who had surgical treatment for flexible flatfoot (FFF), with a follow up of at least 4 years. Ten studies of surgical procedures were included, 8 of them were in regard to arthroereisis, with and without

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concomitant Achilles tendon lengthening. In half of the studies, nonoperative treatment had not been successful (this was not explicitly stated in the other half). For clinical and functional outcomes, the results showed implant associated complication rate of 2.8% for screw loosening or breakage and wound healing problems of 1.6%. At last follow up, chronic pain was present in 2.8% of the patients. American Orthopaedic Foot & Ankle Society (AOFAS) scores improved 23 points from preoperative to latest follow up and was reported in 6 studies. Radiological outcomes were reported in 7 of the 8 studies and showed radiologically measured angles towards the values of a normal pediatric foot at final follow-up. The authors concluded that the quality of these studies is low. Outcome parameters reported are inconsistent, few provide patient-reported outcome measures, and long-term results on definite bony corrections are still missing. Larger studies comparing different therapeutic approaches in symptomatic pediatric FFF are needed (Giannini et al., 2017 which was previously cited in this policy is included in this systematic review).

In a 2021 systematic review, Smith et al. assessed the outcomes of arthroereisis for the treatment of symptomatic pediatric flexible pes planus. 24 studies (18 case series and six comparative studies with overall moderate methodological quality) met the inclusion criteria and radiological, clinical and kinematic outcomes, as well as complications were reviewed. A total of 2550 feet of at least 1399 children were operated on and all studies stated inclusion criteria of flexible pes planus with symptoms of pain or fatigue. Failure of conservative treatment was only a requirement in 13 studies. The results showed a variety of radiological, kinematic, and clinical outcomes used across the 24 studies, with poor homogeneity among them. Three studies did not measure any radiological outcome, ten measured any type of kinematics and only eight assessed patient reported outcomes. The authors concluded that overall results appear encouraging. There is an overall lack of high-quality prospective studies, limited long term data and heterogeneity of outcome measures, and these need to be addressed in future research to truly evaluate if arthroereisis is an effective treatment for symptomatic pediatric flexible pes planus.

Baryeh et al. (2021) conducted a systematic review to examine the outcomes of adult flatfoot deformity (AFFD) when treated surgically with subtalar arthroereisis. Nine studies met the inclusion criteria and were reviewed for both clinical and radiological outcomes as well as reported complications. A total of 167 individuals underwent 190 procedures. Six of the nine studies used the American Orthopaedic Foot and Ankle Society (AOFAS) score, three used the visual analog scale (VAS), one used the SF-36, and one used the Visual analogue scale foot and ankle (VAS-FA). Radiological measurements included Meary's angle, TN, Kite angle, and T1MT. The results showed five papers used the AOFAS hindfoot score with one using the foot and ankle outcome score (FAOS), one used the VAS-FA score and three used the VAS for reporting outcomes. In general, this systematic review suggests treatment with subtalar arthroereisis, either alone or as an adjunct results in improvement of clinical and radiological outcome, however it is unclear if the improvement would have occurred regardless. Only one paper used subtalar arthroereisis as the sole intervention and among the remaining papers, there was heterogeneity among additional procedures used. Sinus tarsi pain is the most common complication and, in this review, resulted in removal of 29% of implants. This review is limited by all studies being case series conducted at single centers, as well as only 2 being prospectively designed. Additionally, the heterogeneity of the procedures used also adds to the difficulty in identifying whether the improvements in clinical and radiological parameters were due to the use of subtalar arthroereisis or as a result of the additional procedures. Additional high-quality studies are needed to establish the best use of subtalar arthroereisis in the management of AAFD.

In a 2020 ECRI clinical evidence assessment on the HyProCure Sinus Tarsi Stent for correcting foot deformities, it was concluded that based on the evidence from 3 small case series at very high risk of bias, results are inconclusive and need validation in multicenter prospective controlled trials that compare HyProCure II to conventional surgical reconstruction and conservative treatment with orthoses.

In a 2020 evidence- based consensus statement on the appropriate clinical management of adult acquired flatfoot deformity, the American College of Foot and Ankle Surgeons stated that subtalar arthroereisis should not be considered as a single corrective procedure for stage IIB AAFD. The rationale for this is that the use of a subtalar implant alone to address pronation of the foot has limited literature demonstrating its use in the flexible deformity without advanced disease of surrounding soft tissues including tendon and ligament. The subtalar implant is designed to be performed with tensioning of the soft tissue structures to allow for their protected healing (Piraino et al., 2020).

A 2020 Hayes health technology assessment (updated in 2023) regarding subtalar arthroereisis for the treatment of adult-acquired flatfoot deformity concluded that based on the results of seven studies with very low quality of evidence, SAS remains an evolving technique for this condition, and there is a need for additional well-designed clinical studies to develop patient selection criteria and evaluate the long-term efficacy and safety.

A 2020 Hayes health technology assessment (updated in 2023) regarding subtalar arthroereisis for the treatment of pediatric flatfoot (FF) focused on this treatment for children with symptomatic flatfoot deformity that does not respond to conservative measures and negatively impacts daily activities of living (ADLs). 13 studies were included and 11 of those

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included children with idiopathic flexible flatfoot (FFF) and 2 included children with spastic FF associated with cerebral palsy (CP). An overall low-quality body of evidence suggests that SA is relatively safe and efficacious for treating idiopathic FFF in children with pain, decreased function, and other symptoms that are refractory to standard medical therapies. However, the majority of studies are retrospective, there are few comparative studies, and no well-designed controlled studies to draw firm conclusions regarding its efficacy and safety. For children with spastic FF, there is a paucity of evidence and the overall quality of the body of evidence is very low. Indications were consistent in studies of idiopathic or spastic FF, but overall substantial heterogeneity exists in surgical approaches, implant devices, and concomitant procedures. Clinical outcome measures varied from validated questionnaires and scales to patient-reported, subjective results (e.g., patient satisfaction with SA). There is a need for additional well-designed clinical studies to develop patient selection criteria and evaluate long-term efficacy and safety.

In a 2020 retrospective comparative study (included in Smolle study above) Bernasconi et al. sought to show that subtalar arthroereisis for treating flexible flatfoot (FFF) provided significant radiographic correction of low longitudinal arch and forefoot abduction in children. From 70 consecutive feet, 62 (31 children) treated at 10.5 years of age were identified and compared to 48 controls (24 children). Multiple measurements of preoperative and most recent postoperative follow-up radiographs were recorded by two observers and compared to assess for correction of the FFF. Ankle and hindfoot range of motion (ROM), the American Orthopedic Foot and Ankle Society Score (AOFAS) hindfoot score and the Visual Analogue Scale foot and ankle (VAS-FA) score were compared with controls without foot symptoms or deformity. Mean follow-up was 62 months. Radiographic measurements demonstrated significant improvement after surgery, but significance was not reached in talonavicular coverage angle and calcaneo-fifth metatarsal angle on dorsoplantar view. In the most recent follow-up, patients had less hindfoot inversion than controls, and lower AOFAS scores due to pain and alignment sub scores. Using the VAS-FA score, children were found to demonstrate higher pain at rest and during activity and felt limited when standing on one leg and running. This improvement remained after the removal of the implant. The authors concluded that STA corrected the low longitudinal arch in symptomatic pediatric FFF but did not correct forefoot abduction in relation to the hindfoot. Mid-term assessment revealed STA provided satisfactory ankle and hindfoot ROM, pain and function levels, but there are limitations when compared to the control. The complication rate in this study is not negligible and resulted in the unplanned removal of the implant in 24% of the children. Limitations of this study include a retrospective design, and a limited patient sample size.

Suh et al. (2019) performed a systematic review to compare radiographic correction, clinical outcomes, complications, and re-operations between lateral column lengthening (LCL) and arthroereisis (AR) for treating symptomatic flatfoot in children. Twenty-one and 13 studies were included in the LCL and AR groups, respectively. The reviewers reported that the LCL group achieved more radiographic corrections and more improvements in the American Orthopedic Foot and Ankle Society (AOFAS) score than the AR group. Complications were more common in the LCL group, and re-operation rates were similar between the two groups.

The National Institute for Health and Care Excellence (2009) guidance concluded that current evidence on the safety and efficacy of sinus tarsi implant insertion for mobile flatfoot was inadequate in quality and quantity and should only be used with special arrangements for clinical governance, consent and audit or research.

Numerous implant systems have received FDA approval through the 510(k) process. Refer to the following website for more information (use product code HWC): https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed April 28, 2025)

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Code	Description
0338T	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; unilateral
0339T	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; bilateral

Transcatheter renal sympathetic denervation (unilateral or bilateral) for resistant hypertension is unproven due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

In 2024, ECRI developed a Clinical Evidence Assessment for the Symplicity Spyral Renal Denervation System (Medtronic plc.) for Treating Refractory Hypertension (HTN). The assessment reported on how Symplicity works to treat refractory HTN, and how well it compares to other treatments. The assessment found that there is very low quality of evidence and mixed results that do not permit conclusions. Two meta-analyses of randomized controlled trials (RCT) data report that Symplicity Renal Denervation System (RDS) does not significantly reduce blood pressure versus controls at up to six-month follow-up. An additional RCT and the only one reporting data at long-term follow-up reported significant blood pressure reduction at 36 months. Additional RCTs with larger populations and long-term follow-up (≥ three years) are needed to determine whether Symplicity provides clinical benefits for this population. Whether Symplicity improves patient-oriented outcomes (e.g., cardiovascular mortality, heart failure, myocardial infarction, quality of life) cannot be determined because available studies provide limited data and report too few events.

In 2024 Hayes developed an Evolving Evidence Review of the Paradise ultrasound renal denervation system (ReCore Medical Inc.) for resistant HTN. The review of full-text clinical studies, and systematic reviews suggest minimal support, and review of guidelines and position statements show weak support for using the Paradise Ultrasound Renal Denervation System (Paradise System) for treating resistant HTN. The included clinical trials demonstrate that ultrasound renal denervation (uRDN) using the Paradise uRDN System (Paradise System) can be effective among those taking a variety of antihypertensive medications; however, the duration of treatment effect is unclear. Use of ultrasound rather than radiofrequency may reduce the risk of thermal damage to the renal artery and may preclude the need for treatment of renal artery branches. The RADIANCE trials (refer to the below) were partly designed to minimize lack of adherence to co-treatment with medication by taking patients off antihypertensive medications for the initial study period (RADIANCE SOLO and RADIANCE-HTN-TRIO) or by switching individuals to a single pill (RADIANCE-HTN-SOLO). However, doing so has resulted in trials enrolling those with less severe HTN, which may limit generalizability. None of the included studies reported quality-of-life (QOL) measures. However, it is possible that the statistically significant reductions in antihypertensive medication burden after treatment with the Paradise System reported by some studies positively affects patients' QOL. Duration of follow-up in the most recent RCT (RADIANCE II, Azizi et al., 2023) is limited to two months, but further analyses are planned. Several clinical trials are active, and a registry study is recruiting; the literature should be monitored for resultant publications. (Azizi et al., 2022 & 2023, and Kario et al., 2022 are included in this evolving evidence review).

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Through a systematic review and meta-analysis, authors Vukadinovic et al. (2024) performed a comprehensive analysis of all randomized, sham-controlled trials investigating RDN with first-and second-generation devices in HTN to determine safety and efficacy of the technology. Safety and efficacy of RDN was assessed by 24-hour and office systolic and diastolic blood pressures, and all cause death, vascular complication, renal artery stenosis > 70%, hypertensive crisis. The authors uncovered ten trials comprising 2478 individuals with HTN while being either off or on treatment. Compared with sham, RDN reduced 24-hour and office systolic blood pressure by 4.4 mmHg and 6.6 mmHg, respectively. The 24-hour and office diastolic blood pressure paralleled these findings. There was no difference in 24-hour and office systolic blood pressure reduction between trials with and without concomitant antihypertensive medication. There was no relevant difference in vascular complications, renal artery stenosis, hypertensive crisis, and all-cause death, between RDN and sham groups. Change of renal function based on estimated glomerular filtration rate was comparable between groups. There was significant heterogeneity between trials. The authors concluded that catheter-based RDN safely reduced 24-hour and office blood pressure for up to six months compared with sham for individuals with HTN with and without concomitant antihypertensive medication irrespective of the RDN modality used. The limitations included the lack of generalizability to this HTN phenotype.

In 2023, the FDA approved the Paradise™ Ultrasound Renal Denervation system (ReCor Medical, Inc., Palo Alto, CA). The Paradise system is an adjunctive treatment option when lifestyle changes and medications have not adequately controlled BP. The ultrasound-based RDN technology is designed to lower BP by denervating the sympathetic nerves surrounding the renal arteries, reducing the overactivity that can lead to HTN. The Paradise system delivers two to three doses of 360-degree ultrasound energy, lasting seven seconds each, through each of the main renal arteries to the surrounding nerves. The Paradise catheter features the exclusive HydroCooling™ system, which circulates sterile water through the balloon catheter during the procedure to help protect the renal artery wall. For more information, refer to the following websites:

- https://www.recormedical.com/recor-medical-and-otsuka-medical-devices-announce-first-fda-approved-renal-denervation-system-for-the-treatment-of-hypertension/. (Accessed May 7, 2025)
- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P220023. (Accessed May 7, 2025)

The Symplicity Spyral™ Renal Denervation System (Medtronic, Inc., Santa Rosa, CA) gained PMA approval on November 17, 2023. The Medtronic Symplicity BP procedure is a minimally invasive procedure that supplies radiofrequency energy to nerves near the kidneys that can become overactive and contribute to high BP. For more information, refer to the following website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P220026. (Accessed May 7, 2025)

In a 2023 Hayes Clinical Research Response on the Symplicity Spyral Renal Denervation System (Medtronic), identifiable abstracts of clinical studies and additional information regarding the Symplicity spiral renal denervation system for treating HTN were evaluated. According to Hayes' report of full-text clinical practice guidelines and position statements, the guidance offers no/unclear support for renal denervation (RDN) in managing resistant HTN. Two manufacturer-sponsored sham-controlled trials found an acceptable safety profile for the Spyral Renal Denervation System and modest improvement in blood pressure (BP) measurement. Spyral is being studied in numerous international trials. It is recommended that these trials be monitored for future results from independent researchers.

In 2023, Kandzari and colleagues conducted a prospective, randomized, sham-controlled, patient and assessor-blinded trial enrolling participants from 56 clinical centers worldwide (SPYRAL HTN-ON MED). The participants were given one to three antihypertensive medications and randomized to radiofrequency RDN or sham-controlled procedures. The main endpoint studied was the baseline-adjusted variation in the mean 24-hour ambulatory systolic BP at six months amongst the groups. The results of this trial showed a treatment difference in the mean 24-hour ambulatory systolic BP from baseline to 6 months between the RDN group (n = 206; - 6.5 ±10.7 mm Hg) and sham control group (n = 131; - 4.5 ±10.3 mm Hg) was - 1.9 mm Hg (95% CI: -4.4 to 0.5 mm Hg; p = 0.12). There was no significant difference between groups in the primary efficacy analysis with a posterior probability of superiority of 0.51 [Bayesian treatment difference: - 0.03 mm Hg (95% CI: -2.82 to 2.77 mm Hg)]. However, there were changes and increases in medication intensity between those in the sham-controlled group. RDN was associated with reduced office systolic BP compared with sham control at six months (adjusted treatment difference: - 4.9 mm Hg; p = 0.0015). The night-time BP reductions and win ratio analysis also favored RDN. There was one adverse safety event among 253 evaluated participants. The authors concluded that there is no significant difference between groups in the primary analysis. However, multiple secondary endpoint analyses favored RDN over sham control (Included in the Fernandes et al. 2023 systematic review and meta-analysis and the 2023 Hayes clinical research response).

In a systematic review and meta-analysis, Fernandes and colleagues (2023) aimed to measure the degree of BP decrease within the sham arm of RCTs with RDN for those with HTN. For this analysis, the outcomes measured were ambulatory/office systolic and diastolic BP changes. In spite of recent data signifying that RDN might be an effective

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treatment for people with resistant HTN when compared to a sham intervention, the results show that the sham intervention for RDN also has a substantial effect on lowering office and ambulatory (24-hour) BP for adults with HTN. This highlights that BP might be sensitive to the placebo-like effects and brings further difficulties in establishing the BP-lowering efficacy of invasive interventions due to the magnitude of the sham effect (Desch et al. 2015 and Kandzari et al. 2023 are included in this systematic review and meta-analysis).

In 2023, the Society for Cardiovascular Angiography & Interventions (SCAI) developed a position statement on RDN for HTN, including patient selection, operator competence, training and techniques, and organizational recommendations. Regarding patient selection, the selection criteria right for RDN identified are the following:

- Those with resistant HTN, defined by BP > 130/80 mm Hg despite being on three medications with maximally tolerated doses from classes with outcomes data (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, calcium channel blockers, thiazide diuretics, and beta blockers).
- Those with uncontrolled HTN, despite trying lifestyle modification and antihypertensive medication, are either intolerant of additional medicines or do not wish to be on additional drugs and are willing to undergo RDN after shared decision-making.
- Priority may be appropriately given to those with higher cardiovascular risk (e.g., comorbidities of coronary artery disease, diabetes, prior transient ischemic attack/cerebrovascular accident, or chronic kidney disease) who may have the most significant benefit from BP reduction (Swaminathan et al., 2023).

The 2023 National Institute for Health and Care Excellence (NICE) Interventional Procedure guidance recommended that percutaneous transluminal renal sympathetic denervation (RSD) for resistant HTN should only be used with unique clinical governance, consent, and audit or research arrangements. It states that the evidence suggests that there are no major safety concerns in the short term, and complications are well recognized such as renal artery damage. The evidence shows that it reduces BP in the short and medium term. Overall, there are uncertainties about how well it works in the long term and whether there are long-term complications.

A clinical consensus by the European Society of Cardiology (ESC) Council on Hypertension and the European Association and Percutaneous Cardiovascular Interventions (EAPCI) proposes that RDN is an adjunct treatment option in uncontrolled resistant HTN, confirmed by ambulatory BP measurements, despite best efforts at lifestyle and pharmacological interventions and that RDN may also be used in those who are unable to tolerate antihypertensive medications in the long term. A shared decision-making process is a key feature and preferably includes those who are well informed on the benefits and limitations of the procedure. Multidisciplinary HTN teams encompassing HTN specialists and interventionalists should gauge the indication and allow/disallow the RDN procedure. Centers executing these procedures require the skills and sources to deal with possible complications. Future research is needed to address open questions and research the influence of BP-lowering with RDN on clinical outcomes and prospective clinical indications outside HTN (Barbato et al., 2023).

Azizi et al. 2023 studied the efficacy and safety of ultrasound RDN through a multi-center, sham-controlled, randomized (2:1) clinical trial (RADIANCE II). Participants (n = 224) and outcome assessors were blinded to treatment assignment. Participants were to abstain from antihypertensive medications until the 2-month follow-up unless prespecified BP criteria were exceeded and were associated with clinical symptoms. The primary efficacy outcome was the mean change in daytime ambulatory SBP at two months. The reduction in daytime ambulatory SBP was greater with uRDN [mean, −7.9 mm Hg (SD, 11.6 mm Hg)] vs the sham procedure [mean, −1.8 mm Hg (SD, 9.5 mm Hg)] [baseline-adjusted between-group difference, −6.3 mm Hg (95% CI, −9.3 to −3.2 mm Hg), p < .001]. The authors concluded that for those with HTN, ultrasound RDN lowered daytime ambulatory SBP at two months in the absence of antihypertensive medications vs. a sham procedure without postprocedural major adverse events. The limitations of the trial consist of the short duration of follow-up, limited enrollment of participants with low cardiovascular risk and without significant comorbidities, and variability in the prevailing state of sympathetic hyperactivity or variable renal nerve ablation. Furthermore, longer follow up will be necessary to assess the impact of the intervention on patient-centered outcomes.

In an effort to evaluate the safety and efficacy of endovascular ultrasound RDN for individuals with resistant hypertension, Azizi et al. (2021) conducted a randomized, single-blind international sham-controlled clinical trial that took place at 28 facilities in the United States and 25 facilities in Europe (RADIANCE-HTN). Individuals aged 18-75 with office-measured BP of at least 140/90 despite the use of at least three antihypertensives (including diuretics) were included. Of 989 total originally enrolled, 136 participants met all inclusion criteria and were randomly assigned to either RDN (n = 69) or sham (n = 67) procedure. Both the participants and those making assessments were masked to randomization. Participating individuals were switched to a daily, fixed-dose, single-pill, including an angiotensin receptor blocker, a calcium channel blocker, and a thiazide diuretic, which continued for four weeks. Change in daytime ambulatory systolic BP at two months in the intention-to-treat group was the primary endpoint of the study, along with safety. With measured adherence to combination medication similar in both groups (82% in the RDN group vs 82% in the sham group), the RDN group

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showed a reduced ambulatory systolic BP compared to the sham procedure. The median between-group difference was -4.5 mm Hg, and among participants with complete ambulatory BP data, the difference was -5.8 mm Hg. No difference in safety outcomes was noted between the two groups. The authors concluded that ultrasound RDN resulted in reduced BP after two months in participants with resistant HTN compared to the sham procedure. They suggest that if studies continue to demonstrate the safety and BP-lowering effects of RDN, it may become an option (potentially as an alternative to the addition of further antihypertensive medication) for treating individuals with resistant hypertension.

In 2022, Azizi et al., conducted a prespecified evaluation after this trial. At six months post randomization a smaller quantity of drugs was added in the uRDN group [n = 64, mean (SD), 0.7 (1.0) medications] vs. sham [n = 65, mean (SD), 1.1 (1.1) medications; p = .045], and fewer participants in the uRDN group took aldosterone antagonists at six months [26 of 65 (40.0%) vs. 39 of 64 (60.9%); p = .02]. The authors concluded that for individuals with resistant HTN, originally randomly assigned to uRDN or a sham procedure who had a persistent rise of BP two months after the procedure, a protocolized increase of antihypertensive medications resulted in a comparable BP decrease at six months in both groups, with less added drugs, particularly aldosterone antagonists, in the uRDN group. Limitations of the trial include a short duration of follow-up. Research with longer follow up is needed to evaluate the long-term durability and safety outcomes of uRDN in individuals with RHTN. The authors indicate that extended follow up is planned.

In 2022, Kario et al. conducted an RCT (REQUIRE trial) to explore the BP -lowering efficacy of RDN for treating individuals with resistant HTN. The prime endpoint was the difference in baseline systolic BP at three months. The study included 143 individuals, with 72 assigned to the RDN group and 71 to sham control. The outcomes showed that reduction from baseline in 24-hour ambulatory systolic BP at three months was not significantly different among the RDN (-6.6 mmHg) and sham control (-6.5 mmHg) groups (difference: -0.1, 95% confidence interval -5.5, 5.3; p = 0.971). Decreases from baseline in home and office systolic BP [differences: -1.8 mmHg (p = 0.488) and -2.0 mmHg (p = 0.511), respectively], and medication load, did not differ significantly between the two groups. The procedure-device-related major adverse events were not seen. Though BP decrease after RDN was comparable to other sham-controlled studies, the sham group in this study established a much more substantial reduction. Limitations to the study include an absence of standardization of antihypertensive medications or objective measurement of medication adherence, absence of double blinding, marked seasonal variations in the temperature and BP, and relatively short duration of follow-up.

Bhatt, et al conducted a 36-month follow-up results from the single-blind, multicenter, sham-controlled, randomized trial SYMPLICITY HTN-3 trial (2022). The study aimed showed safety but not efficacy of the Simplicity system at six months post randomization. A total of 88 centers were included, and adults with treatment-resistant HTN on stable, maximally tolerated doses of three or more medications, including a diuretic, with a systolic BP of 160mmHg or more (seated) and a 24 hour ambulatory systolic BP of 135 mmHg or more were randomized in a 2:1 ratio to renal artery denervation using the single electrode (Flex) catheter or sham control. The participants were unmasked at the six-month point, where the eligible participants in the sham control group meeting inclusion criteria were given the option to cross over to the treatment group. The changes in systolic BP were then followed up to 36 months and analyzed by comparing groups. Of 1442 participants, 364 received active treatment, and 171 received sham control; 219 individuals were available for 36-month follow-up, 63 in the crossover group, and 33 in the non-crossover group. The results showed that the change in 24 h ambulatory systolic BP at 36 months was -15·6 mm Hg (SD 20·8) in the renal artery denervation group and -0·3 mm Hg (15·1) in the sham control group [adjusted treatment difference -16·5 mm Hg (95% CI -20·5 to -12·5); p ≤ 0·0001]. Without imputation, the renal artery denervation group spent a significantly longer time in the therapeutic BP range (i.e., better BP control) than participants in the sham control group [18% (SD 25·0) for the renal artery denervation group vs. 9% (SD 18·8) for the sham control group; p ≤ 0·0001] despite a similar medication burden, with consistent and significant results with imputation. Rates of adverse events were similar across treatment groups, with no evidence of late-emerging complications from renal artery denervation. The rate of the composite safety endpoint to 48 months, including all-cause death, new-onset end-stage renal disease, a significant embolic event resulting in end-organ damage, vascular complication, renal artery re-intervention, and hypertensive emergency was 15% (54 of 352 individuals) for the renal artery denervation group, 14% (13 of 96 individuals) for the crossover group, and 14% (10 of 69 individuals) for the non-crossover group. The authors concluded that this final report of the SYMPLICITY HTN-3 trial adds to the evidence supporting renal artery denervation's safety 36 months after the procedure. From 12 months to 36 months after the procedure, those who were originally randomly assigned to receive renal artery denervation had more significant reductions in BP and better BP control than participants who received sham control. The findings are however limited by lack of randomization after six months.

The 2021 SCAI and NKF expert consensus routable proceedings on RDN for individuals with HTN. The following recommendations were made on RDN safety and effectiveness:

- The efficacy of RDN for the treatment of uncontrolled HTN has been consistently demonstrated in sham-controlled, randomized trials both in the presence and absence of medications.

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- Current evidence with RDN suggests a constant reduction in BP over the day and night (the “always on” effect) that is distinct from pharmacokinetic profiles, dosing regimens with medications and non-adherence. This observation may improve BP stability and TTR.
- Both randomized trials and registries support the early and late-term safety of RDN.
- RDN is associated with improvements in BP and reductions in medication number and/or dose.
- Although registry data suggests long-term durability in BP reduction following RDN, longer-term surveillance of existing trials and more studies may inform durability and impact clinical outcomes. Clinically useful, reliable predictors of RDN responsiveness need to be identified.

The following recommendations were made on the incorporation of RDN into clinical practice:
- Criteria for considering RDN should consider the severity of HTN, coexisting medical conditions, patient preference, and the healthcare provider team.
- Future considerations regarding the implementation of care pathways for device-based interventions for HTN should likewise consider patient preferences and self-reported health status.
- Misalignment between patient preferences and provider referral for therapies such as RDN needs further exploration.
- Coding and reimbursement for uncontrolled HTN would substantially impact care pathways, influence research initiatives, and have implications for reimbursement (Kandzari et al., 2021).

In a systematic review and meta-analysis of blinded, randomized, placebo-controlled trials, Ahmad et al. (2021) sought to compare the effect of RDN for individuals taking medication for HTN and those not taking medication. Seven eligible trials were identified, including a total of 1,368 individuals. A review of the data showed that RDN significantly reduced ambulatory systolic (mean difference 3.61 mm Hg; 95% CI: 4.89 to 2.33 mm Hg; $p < 0.0001$), office systolic (5.86 mm Hg; 95% CI: 7.77 to 3.94 mm Hg; $p < 0.0001$), and office diastolic (3.63 mm Hg; 95% CI: 4.77 to 2.50; $p < 0.0001$) BP. The weighted mean follow-up duration was 4.5 months. The researchers indicate that the review of these studies found consistent evidence that RDN can reduce ambulatory and office BP, although the reduction appears to be modest (approximately 4/2 mm Hg). The reduction appeared to be similar between individuals taking antihypertension medications and those who were not, but there was no indication whether the reduction would persist over time. The authors concluded that RDN could be a useful strategy for individuals with HTN, especially if they are unwilling to add antihypertensive medications; however, larger scale, high-quality studies are needed to help determine the safety and potential long-term effect of RDN. Evidence addressing the effect of the therapy on end-organ damage or patient-centered outcome would also be useful (The studies by Azizi et al., 2021, and Desch 2015, were included in this systematic review).

Pisano et al. (2021) published a Cochrane systematic review of RCTs evaluating the short- and long-term effects of RDN in individuals with resistant HTN. Clinical outcomes included cardiovascular events (fatal and non-fatal), hospital admissions, quality of life, all-cause mortality, BP control, cardiovascular and metabolic profile, left ventricular hypertrophy, kidney function, and potential adverse effects of RDN treatment. Selection criteria included RCT comparing RDN to standard therapy or sham treatment. After excluding studies not meeting the criteria, 15 studies with 1416 participants were evaluated. Many studies had unclear or high risk of bias for blinding/allocation concealment. The review found low-certainty evidence that RDN had little or no effect on the risk of myocardial infarction, ischemic stroke, unstable angina, or hospitalization. Moderate-certainty evidence suggested that RDN could reduce 24-hour ambulatory BP monitoring (ABPM) systolic BP, diastolic BP, and office diastolic BP. RDN had little or no effect on office systolic BP. Moderate-certainty evidence also suggested that this procedure may not reduce serum creatinine or increase estimated glomerular filtration rate or creatinine clearance. In summary, the authors concluded that for individuals with resistant HTN, the evidence is insufficient to support the clinical use of the RDN procedure for improving cardiovascular outcomes and renal function; however, there is moderate-certainty evidence that it may improve 24-hour ABPM and diastolic office-measured BP. Additional high-quality clinical trials which seek to measure patient-centered outcomes and include longer follow-up periods, larger sample sizes, and more standardized procedures are required in order to clarify the clinical utility of RDN for resistant HTN (Studies by Desch et al., 2015, Bhatt et al., 2014, and Esler et al., 2012, previously cited in this policy, were included in this review).

Schmieder et al. (2021) published a position statement on behalf of the European Society of Hypertension regarding the use of RDN for lowering BP, suggesting a structured pathway for clinical use of RDN, including standardized shared decision-making to select the most appropriate treatment option for individuals with HTN. This recommendation was made based on results of recent sham-controlled clinical trials; however, the authors point out the knowledge gaps related to this procedure that continue to exist, including predictors of BP response to RDN, predictors of efficacy, direct comparison of different ablative techniques, long term efficacy, safety, and safety for individuals with decreased glomerular filtration rates, impact related to hypertensive comorbidities, cost-effectiveness, and individual perspective and preference. In addition, the authors stress the importance of establishing a structured and transparent way to qualify facilities to perform RDN.

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Silverwatch et al. (2021) published a systematic review and network meta-analysis (NMA) of RCTs comparing the efficacy and safety of existing RDN interventions for uncontrolled HTN and resistant HTN to determine their effects on several intermediate and clinical outcomes. Twenty RCTs were included, with 2,152 participants (mean ages 48-64 years old) with resistant HTN and/or uncontrolled HTN and follow-up time ranging from two to six months. NMA and frequentist framework were used to evaluate RDN interventions such as radiofrequency in the main renal artery (MRA) and branches, radiofrequency in MRA, radiofrequency in MRA plus antihypertensive therapy (AHT), US in MRA, sham, and AHT. The data findings were that radiofrequency in MRA, and branches were the best intervention to reduce 24-hour ambulatory, daytime, and nighttime SBP and DBP compared to other interventions; only 24-hour ambulatory SBP and DBP were significantly reduced in comparison. Radiofrequency in MRA plus AHT was the best intervention to lower office SBP and DBP compared to other interventions, but neither was significant. The leading RDN interventions were similar after analysis in six-month follow-up and resistant HTN only trials. The authors concluded that scarce data and uncommonly described outcomes in the existing trials led to no significant difference in RDN on clinical outcomes. Therefore, more clinical outcome data is needed for future trials to further the safety and efficacy of RDN interventions(The studies by Desch et al., 2015, and Bhatt et al., 2014, previously cited in this policy, are included in this systematic review).

A systematic review and meta-analysis regarding the state of RSD for managing individuals with HTN was published by Syed et al. in 2021. Eight studies, with a total of 1363 individuals, were included. The mean age was 56 years of age ±2.6 years, and 29% of participants included were women. Data was pooled from RCT, and a comparison of RSD in managing HTN to sham procedures was performed. The median maximum follow-up was six-month range (three-12 months). Data showed a greater reduction in ambulatory systolic blood pressure (ASBP), ambulatory diastolic blood pressure (ADBP), office systolic blood pressure (OSBP), and office diastolic blood pressure (ODBP) with RSD. The authors concluded that the use of RSD for the management of HTN demonstrated reduced ambulatory and office BP compared to sham procedure(s); however, additional high-quality RCTs of RSD are needed to assess the impact on clinical outcomes and confirm safety and reproducibility (The studies by Desch et al., 2015, Bhatt et al., 2014, and Esler et al., 2012, were previously cited in this policy are included in this systematic review).

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Code	Description
0347T	Placement of interstitial device(s) in bone for radiostereometric analysis (RSA)
0348T	Radiologic examination, radiostereometric analysis (RSA); spine, (includes cervical, thoracic and lumbosacral, when performed)
0349T	Radiologic examination, radiostereometric analysis (RSA); upper extremity(ies), (includes shoulder, elbow, and wrist, when performed)
0350T	Radiologic examination, radiostereometric analysis (RSA); lower extremity(ies), (includes hip, proximal femur, knee, and ankle, when performed)

Radiostereometric analysis (RSA) is unproven and not medically necessary for all indications due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Radiostereometric analysis (RSA), also known as radiostereometry and roentgen stereophotogrammetry analysis, is a technique used to predict the stability of joint implants or fracture healing by assessing early movement. Small tantalum markers are embedded into the bone, and then postoperative biplanar x-rays are taken through a calibration cage, which has known reference points. These images are analyzed with an RSA software package that calculates micromotion between the implant and bone in 3D. These measurements are then converted into the maximal total point motion. By repeating the x-ray analysis at 6-month intervals, the maximal total point motions can be compared (Aspinall and Dunbar, 2009). Owing to better precision, low dose computed tomography (CT) based RSA is being explored for orthopedic research (Sandberg et al., 2023). RSA is routinely used in clinical research; however, evidence is lacking with regard to the utility for routine clinical use. Large randomized controlled trails comparing RSA to other imaging techniques are needed to determine whether this technology is more effective and improves health outcomes over conventional methods.

Orthopedic Implants

van der Lelij et al. (2024) conducted a secondary analysis of five studies on RSA and tibial implant migration and patient reported outcome measures (PROMs) with ten year follow up. Individual migration data was collected from five randomized RSA studies that included 300 participants. RSA radiographs were taken on the day after surgery, and subsequent radiographs were taken at 3 months, one year, and two, five, seven and ten years. PROMs were measured using the Knee Society Score (KSS) and Knee Injury and Osteoarthritis Outcome Score (KOOS) and were obtained preoperatively with the same interval as RSA measures. During the 10-year follow-up period, 7 implants were revised because of infection (n 2), component loosening (n = 2), instability (n = 1), or insert wear (n = 2). Six different knee replacement systems were analyzed, and showed similar rates of migration of 0.70 mm to 1.84 mm over ten years. PROM clinical scores showed that there was no significant association between KSS, and KOOS and implant migration through the ten year follow up indicating no association between the migration and PROMs. Improvement in PROMs after TKA can be related to aspects other than the prosthesis itself, such as individual patient factors. However, the

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performance of the implant can be measured objectively by RSA. This suggests that both are needed for a comprehensive evaluation of TKA implant performance and they cannot be used interchangeably. Future studies should address whether these findings can be generalized to other arthroplasty implant designs.

Pijls et al. (2018) conducted a systematic review and meta-analysis to evaluate the early and long-term migration patterns of tibial components of total knee replacement (TKR) of all known RSA studies. The inclusion criteria were primary TKR, and maximal total point motion (MTPM). Fifty three studies comprised of 111 study groups and 2,470 knees were included. Prostheses were classified according to prosthesis, fixation and insert (PFI) methodology, and a study group was defined as a group of patients in a study with the same PFI. Migration pattern was defined as at least 2 postoperative follow-up moments within the first 2 years of follow-up. One year follow up was the most frequently reported and used for the meta-analysis. The results showed that the pooled increase in migration between 6 months and 1 year in MTPM was 0.04 mm (CI 0.02–0.07) based on 70 study groups, and between 1 and 2 years was 0.04 mm (CI 0.02–0.06) based on 105 study groups. 8 study groups reported MTPM migration results up to 10 years' follow-up and the majority of TKR stabilized during follow-up, although 2 uncemented types of TKR continued to migrate. The majority of early migration occurs in the first 6 postoperative months followed by a period of no or very little migration within the bone. The authors concluded that RSA has a place in monitoring of new TKR migration and should be part of all phased introduction of new implants. This SR is limited by the lack of standardized reporting of outcomes in the included studies, making an accurate assessment on clinical efficacy not possible.

In a 2017 systematic review, Ten Brinke et al. evaluated 23 studies to investigate the accuracy and precision of RSA to analyze early migration of prostheses of the upper limb [shoulder (14), elbow (4), wrist, and 5 involving the trapeziometacarpal (TMC) joint]. Due to the small number of studies on RSA for the upper limb, all types of study design were included. Accuracy data were collected from studies that compared RSA with another method that calculates migration and has a substantially better resolution. The precision of translation and rotation values was assessed by all results from double examinations. The standard deviations (SDs) of the migration calculated using double examination was used to determine precision, defined as 1.96 × SD. Precision was calculated separately for the shoulder, elbow, and TMC joint. If prosthesis components were analyzed separately, precision was calculated for each component. If precision was given for all 3 axes (the x-, y-, and z-axis), the lowest precision was used to calculate the mean precision. For accuracy, there were no studies that reported accuracy data from marker and model based RSA despite ISO standards calling for both measurements as part of clinical studies. For precision, the values of translation measurements were comparable for those seen with RSA of total hip and knee arthroplasty, with values for the shoulder in the 0.06-0.88 mm, 0.05-10.7° range, elbow 0.05-0.34 mm and 0.16–0.76° range, and 0.16–1.83 mm and 11–124° range for the trapeziometacarpal joint. The authors concluded that RSA is a highly precise technique for detecting early migration of upper limb implants. This review is limited by the small number of studies analyzed and the lack of the studies adherence to ISO guidelines for precision. Further research is needed in assessing the value of RSA for upper limb arthroplasty.

Bone Fracture Healing

In 2023 Bizzoca et al. conducted a literature search to assess biomechanical healing of fracture sites, including RSA. This research shows that RSA may be a promising technology to assess bone healing, but overcoming its limitations are significant. RSA is a highly demanding technique that requires implantation of tantalum markers, specialized radiographic imaging over a calibration cage, dedicated software, and highly specialized and trained radiographers to interpret results. Future development of calibration objects designed for RSA with standard near-orthogonal radiographs might make this technique more widely applicable. The development of marker-free methods such as digitally reconstructed radiograph RSA and model-based method RSA may be also useful in improving this method.

Lee and Copp (2022) conducted a review of published literature on the use of new and emerging technologies to assess fracture healing. RSA was included in this review and the results have shown to be accurate, precise, and safe in evaluating various aspects of fracture care including the early detection of nonunion. However, challenges remain, including implantation difficulty in some areas, as well as difficulty in inducible micromotion at various stages in healing. The authors concluded that RSA is a potentially powerful tool in fracture care, and more research with larger patient populations is needed to validate these findings.

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Code	Description
0358T	Bioelectrical impedance analysis whole body composition assessment, with interpretation and report

Bioelectrical impedance analysis whole body composition assessment is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Bioelectrical impedance analysis (BIA) is a commonly used method for estimating body composition, in particular body fat. Since the advent of the first commercially available devices in the mid-1980s the method has become popular owing to its ease of use, portability of the equipment and its relatively low cost compared to some of the other methods of body composition analysis. BIA determines the electrical impedance, or opposition to the flow of an electric current through body tissues which can then be used to calculate an estimate of total body water (TBW). TBW can be used to estimate fat-free body mass and, by difference with body weight, body fat.

In a randomized, controlled crossover pilot trial, Schierbauer et al. (2023) investigated whether recent fluid intake could influence bioelectrical impedance analysis (BIA) results, “since equilibration of fluid between intra- and extracellular spaces may take several hours and furthermore, ingested fluids may not be fully absorbed”. Before having BIA, eighteen healthy individuals consumed isotonic 0.9% sodium-chloride (ISO), 5% glucose (GLU) or Ringer (RIN) solutions. BIAs were then conducted every ten minutes for a total of 120 minutes. The researchers “found statistically significant interactions between the effects of solution ingestion and time for intra- (ICW, $p < 0.01$) and extracellular water (ECW, $p < 0.0001$), skeletal muscle mass (SMM, $p < 0.001$) and body fat mass (FM, $p < 0.01$), respectively. Simple main effects analysis showed that time had a statistically significant effect on changes in ICW ($p < 0.01$), ECW ($p < 0.01$), SMM ($p < 0.01$) and FM ($p < 0.01$), while fluid intake did not have a significant effect.” The authors concluded that this trial demonstrated all fluids could impact conductivity in addition to the calculation of body compartments. They further concluded that these results “highlight the importance of a standardized pre-measurement nutrition, with particular attention to hydration status when using a BIA for the evaluation of body composition.”

Campa et al. (2022) conducted a systematic review to compare the accuracy of and Bioelectrical Impedance Vector Analysis (BIVA) vs. reference methods for the assessment of body composition in athletes. Forty-two studies published between 1988 and 2021 were included. Twenty-three studies had an overall good rating in terms of quality, while 13 were rated as fair and 6 as poor, resulting in a low to moderate risk of bias. The results showed that fat mass was inconsistently determined using BIA vs. the reference methods, regardless of the BIA technology. When using the foot to hand technology with predictive equations, there was consistency between BIA and the reference methods measurements of fat-free mass, total body, intra and extra cellular water. However, an underestimation in fat-free mass and body fluids was found when using generalized predictive equations. The authors concluded that BIA and BIVA can be used for assessing body composition in athletes, provided that other reference methods such as foot-to-hand technology, predictive equations, and BIVA references are used.

A systematic review aimed to investigate if multi-frequency bioelectric impedance (MF-BI) is a valid tool to determine body composition in patients with obesity was performed by Becroft et al. (2019). Sixteen studies were eligible for inclusion. Sample sizes ranged from 15 to 157, with body mass index (BMI) 26-48 kg/m2. MF-BI underestimated fat mass (FM) in 11 studies and overestimated fat-free mass (FFM) in nine studies in comparison with reference methods. Correlations of absolute values from MF-BI and reference methods for FM and FFM were high, however, agreement was lower at an individual level. When adjustments for BMI were made to machine algorithms, measurement accuracy improved. The authors concluded that MF-BI is reliable for use at a group level. Multiple variables contributed to a lack of consistency among studies included, highlighting the need for more robust studies that control variables to establish clear validity assessment.

A 2019 ECRI report on body composition analyzers for diagnosis and management of obesity found that BIA clinical validity and utility for assessing obesity in individuals with BMI > 25 kg/m2 is unclear. Diagnostic cohort studies of varying

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size and quality reported only moderate agreement between BIA and reference body composition analysis methods. BIA methods varied across studies. Clinical guidelines consider BIA to be of unproven validity or impractical for obesity screening (ECRI, 2019).

In 2019, the American Society for Parenteral and Enteral Nutrition (ASPEN) conducted a systematic review to use the best available evidence to develop guidelines on the validity of different body composition methods. Regarding BIA, no recommendations could be made due to limited data, or the proprietary nature of specific devices.

Fonseca et al. (2018) performed a study to investigate the validity of an eight-contact electrode BIA system within a household scale for assessing whole body composition in patients with COPD. Seventeen patients with COPD underwent dual-energy X-ray absorptiometry (DXA) and an eight-contact electrode BIA system for body composition assessment. There was a strong inter-method correlation for FM, FFM, and lean mass, but the correlation was moderate for bone mineral content. In the agreement analysis, the values between DXA and the BIA system differed by only 0.15 kg, 0.26 kg, -0.13 kg, and -0.55 kg for FFM, lean mass, bone mineral content, and FM, respectively. The authors concluded that the eight-contact electrode BIA system was shown to be a valid tool in the assessment of whole-body composition in the sample of patients with COPD. The small sample size limits the conclusions of this study.

The aim of a study by Thivel et al. (2018) was to assess the sensitivity of BIA in tracking body composition changes in adolescents with various degrees of obesity. Whole-body and segmental body composition were assessed by BIA and DXA among 196 obese adolescents, before and after a 3-month weight loss program. Except for the measurement of FFM (kg), the percentage of variation between M0 and M3 for FM% and FMkg are significantly correlated and show significant concordance between DXA and BIA. FMkg and FM% changes between M0 and M3 are similarly tracked by DXA and BIA. The authors found inconsistent and low correlations and concordances between the two devices when tracking FM% changes whatever the degree of weight and FM variations. The accuracy of body composition assessment using BIA decreases with increasing obesity, and its reliability to track changes is reduced with high initial or variations of body weight, FM, FFM and BMI.

Brantlov et al. (2017) conducted a systematic review to study the degree to which BIA publications conducted in healthy pediatric populations (aged 0-17 years) were standardized. Internationally recognized electronic databases and hand searching of the reference lists was conducted to identify relevant publications. The review was limited to lead-type BIA devices for whole-body, segmental- and focal impedance measurements. In total, 71 papers published between 1988 and 2016 were included. To evaluate the degree of standardization of the papers, a recently published review detailing critical factors that may impact on BIA measurements in children was used as a model for structuring and extracting data. The results showed a general lack of BIA standardization, or its reporting, which hinders comparison of data between studies and could potentially lead to erroneous measurements. The authors concluded that if the BIA technique is accepted clinically for routine use in pediatric populations, but that there is a need for an increased focus on the importance of improved standardization and its reporting in future studies.

Haverkort et al. (2015) conducted a systematic review to explore the variability of empirical prediction equations used in BIA estimations and to evaluate the validity of BIA estimations in adult surgical and oncological patients. Studies developing new empirical prediction equations and studies evaluating the validity of BIA estimations compared with a reference method were included. Only studies using BIA devices measuring the entire body were included. To illustrate variability between equations, fixed normal reference values of resistance values were entered into the existing empirical prediction equations of the included studies. The validity was expressed by the difference in means between BIA estimates and the reference method, and relative difference in %. Substantial variability between equations for groups was found for TBW and FFM. BIA mainly under-estimated TBW (range relative difference -18.8% to + 7.2%) and FFM (range relative differences -15.2% to + 3.8%). Estimates of the FM demonstrated large variability (range relative difference -15.7% to + 43.1%). The authors concluded that application of equations validated in healthy subjects to predict body composition performs less well in oncologic and surgical patients. They suggested that BIA estimations can only be useful when performed longitudinally and under the same standard conditions.

Johnstone et al. (2014) conducted a study utilizing three groups of six obese men to evaluate the accuracy of bioelectrical impedance spectroscopy (BIS) in measuring the following: (FM, TBW and extracellular water (ECW) changes induced by different degrees of caloric deficit in obese men. Each group of men were instructed to participate in either (i) a total fast (for 6 days); (ii) a very low calorie diet (VLCD) (2.5 MJ/day for 3 weeks); or (iii) a low calorie diet (LCD) (5.2 MJ/day for 6 weeks). FM was measured using a 4-compartment (4-C) model. TBW and ECW were determined by dilution methods. TBW, ECW and FM were also assessed with BIS. Body weight loss in the fasting group was 6.0 ±1.3 kg over 6 days; the VLCD group lost 9.2 ±1.2 kg over 21 days and the LCD group lost 12.6 ±2.4 kg over 42 days. BIS underestimated FM changes (bias = -3.3 ±3.8 kg) and overestimated changes in TBW and ECW by + 1.8 ±4.8 kg and + 2.3 ±6.4 kg,

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respectively. The measurement error was consistently larger in the fasting group and the magnitude of the bias is greater with greater weight loss.

Widen et al. (2014) attempted to provide validation of BIA. The purpose of the study was to measure the TBW and percent body fat before and 12 months after bariatric surgery. The findings showed that the T0 to T12 median (IQR) change in deuterium TBW and 3C % fat was -6.4 L (6.4 L) and -14.8% (13.4%), respectively. There were no statistically significant differences between deuterium and BIA determined TBW [median (IQR) difference: T0 -0.1 L (7.1 L), p = 0.75; T12 0.2 L (5.7 L), p = 0.35; ∆ 0.35 L (6.3 L), p = 1.0]. Compared with 3C, BIA underestimated % fat at T0 and T12 [T0 -3.3 (5.6), p < 0.001; T12 -1.7 (5.2), p = 0.04] but not change [0.7 (8.2), p = 0.38]. Except for % fat change, Bland-Altman plots indicated no proportional bias. However, 95% limits of agreement were wide (TBW 15-22 L % fat 19-20%). According to the authors, BIA may be appropriate for evaluating group level response among severely obese adults. The authors state that clinically meaningful differences in the accuracy of BIA between individuals exist.

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Code	Description
0394T	High dose rate electronic brachytherapy, skin surface application, per fraction, includes basic dosimetry, when performed
0395T	High dose rate electronic brachytherapy, interstitial or intracavitary treatment, per fraction, includes basic dosimetry, when performed

High dose rate electronic brachytherapy is unproven and not medically necessary for treating all indications due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Traditional brachytherapy refers to the placement of radioactive sources on or inside the cancer tissues. Based on the type of sources, brachytherapy can be classified as radionuclide and electronic brachytherapy. Electronic brachytherapy is a form of radiotherapy that delivers a very high dose of radiation inside or very close to the cancer tissues. These devices utilize a miniaturized X-ray source to deliver radiation at relatively high dose rates to the target volume. Electronic brachytherapy eliminates some of the accidents related to radionuclide brachytherapy such as loss of sources, radiation leakage in off state, transportation accidents and radioactive waste. It finds wide applications in the treatment of cancers including skin, breast, endometrium, cervix and spinal metastasis. Electronic brachytherapy is a promising technology of the future and could potentially replace radionuclide brachytherapy (Ramachandran 2017).

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Breast Cancer

National Comprehensive Cancer Network (NCCN) guidelines on breast cancer do not specifically address electronic brachytherapy (NCCN, 2024).

An American Brachytherapy Society consensus statement states the following: In light of a randomized trial in breast showing higher rates of recurrence and the lack of prospective data with mature follow up with other sites, as well as concerns regarding dosimetry, it is not recommended that electronic brachytherapy be utilized for accelerated partial breast irradiation, non-melanomatous skin cancers, or vaginal cuff brachytherapy outside prospective clinical trials at this time (ABS 2019).

An ECRI product brief found the evidence inconclusive for electronic brachytherapy (Axxent) as an adjuvant treatment for breast cancer. Randomized controlled trials comparing electronic brachytherapy with external beam radiation therapy and conventional brachytherapy are needed (ECRI, 2019).

A National Institute for Health and Care Excellence (NICE) report concluded that there is a lack of robust evidence evaluating the Axxent electronic brachytherapy system for treating early-stage breast cancer. Key uncertainties around the evidence are that the available studies include patients for whom the technology is not recommended by the manufacturer, and there is a lack of long-term follow-up evidence (NICE, 2016).

Dooley et al. (2011) describe patient, tumor, and surgical characteristics from a prospective, nonrandomized, multicenter study of electronic brachytherapy to deliver radiation to the tumor bed post-lumpectomy in eligible patients with breast cancer. Forty-four patients were treated with APBI using the Axxent electronic brachytherapy system following lumpectomy. The prescription dose of 34 Gy in 10 fractions over 5 days was delivered in 42 of 44 participants. The authors concluded that early-stage breast cancer can be treated with breast conserving surgery and APBI using electronic brachytherapy. Treatment was well tolerated, and these early outcomes were similar to the early outcomes with iridium-based balloon brachytherapy. This study is limited by small numbers and lack of randomization or comparison of outcomes to established radiation therapy techniques.

Mehta et al. (2010) completed a phase IV prospective, non-randomized trial of 44 patients to evaluate the safety and device effectiveness of the Axxent electronic brachytherapy system. The study evaluated 44 patients. The subjects were over 50 years of age, had completely resected invasive ductal carcinoma or ductal carcinoma in situ and negative microscopic margins of equal to or greater than 1 mm. The treatment was completed with a balloon applicator with treatments twice per day for 5 days. Treatment was successfully completed in 42/44 patients. All 44 patients were followed up at one month, 43/44 followed up to 6 months and 36 of the 44 participants completed follow up at 1 year. No tumor recurrences were reported up to 1 year. The infection rate was high at 11%. Cosmetic evaluation was rated as good or excellent (minimal or no identifiable effects of radiation). The authors concluded that the electronic brachytherapy system performed as expected with similar acute toxicity profiles to other high-rate approaches in patients with resected, early breast cancer with no serious acute toxicities or serious AEs. This study is limited by small numbers, short-term follow-up and lack of randomization or comparison of outcomes to established radiation therapy techniques.

Skin Cancer

NCCN guidelines on basal cell skin cancer (2025a), squamous cell skin cancer (2025d), and cutaneous melanoma (2025c) state that there are insufficient long-term safety and efficacy data to support the routine use of electronic surface brachytherapy.

An active multicenter, interventional clinical trial is currently underway to study electronic skin surface brachytherapy for cutaneous basal cell and squamous cell carcinoma using a new brachytherapy system (Nucletron's Esteya Electronic Skin Surface Brachytherapy System). The study includes 36 individuals with early stage basal or squamous cell carcinoma, and is assessing the efficacy, safety, cosmetic results, and effect of this new system on quality of life. The trial is expected to be completed in May 2025. ClinicalTrials.gov ID NCT02131805.

An ECRI clinical evidence assessment for electronic brachytherapy (EBT) for nonmelanoma skin cancer (NMSC) found that the evidence for this procedure is of very low quality, and is inconclusive. The assessment states that while EBT appears to be safe for use in NMSC, the available evidence does not sufficiently show long-term efficacy or safety data, nor does it show its comparison to using Mohs surgery or other radiation procedures. Additional research consisting of large randomized controlled trials involving Mohs surgery and long-term follow up are needed (ECRI, 2023).

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An American Brachytherapy Society consensus statement for skin cancer brachytherapy states that **s**tudies of electronic brachytherapy for keratinocyte carcinoma (previously nonmelanoma skin cancer) (KC) are promising and the current recommendation is that it be used in prospective registries or clinical trials (ABS 2020).

An ECRI clinical evidence assessment found the evidence inconclusive for electronic brachytherapy [using Axxent® Electronic Brachytherapy (eBx®) System] as a treatment for nonmelanoma skin cancer. Low-quality evidence showed no differences in outcomes between electronic brachytherapy (Axxent) and Mohs surgery, but the studies were at very high risk of bias. Randomized controlled trials comparing Axxent with Mohs surgery or other brachytherapy systems are needed to validate findings and assess long-term outcomes (ECRI, 2021).

American Academy of Dermatology guidelines of care for the management of primary cutaneous melanoma state that there is no data to support the use of electronic surface brachytherapy for treating cutaneous melanoma (AAD 2018c).

American Academy of Dermatology guidelines of care for the management of nonmelanoma skin cancers state that there is insufficient evidence to make a recommendation on the routine use of electronic surface brachytherapy in the treatment of basal cell carcinoma or cutaneous squamous cell carcinoma. Long-term safety and effectiveness data are lacking (AAD 2018a,b).

In a comparative effectiveness review on treatments for basal cell and squamous cell carcinoma of the skin, the Agency for Healthcare Research and Quality (AHRQ) concluded that there is no clear evidence to support the benefits of brachytherapy for these indications (Drucker et al., 2017).

An American Academy of Dermatology position statement on electronic surface brachytherapy for BCC and SCC (2016, revised 2021) presents the following guiding principles:

- Based on current evidence, surgical management remains the most effective treatment for basal cell and squamous cell carcinomas, providing the highest cure rates.
- Additional research is needed on electronic surface brachytherapy, particularly on long term outcomes.
- Electronic surface brachytherapy may be considered as a secondary option for the treatment of basal cell and squamous cell carcinomas in special circumstances and after the benefits and risks of treatment alternatives have been discussed with the patient.

Ballester-Sánchez et al. (2016) assessed outcomes from two consecutive prospective, single-center, non-randomized, pilot studies using different radiation doses of electronic brachytherapy with the Esteya® system for treating superficial and nodular basal cell carcinoma. Twenty patients were treated in each study. Group 1 was treated with 36.6 Gy in 6 fractions of 6.1 Gy, and Group 2 with 42 Gy in 6 fractions of 7 Gy. Cure rate, acute toxicity and late toxicity related to cosmesis were analyzed. Group 1 achieved a 90% clinical cure rate at 1 year. Group 2 achieved a 95% clinical cure rate at 1 year. The differences in acute toxicity and cosmetic results between the two treatment groups were not statistically significant. The authors noted that the role of electronic brachytherapy in the treatment of basal cell carcinoma is still to be defined. Both studies were limited by small numbers, short-term follow-up and lack of randomization or comparison of outcomes to established surgical treatment (e.g., Mohs surgery).

Delishaj et al. (2015) retrospectively evaluated 57 lesions in 39 elderly patients affected with nonmelanoma skin cancer (NMSC) treated with high-dose rate (HDR) brachytherapy using a Valencia applicator to estimate tumor control, toxicity, and cosmetic outcomes. All lesions had a diameter ≤ 25 mm (median: 12.5 mm) and a depth ≤ 4 mm. Twelve lesions were treated as supplementary therapy after surgery treatment. The total dose was chosen based on the lesion dimensions, age, and performance status. The dose prescription was delivered as two/three fractions a week, with a minimum interval of 48 hours between fractions. After 12 months median follow-up, 55 lesions (96.5%) completely regressed and only two lesions persisted. No recurrences were observed, and the treatment was very well tolerated with no Grade 3 or higher acute or late toxicities. The authors concluded that this treatment was safe and effective in elderly patients. The limitation of this study compared with studies of more established treatments for NMSC was the relatively short follow-up and small number of patients due to the age of the patients (mean age 84 years) as well as comorbidities.

Other Indications

Clinical evidence evaluating the safety and efficacy of high dose rate electronic brachytherapy for treating other indications is limited at this time.

Hitova-Topkarova et al., (2023) conducted a systematic literature review on the use of electronic brachytherapy for endometrial and cervical cancers. Out of nine selected studies, 72 individuals “received treatment with AxxentXoft vaginal applicator, 29 were treated with the Intrabeam vaginal applicator, and eight with AxxentXoft cervical applicator”. The authors stated that while more clinical data is needed, these studies showed electronic brachytherapy as safe and well

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tolerated, and “has the potential to achieve equivalent tumor control while minimizing bowel and urinary toxicity thus improving the quality of life” for gynecological cancers. A limitation of this study is the type of study, and small patient population.

A 2021 ECRI clinical evidence assessment regarding the Axxent Electronic Brachytherapy System (iCAD, Inc.), focused on its safety and effectiveness in treating gynecological cancers and how it compares with conventional brachytherapy. Seven case series were assessed, all of which were at high risk of bias, due to 2 or more of the following: small study size, retrospective design, single-center focus, and lack of parallel controls. Additionally, some studies enrolled patients with various types and stages of gynecologic cancers or used external beam radiation therapy (EBRT) in addition to electronic brachytherapy (EBT), or 192Ir high-dose-rate (HDR) brachytherapy before EBT treatment, both of which limits evidence interpretation. One study enrolled patients both with and without previous chemotherapy, further confounding results. Furthermore, two studies may have had patient overlap, but reported on different outcomes of interest. It was concluded that the evidence is inconclusive and does not demonstrate that electronic brachytherapy with the Axxent system improves outcomes in women with gynecological cancers better than conventional brachytherapy and large trials that assess its effectiveness in each type of cancer are needed.

An American Brachytherapy Society consensus statement states the following: In light of a randomized trial in breast showing higher rates of recurrence and the lack of prospective data with mature follow up with other sites, as well as concerns regarding dosimetry, it is not recommended that electronic brachytherapy be utilized for accelerated partial breast irradiation, non-melanomatous skin cancers, or vaginal cuff brachytherapy outside prospective clinical trials at this time (ABS 2019).

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Code	Description
0397T	Endoscopic retrograde cholangiopancreatography (ERCP), with optical endomicroscopy (List separately in addition to code for primary procedure)
43206	Esophagoscopy, flexible, transoral; with optical endomicroscopy
43252	Esophagogastroduodenoscopy, flexible, transoral; with optical endomicroscopy
88375	Optical endomicroscopic image(s), interpretation and report, real-time or referred, each endoscopic session

Confocal laser endomicroscopy (CLE), also known as confocal fluorescent endomicroscopy and optical endomicroscopy is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Optical endomicroscopy also referred to as confocal endomicroscopy (CEM) or optical biopsy is an endoscopic procedure that is being used to provide high-resolution images of the mucosal layer of the gastrointestinal (GI) tract. This technique can be performed with probe-based or needle-based systems that pass through the accessory channel of an endoscope or with integrated endoscopic systems. Endomicroscopy can potentially expand the imaging capabilities of flexible endoscopy by obtaining optical biopsies (method that uses the interaction of light and tissue to make a diagnosis rather than using tissue excision). CEM has been used in individuals suspected of colon cancer, gastric cancer, celiac disease, pancreaticobiliary disease, Barrett's esophagus (BE) and for the identification of Helicobacter pylori infection.

Tanisaka et al. (2024) conducted a case series to evaluate the feasibility and safety of probe-based confocal laser endomicroscopy (pCLE) under direct cholangioscopic visualization for biliary strictures that cannot be definitively diagnosed by endoscopic retrograde cholangiopancreatography (ERCP). The authors indicated that there were no previous studies that evaluated pCLE under direct cholangioscopic visualization for biliary strictures undiagnosed by ERCP using fluoroscopy. They evaluated this in 3 different cases. Results indicated that pCLE findings provided accurate diagnoses in three cases, with no adverse events reported. In case 1, a protruding lesion was clearly detected through POCS, and pCLE findings indicated malignancy. In cases 2 and 3, malignancy could not be ruled out during initial ERCP, so pCLE under direct cholangioscopic visualization was performed, showing no signs of malignancy. The combined pCLE and POCS findings confirmed benign strictures. Since the specific cause of the biliary stricture in case 2 remains unidentified, the reviewers will continue to monitor the individual closely. This case series has several limitations; the small number of cases makes it impossible to demonstrate the efficacy of pCLE under cholangioscopy for diagnosing biliary stricture. Second, while the cases suggest the feasibility of pCLE under direct cholangioscopic visualization for biliary strictures not definitively diagnosed through ERCP using fluoroscopy, future research should evaluate biliary strictures not diagnosed through ERCP using POCS. The authors conclude that pCLE under direct cholangioscopic visualization for indeterminate biliary strictures appears to be feasible and safe, further large sample studies are needed to confirm its effectiveness in making an accurate diagnosis.

The 2023 ASGE guideline on the role of endoscopy in the diagnosis of malignancy in the biliary stricture of undetermined etiology: summary and recommendations indicated that CLE is difficult to master. Therefore, its widespread adoption is likely limited in the near future. Higher quality data is needed with future studies addressing the role of novel imaging modalities such as CLE in the diagnosis of malignancy in biliary strictures of undetermined etiology. (Fujii-Lau et al.,2023).

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In a 2023 Hayes technology assessment on pCLE for surveillance of BE, it was determined that there was an overall low-quality and insufficient evidence. The conclusion indicated that pCLE is relatively safe but has not demonstrated significant enhancements in diagnostic accuracy or in guiding the management of BE (Updated 2024).

Canakis et al. (2022) conducted a systematic review and meta-analysis to determine the diagnostic performance of pCLE in detecting GC. Seven studies were included in the final analysis, involving a total of 567 individuals (average age 61.7 years, 364 males) with 611 gastric lesions. Most of these studies were conducted in Asia, specifically in South Korea, China, and Japan, with one study conducted in Brazil. Pooled performance metrics of pCLE included a sensitivity of 87.9% (95%CI 81.4-92.4; p < 0.001; I2 = 0%), specificity 96.5% (95%CI 91.5-98.6; p < 0.001; I2 = 51.84%), and an accuracy of 94.7% (95%CI 89.5-97.4; p < 0.001; I2 = 65.44%).Although a standardized system exists, the widespread adoption of pCLE for GC has faced several challenges. The learning curve for pCLE is steep, as diagnostic accuracy relies on experience and training. While pCLE is easier to learn for colon polyps and inflammatory bowel disease, GC lesions pose unique challenges due to gastric secretions and precise probe positioning. Additionally, the low incidence of early GC in Western countries complicates training endoscopists in pCLE use. The potential to supplement or replace physical biopsies with pCLE is promising therapeutically. The authors indicate that this analysis has several limitations. The studies were conducted by experienced clinicians at high-volume centers in Asia, where GC incidence is higher. These results may not be generalizable to countries with low GC incidence. Since pCLE cannot survey the entire stomach, endoscopists must identify areas of concern, making the diagnostic yield of pCLE alone less relevant clinically. Additionally, direct comparisons between pCLE and other endoscopic methods, like narrow-band imaging, have not been extensively studied. In summary, pCLE shows promise for real-time diagnosis of lesions suspicious for GC, with high diagnostic accuracy demonstrated in the current study. However, larger randomized controlled trials are necessary to validate these results before it can be widely adopted.

Mi et al. (2022) conducted a meta-analysis to assess the accuracy of pCLE to diagnose indeterminate biliary strictures and to compare pCLE and ERCP with brush pathology. Tissue sampling by ERCP is routinely performed to evaluate indeterminate biliary strictures. Eighteen studies evaluated the accuracy of pCLE diagnosis of indeterminate biliary strictures comprising a total of 750 lesions. The summary estimates for the pCLE diagnosis of indeterminate biliary strictures were: sensitivity 0.88 [95% confidence interval (CI), 0.84-0.91]; specificity 0.79 (95% CI 0.74-0.83); and Diagnostic Odds Ratio (DOR) 24.63 (95% CI 15.76-38.48). The summary estimates for tissue sampling by ERCP diagnosis for indeterminate biliary strictures were: sensitivity 0.54 (95% CI 0.49-0.59); specificity 0.96 (95% CI 0.94-0.98); and DOR 11.31 (95% CI 3.90-32.82). The area under the sROC curve of pCLE diagnosis of indeterminate biliary strictures is 0.90 higher than 0.65 of tissue sampling by ERCP. Study limitations include indicate that most of the studies were retrospective studies, and there was potential selective bias needing further prospective studies to confirm. Then, the inadequate quality of some of the included studies may affect the results of the meta-analysis. The authors also note that some individuals in some of the included studies were followed up rather than pathology as the gold standard. Overall, the authors indicate that pCLE is a reliable and accurate method for diagnosing indeterminate biliary strictures, especially when reaching the biliary strictures by cholangioscopy. With the development of diagnostic classifications and advances in technology, pCLE will improve the accuracy of diagnosing indeterminate biliary strictures. The pCLE is a promising technique that provides real-time microscopic images of the bile ducts to make an accurate diagnosis of indeterminate biliary strictures rather than the current ERCP by tissue sampling that comes with limitations.

The ACG updated 2022 clinical guideline on Diagnosis and Management of Barrett's Esophagus offers recommendations for the diagnosis, screening, surveillance, and endoscopic and medical therapy of Barrett’s Esophagus. A variety of advanced imaging techniques have been developed in an effort to improve the detection of dysplasia and esophageal adenocarcinoma (EAC) and thereby improve on the Seattle protocol in combination with high-definition white light endoscopy. CLE uses blue laser light to illuminate the esophageal tissue after intravenous injection of fluorescein. This allows for real-time in vivo imaging at high magnification to take optical targeted biopsies. To date, two systems have been developed; endoscope and probe based, with only the second still being commercially available. The most recent systematic review and meta-analysis of 7 studies of 473 individuals who combined both probe-based and endoscope-based systems found a pooled sensitivity for per patient analysis when compared with histopathology of 89% (95% CI 0.82–0.94; I^2 = 31.6%) and specificity of 83% (95% CI 0.78–0.86; I^2 = 90.1%). While results are promising, there are multiple limitations, including the need for intravenous fluorescein, training in image interpretation, and time to complete the examination. Given that many of these studies were performed in centers with a high prevalence of dysplasia/neoplasia, the relevance of these data to a general observation population is unknown. Despite the limitations, in centers with a high prevalence of neoplasia or dysplasia, CLE may be helpful in targeting biopsies and guiding therapy, although the value above that of high-definition white light and electronic chromoendoscopy is unclear.

The AGA in a 2022 Clinical Practice Update on advances and innovation regarding the screening and surveillance of Barrett’s esophagus provided the best practice advice indicating that advanced imaging technologies may be used as adjunctive imaging techniques to identify dysplasia. The panel was supportive of the need to have improved imaging

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technologies to better identify areas of dysplasia and early cancer. Technologies considered for this discussion included CLE or volumetric laser endomicroscopy. A meta-analysis of 14 studies of 789 individuals with 4047 lesions found CLE had a per-lesion analysis pooled sensitivity and specificity of 77% [95% confidence interval (CI), 0.73–0.81] and 89% (95% CI, 0.87–0.90), respectively. A separate meta-analysis of 5 studies involving 251 individuals assessing within-patient comparisons of narrow band imaging and CLE found the pooled additional detection rate of CLE for per-lesion detection of neoplasia in individuals with BE was 19.3% (95% CI, 0.05–0.33), but a comparable per-patient pooled sensitivity and specificity. Volumetric laser endomicroscopy, though not currently available commercially, has introduced several new advances with regards to imaging in BE, including laser marking and the interpretation of imaging using artificial intelligence. The panelists felt strongly this was an important area where further improvement is needed, but that the use of these techniques was not required for a high-quality exam and the data to date did not support its routine use. Nevertheless, the panel felt these technologies were promising and supported potential benefits in certain cases while being performed at expert centers.

Vithayathil et al (2022) conducted a randomized crossover trial with the primary aim to evaluate the diagnostic accuracy for dysplasia of autofluorescence imaging (AFI)-guided pCLE compared with high-resolution white-light endoscopy (HRWLE) and Seattle protocol biopsies in individuals with BE and no endoscopically visible lesions. The secondary aim was to evaluate the added diagnostic value of molecular biomarkers, the time to perform standard and experimental procedures, and the acceptability by individuals of optical dysplasia diagnosis. A total of 154 individuals were recruited, of whom eight were excluded based on presence of clear macroscopic lesions consistent with BE-related neoplasia upon first endoscopy. A total of 134 patients completed both arms of the study, with crossover occurring after a 6-to-12-week interval. Endoscopists were blinded to the endoscopy and histology results of the pretrial endoscopy and other study arm. In the per-lesion analysis, optical diagnosis by CLE had a sensitivity and specificity for high-grade dysplasia (HGD)/intramucosal cancer (IMC) of 69.2% and 73.2%, respectively. In the per-patient analysis, there was no difference in the sensitivity of CLE for dysplasia compared with Seattle protocol for HGD/IMC (76.5% for both; p = 1.00) or all grades of dysplasia (74.3% vs. 80.0%, respectively; p = .48). The specificity of CLE was 60.7% for HGD and 66.7% for all grades of dysplasia. Use of a 3-biomarker panel consisting of one or more of optical dysplasia on CLE, aberrant p53 on immunohistochemistry, and/or aneuploidy on flow cytometry was associated with a per-patient sensitivity and specificity of 94.1% and 49.6% for HGD and 91.4% and56.6% for all grades of dysplasia, respectively. Study limitations included the following; the referral histology within the prior 12 months was only available in 64.2% of cases, secondly based on the crossover study design, it could not be excluded that prior biopsy sites may have appeared as irregularities on second endoscopy, variations in endoscopists indicated that two had a low sensitivity for detecting dysplasia, and lastly, the results may not be generalized across the general public since the study was only performed at two high volume tertiary referral centers. The authors concluded that CLE has similar diagnostic accuracy for dysplasia compared with standard Seattle protocol endoscopy. In addition, the trial provides a methodological model for future studies investigating the endoscopic diagnosis of flat dysplasia. The addition of the use of molecular biomarkers could improve diagnostic accuracy.

Park et al. (2019) conducted a randomized controlled trial assessing pCLE and if this procedure could increase the yield of endoscopic biopsy for GC compared with white light endoscopy (WLE). There was a total of 30 gastric cancers and 61 undifferentiated-type GCs were examined in the pilot and confirmatory studies, separately. All lesions in the pCLE and WLE groups were initially evaluated through WLE. In the pCLE group, lesions were further examined through pCLE. In the pilot study, five and three biopsy specimens were obtained for histopathological examination and tumor marker analysis, respectively. In the confirmatory study, six biopsy specimens for histopathological evaluation were obtained. The proportion of cancer cells in biopsy samples of poorly differentiated adenocarcinoma or signet ring cell carcinoma was higher in the pCLE group than in the WLE group in both the pilot and confirmatory studies (pilot: median proportion, 65% vs 30%, p = 0.010; confirmatory: mean ±standard deviation, 49.5 ±29.3 vs 29.3 ±13.7, p = 0.002). The expression ratio of tumor markers including carcinoembryonic antigen, GW112, HOX transcript antisense RNA, and H19 tended to be higher in the pCLE group than in the WLE group. Although the proportion of cancer cells in biopsy samples was higher in the pCLE-targeted biopsy than in the WLE-targeted biopsy, the unsuccessful examination in two individuals with small early GC, may demonstrate a limitation. Other limitations included different biopsy samples were used for histopathological examination of tumor markers there may be a learning curve for the pCLE examination, and lack of data on individuals' outcomes, limiting the conclusions that can be drawn on the clinical utility of this technology. Results will need to be validated with further studies on this new emerging technique.

The 2019 ASGE guideline on screening and surveillance in individuals with BE is based on systematic reviews of the evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology. In individuals with BE undergoing surveillance, the authors suggest against routine use of CLE compared with WLE with Seattle protocol biopsy sampling (conditional recommendation, low quality of evidence).

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Xiong et al (2017) performed a systematic literature review and meta-analysis to assess the accuracy of within-patient comparisons of narrow band imaging (NBI) and (CLE) for diagnosis of high-grade dysplasia (HGD)/esophageal adenocarcinoma (EAC) in individuals with BE. Five studies involving 251 individuals, reported within-patient comparisons of NBI and CLE, were eligible for meta-analysis. Compared with NBI, pooled additional detection rate of CLE for per-lesion detection of neoplasia in individuals with BE was 19.3% (95% CI: 0.05—0.33, I2 = 74.6%). The pooled sensitivity of NBI was 62.8% (95% CI: 0.56—0.69, I2 = 94.6%), which was lower (not significantly) than that of CLE (72.3%, 95% CI: 0.66—0.78, I2 = 89.3%). The pooled specificity of NBI and CLE were similar [85.3% (95% CI: 0.84—0.87, I2 = 92.1%) vs 83.8% (95% CI: 0.82—0.85, I2 = 96.8%)]. This systematic review and meta-analysis have shown that when compared with NBI, CLE significantly increased the per-lesion detection rate of esophageal neoplasia, HGD and EAC, in BE. Whether CLE is superior to NBI in neoplasia detection at per-patient level and in terms of patient outcomes needs to be further investigated.

In a 2016 systematic review and meta-analysis, the position of the American Society for Gastrointestinal Endoscopy (ASGE) is that chromoendoscopy, including CLE has demonstrated efficacy for surveillance of individuals with nondysplastic BE. Because most of the studies evaluated were performed by practitioners at large centers with limited data regarding experience by specialists in the general community settings, they endorse this technology when performed by endoscopists proficient in these techniques. Other advanced imaging modalities hold promise for BE surveillance, but further studies are needed.

A systematic review and meta-analysis was conducted by Fugazza et al. (2016), analyzing the current literature on CLE and evaluating the applicability and diagnostic yield of CLE in individuals with GI and pancreatobiliary diseases. Both prospective and retrospective studies were eligible, identifying 102 studies for inclusion conducted in 16 different countries between 2004 and 2015 (n = 6943). The meta-analysis demonstrated that combining CLE with endoscopic retrograde cholangiopancreatography (ERCP) yields high sensitivity (90%) in the assessment of biliary strictures, demonstrating it as a useful tool for differentiating benign from malignant biliary strictures in individuals with biliary neoplasia. CLE for the surveillance of BE does not appear to be sensitive enough to replace current standard of care such as the Seattle biopsy protocol. For the stomach and duodenum, CLE demonstrated high sensitivity, specificity, accuracy, and positive and negative predictive values in comparison with both histopathology and other endoscopic techniques (e.g., white light endoscopy, narrow band imaging, and chromoendoscopy). However, these data were used with caution based on a limited number of publications. CLE is associated with a pooled sensitivity and specificity of 83% and 90%, respectively, in the detection of colorectal neoplasms and malignant foci in polypoid lesions. Graft-versus-host disease, infectious colitis and irritable bowel syndrome have been less extensively studied, but outcomes are promising. Limitations to the studies reviewed included the total evidence per organ was limited and often too low to draw definitive conclusions, as well as high heterogeneity, and that studies were primarily conducted in specialized centers. In spite of these limitations, the authors concluded that CLE has unique advantages and can provide real-time histological examination during diagnostic and therapeutic procedures. Further clinical trials are needed to assess the applicability and implementation of CLE in routine clinical practice, as currently very few such studies exist.

In a systematic review and meta-analysis, Su et al. (2013) assessed the effectiveness of CLE for discriminating colorectal neoplasms from non-neoplasms. The secondary aim of the review was to compare the efficacy of endomicroscopy and chromoendoscopy for diagnosing colorectal neoplasms. Pooled sensitivity and specificity were compared using univariate regression analysis according to prespecified subgroups. Pooled relative risk was computed to compare the accuracy of endomicroscopy and chromoendoscopy. Fifteen studies (published between 2000 and 2012) involving 719 individuals and 2290 specimens were included in the analysis. The pooled sensitivity of all studies was 0.94, and pooled specificity was 0.95. Real-time CLE yielded higher sensitivity and specificity than blinded CLE. For real-time CLE, endoscopy-based systems had better sensitivity and specificity than probe-based systems. CLE yielded equivalent accuracy compared with magnifying virtual chromoendoscopy and magnifying pigment chromoendoscopy. The authors concluded that CLE is comparable to colonoscopic histopathology in diagnosing colorectal neoplasms, and that CLE is better when used in conjunction with conventional endoscopy. According to the authors, this review was limited by the relatively high heterogeneity presented across the 15 enrolled studies. The authors stated that there is a need for prospective randomized studies to obtain unbiased results on the effectiveness of CLE along with standardization of the procedure and a comparison between this strategy and conventional colonoscopy.

In a prospective, multicenter, RCT, Wallace et al. (2012) assessed if use of pCLE in addition to high-definition white light (HDWL) could aid in determination of residual BE. After an initial attempt at ablation, individuals were followed-up either with HDWL endoscopy or HDWL plus pCLE, with treatment of residual metaplasia or neoplasia based on endoscopic findings and pCLE used to avoid overtreatment. The study was closed after the interim analysis due to low conditional power resulting from lack of difference between groups as well as higher-than-expected residual BE in both arms. After enrollment was halted, all individuals who had been randomized were followed to study completion. Among the 119 individuals with follow-up, there was no difference in the proportion of individuals achieving optimal outcomes in the two

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groups. Other outcomes were similar in the 2 groups. The authors concluded that this study yields no evidence that the addition of pCLE to HDWL imaging for detection of residual BE or neoplasia can provide improved treatment.

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Code	Description
0408T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator with transvenous electrodes
0409T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator only
0410T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; atrial electrode only
0411T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; ventricular electrode only

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Code	Description
0412T	Removal of permanent cardiac contractility modulation system; pulse generator only
0413T	Removal of permanent cardiac contractility modulation system; transvenous electrode (atrial or ventricular)
0414T	Removal and replacement of permanent cardiac contractility modulation system pulse generator only
0415T	Repositioning of previously implanted cardiac contractility modulation transvenous electrode, (atrial or ventricular lead)
0416T	Relocation of skin pocket for implanted cardiac contractility modulation pulse generator
0417T	Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, including review and report, implantable cardiac contractility modulation system
0418T	Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording and disconnection per patient encounter, implantable cardiac contractility modulation system
K1030	External recharging system for battery (internal) for use with implanted cardiac contractility modulation generator, replacement only

Cardiac contractility modulation (CCM), using an implantable device, is generally unproven and not medically necessary for treating chronic heart failure (HF) due to insufficient quality evidence of safety and/or efficacy. Future robust randomized controlled trials (RCTs) are warranted. However, based on review on a case-by-case basis, CCM may be covered for individuals where medical director review indicates potential benefit.

Clinical Evidence

Cardiac contractility modulation (CCM) signals are nonexcitatory electrical signals delivered during the cardiac absolute refractory period (between beats) that enhance the strength of cardiac muscular contraction. Cardiac contractility modulation signals are provided by a pacemaker-like device that is implanted under the skin of the upper chest, along with electrical leads that are placed in the heart's right ventricle through the veins. After the procedure, the physician programs the delivery of CCM® therapy for each individual and activates the device. The implanted device then sends precisely calibrated and timed electrical pulses to the heart muscle. In contrast to a pacemaker or a defibrillator, the system is designed to modulate the strength of contraction of the heart muscle rather than the rhythm (Impulse Dynamics website).

The Optimizer™ implantable CCM system received Food and Drug Administration (FDA) premarket approval (P180036) on March 21, 2019. Based on this FDA approval, the device is indicated to improve six-minute hall walk distance, quality of life (QOL), and functional status of individuals with New York Heart Association (NYHA) Class III HF who remain symptomatic despite guideline-directed medical therapy, who are in normal sinus rhythm, are not indicated for cardiac resynchronization therapy (CRT), and have a left ventricular ejection fraction (LVEF) ranging from 25% to 45%. In January 2025, the Optimizer Smart Mini and Lite Systems were under a Class II device recall as CCM therapy may cease to be delivered if the device incorrectly detects a charging error. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P180036. (Accessed April 11, 2025)

The American College of Cardiology (ACC), American Heart Association (AHA), American Society of Echocardiography (ASE), Heart Failure Society of America (HFSA), Heart Rhythm Society (HRS), Society for Cardiovascular Angiography and Interventions (SCAI), Society of Cardiovascular Computed Tomography (SCCT), and Society for Cardiovascular Magnetic Resonance (SCMR) Appropriate Use Criteria (AUC) was developed to evaluate clinical scenarios where implantable cardioverter defibrillators (ICDs), CRT, CCM, and pacing therapies are often considered. According to the AUC, CCM has shown promise as a treatment for those with chronic HF with reduced ejection fraction, particularly for individuals who are not candidates for CRT. The AUC recommendation of "May Be Appropriate" was given for individuals who are not a candidate for CRT [QRS < 130 milliseconds (ms)], NYHA functional class of II and III – IV, with a LVEF 25% to 45%. The authors noted there are currently no practice guideline recommendations for CCM and that although CCM offers potential benefits in improving heart function and QOL, further research is necessary to assess long-term clinical outcomes and the effects of CCM on reverse remodeling in larger patient groups (Russo et al., 2025).

The ACC decision pathway for management of HF with preserved ejection fraction states CCM benefits remain ambiguous and should be considered only within the context of clinical trials (Kittleson et al. 2023).

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The AHA/ACC/HFSA developed a guideline for the management of HF intended to provide patient-centric recommendations for clinicians to prevent, diagnose, and manage patients with HF. The guideline text states that CCM has been associated with augmentation of left ventricular contractile performance. Cardiac contractility modulation is FDA-approved for patients with NYHA class III with LVEF of 25% to 45% who are not candidates for CRT. Four RCTs have shown benefits in exercise capacity and QOL but, as of yet, no benefits in death or hospitalizations. Most patients in these trials had class III congestive heart failure. The guideline, however, does not provide any specific recommendation for the use of CCM but lists CCM as one of the technologies that should be further studied in the evidence gap section of the guideline (Heidenreich et al. 2022).

Linde et al. (2022) conducted a prospective, multicenter, single-arm, pilot study of CCM in individuals with heart failure with preserved ejection fraction (HFpEF). The study included 47 individuals with HFpEF and NYHA class II or III who were followed for 24 weeks after CCM device implantation. Individuals returned for follow-up visits at two, twelve, and twenty-four weeks. The primary efficacy endpoint [mean change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score] improved by18.0 ±16.6 points ($p < 0.001$) and there was an event-free rate of 93.6% for the primary safety endpoint (device- and procedure-related complications). The authors noted no obvious impact on safety and significant improvement in observed health status. The authors suggest CCM use may be promising and benefit individuals with HFpEF, although future RCTs with a longer follow-up time are recommended. Study limitations include small sample size and the single-arm design with lack of control group.

The 2021 European Society of Cardiology guideline for the diagnosis and treatment of heart failure notes that CCM was associated with a small improvement in exercise tolerance and QOL for patients with NYHA class III-IV HF, with an LVEF ≥ 25% to ≤ 45% and QRS duration < 130ms. However, the evidence was considered insufficient to support specific guideline recommendations for a reduction in mortality or hospitalization. The guideline recommended larger RCTs for CCM therapy (McDonagh et al., 2022).

Fastner et al. (2021) conducted an observational study comparing long-term therapeutic effects of CCM therapy in individuals with ischemic (ICM) versus non-ischemic cardiomyopathy (NICM). The functional parameters compared include LVEF, tricuspid annular plane systolic excursion (TAPSE), Kidney Disease Improving Global Outcomes (KDIGO) chronic kidney disease stage, and changes in NYHA class. Observed mortality rates at one and three years were compared to those predicted by the Meta-Analysis Global Group in Chronic (MAGGIC) HF risk score and observed mortality rates were compared between groups for the entire follow-up period. Between 2002 and 2019, 174 consecutive individuals with chronic HF and CCM device implantation were included in the analysis. LVEF was significantly higher in individuals with NICM after three years of CCM therapy (35 ±nine versus 30 ±nine percent; $p = 0.0211$), and after five years, also TAPSE of individuals with NICM was significantly higher (21 ±five versus 18 ±five%; $p = 0.0437$). There were no differences in other effectiveness parameters. Over the entire follow-up period, 35% of all individuals died; only in individuals with ICM was mortality lower than predicted at three years (35 versus 43%, $p = 0.0395$). The authors concluded that regarding improvement of biventricular systolic function, individuals with NICM appeared to benefit principally from CCM therapy. Limitations included the retrospective and observational nature of the study, and lack of control group receiving a different intervention.

Giallauria et al. (2020) conducted an individual data meta-analysis of all prospective RCTs of CCM versus control that measured functional capacity and/or QOL questionnaires in individuals with HF plus data from one single arm study. Peak oxygen consumption, six minute walk test distance and QOL measured by Minnesota Living with Heart Failure Questionnaire (MLWHFQ). Five trials were identified, four RCTs (n = 801) for all endpoints of interest and one single arm study. The analysis of individual participant data revealed that compared with control, CCM significantly improved functional capacity and HF-related QOL. Limitations include relatively young and predominantly male cohorts, individuals with permanent atrial fibrillation were excluded, and the studies analyzed differed in design limiting the ability to define representative results across different individual subgroups. The authors recommend larger, well-conducted RCTs using parallel double-blind designs in order to determine the effect of CCM on mortality and morbidity outcomes before CCM can be widely recommended. Studies in less compromised individuals with HF, more women and older individuals are also encouraged. [Kadish et al., (2011), Borggrefe et al., (2008), and Neelagaru et al., (2006), which were previously cited in this policy, were included in this meta-analysis. Abraham et al. 2018 was also included in this review].

An ECRI clinical evidence assessment compared the Optimizer Smart System use with that of optimal medical therapy (OMT) in individuals with (HF). The systematic review included four high-quality RCT and one study that was used as a comparison group to RCT. ECRI found the evidence to be somewhat favorable that the Optimizer is more effective than OMT for improving functional status and QOL in individuals with moderate to severe, chronic HF. The assessment found it was unclear whether Optimizer reduced mortality rates or HF-related hospitalization rates due to a high risk of bias in two of the studies which had a single-center focus and/or lack of randomization and blinding. Longer term follow up comparing

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Optimizer with OMT with a focus on mortality and HF-related hospitalization is recommended. The January 2025 update resulted in a change in rating from “favorable” to “raises concerns” rating. (ECRI, 2019; updated 2025).

A Hayes Health Technology Assessment reviewed the use of CCM with the Optimizer Smart System as an adjunct to OMT in individuals with NYHA functional class III HF. Four fair quality RCTs, five poor-quality studies and one very poor-quality cohort study were identified that evaluated the safety and efficacy of CCM using the Optimizer Smart System for management of HF and were included in the review. The studies compared OMT alone with CCM therapy plus OMT. The review found there was a low-quality body of evidence suggesting that CCM with the Optimizer Smart System as an adjunct to OMT may improve outcomes related to cardiopulmonary stress tests, functional class severity and QOL. The clinical significance of these findings and whether the effect is significantly better than with OMT alone remains uncertain. In individuals with HF and an ejection fraction of ≤ 25%, limited evidence suggests that CCM therapy may be less effective. Additional well-designed comparative studies are recommended to determine whether CCM with the Optimizer Smart System is safe and more effective than OMT alone. The authors concluded that the technology has potential but unproven benefits. The Hayes 2024 update included five low-quality evidence from eight studies but this did not change the current rating (Hayes, 2019; updated 2024).

A National Institute for Health and Care Excellence (NICE) guideline concluded that current evidence on CCM for HF raises no major safety concerns. However, the guideline found inadequate evidence on the quantity and quality of efficacy and states this procedure should only be used in the context of research. The guideline recommends further RCTs addressing details of patient selection, duration and timing of stimulation, and duration of effect of stimulation. Additionally, outcomes should include oxygen consumption, ejection fraction, NYHA classification, and patient-reported outcomes, including QOL (2019).

Kloppe et al. (2016) conducted a single center pilot evaluation study involving 19 medically refractory symptomatic individuals with HF and reduced left ventricular function who underwent implantation of an Optimizer system. Participants were randomized into one of two treatment groups: five hours a day CCM treatment or 12 h/day CCM treatment. Subjects and evaluating physicians were blinded to the study group. Subjects returned to the hospital after 12 and 24 weeks. Efficacy evaluations included changes from baseline to 24 weeks in MLWHFQ, maximal oxygen consumption in the cardio-pulmonary stress test (peak VO2), NYHA classification, six-minute walk distance, and ejection fraction. At the end of 24 weeks, clinical improvement was observed in the entire cohort in all efficacy measures. There were no significant differences, either clinically or statistically, between the groups receiving CCM for five h/day versus 12 h/day. Given the small sample size, further studies are warranted. Additionally, the design of the study does not allow comparison of CCM to other approaches.

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Code	Description
0440T	Ablation, percutaneous, cryoablation, includes imaging guidance; upper extremity distal/peripheral nerve
0441T	Ablation, percutaneous, cryoablation, includes imaging guidance; lower extremity distal/peripheral nerve
0442T	Ablation, percutaneous, cryoablation, includes imaging guidance; nerve plexus or other truncal nerve (e.g., brachial plexus, pudendal nerve)

Percutaneous cryoablation of upper/lower extremity distal/peripheral nerve(s), of nerve plexuses or of other truncal nerves for the treatment of chronic pain is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy.

Clinical Evidence

In a clinical evidence assessment, ECRI (2023) concluded that the evidence for iovera System (Pacira Biosciences, Inc.) for treating knee osteoarthritis (OA) pain is unclear when addressing clinical utility. The evidence identified by ECRI suggests that whether iovera reduces postoperative pain and opioid use and improves functionality and quality of life compared with standard care in individuals who underwent total knee arthroplasty (TKA) is unclear because available studies (two RCTS and three non-randomized controlled studies), all at high risk of bias, report conflicting results. Limitations include comparison groups, follow-up time, and outcome reporting varied widely across studies, which precludes generalizing study results.

Panagopoulos et al., 2023 compared radiofrequency ablation and cryoneurolysis of the genicular nerves for the symptomatic pain management in knee OA in a study protocol of a prospective, randomized, single-blinded clinical trial. Out of 70 individuals with knee osteoarthritis (KOA), two groups were created randomly [Cooled radiofrequency ablation (CRFA) and CRYO group] with 35 participants in each. The trial's primary outcome is the efficacy of CRFA or CRYO, which was measured at 2-, 4-, 12-, and 24 weeks post-intervention using the numerical rating pain scale (NRPS). The safety of the two techniques was also assessed, and the clinical evaluation using the knee injury osteoarthritis outcomes score (KOOS), the Oxford knee score (OKS), and the 7-point scale of patient global impression of changes (PGIC). The limitations of this trial include the fact that the effectiveness of these treatments relies heavily on exact spotting of the genicular nerves and that we cannot spot all the nerves of the knee joint capsule. The extent of nerve damage and its capacity to regenerate also depends on parameters that cannot be fully controlled in this clinical trial. The authors concluded that the two techniques can block pain transmission through genicular nerves in diverse ways. This is the first clinical trial to compare CRFA and CRYO and draw conclusions about their safety and efficacy.

In a Hayes evolving evidence review created in 2022, the iovera (Pacira BioSciences Inc.) System was evaluated for pain associated with TKA. A review of full-text clinical studies and systematic reviews suggests minimal support for using iovera for pain management associated with TKA. The review of full-text clinical practice guidelines and position statements guidance confers no/unclear support for using cryotherapeutic techniques for pain management associated with TKA. This evolving evidence review was updated in 2025 and reflects 3 newly published studies that may meet the inclusion criteria set out in the report published in 2022 although the impact of the new studies are unlikely to change in the current level of support.

Grigsby et al. (2021) published the results of a pilot study evaluating the safety and efficacy of percutaneous cryoneurolysis for the treatment of occipital neuralgia (ON) related pain. A total of 26 individuals (mean age 49.1 years) participated in this prospective, multicenter, nonrandomized cohort study which assessed the degree and duration of the

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effect of cryotherapy for pain reduction in individuals with either unilateral or bilateral ON. Results were measured by assessing level of pain due to ON based on an 11-point numeric scale at baseline and day 7. Ongoing treatment effect was measured at day 30 and day 56 by patient inquiry with “effect”, “no effect” or “no longer effective” as possible responses. Overall, a clinically important improvement of symptoms (≥ 2 points in numeric rating scale) was reported by 64% of participants on day 7, with similar results lasting through day 30. Pain reduction continued for 50% of participants on day 30 and for 35% of participants on day 56. No adverse events were reported. The authors concluded that cryoneurolysis provided substantial relief from pain related to ON ≤ 30 days after treatment with no safety issues, however several limitations to this study were noted. The study was uncontrolled and unblinded in design, so cryoneurolysis was unable to be compared with other ON treatments, and the lack of a control group introduced potential for bias. In addition, the study had a very small population size and did not include outcome measures assessing impact of treatment with cryoneurolysis on quality of life. The researchers recommend more-rigorous clinical trials including a larger population, comparator group(s), and better characterization of participants at baseline to establish efficacy and safety.

In a 2022 Evolving Evidence Review, Hayes reported on the state of the evidence regarding the FDA-approved iovera system for treatment of chronic knee pain due to OA. One fair quality randomized sham-controlled clinical trial and one systematic review was identified. Although no serious treatment-related adverse events were reported, the randomized sham-controlled trial suggested short-term improvement in pain and function; by 6 months post-treatment advantages diminished. The systematic review included only one study addressing the use of iovera for knee pain due to OA (the randomized sham-controlled trial mentioned above). Other studies included addressed iovera as an adjunct to TKA. No clinical practice guidelines or position statements provided recommendations or support for the iovera system for treatment of knee pain due to OA. Hayes indicates that further high-quality studies are required to compare iovera with standard care or potential alternatives for treating knee pain from OA and evaluate clinical benefit from repeat iovera treatments. According to the 2024 update, there are no relevant newly published studies that may meet the inclusion criteria set out in the report published in 2022.

On March 24, 2017, the FDA cleared the iovera system under the 501(k) pathway. The system destroys tissue during surgical procedures by applying freezing cold. It can also be used to produce lesions in peripheral nervous tissue by applying cold to the selected site to block pain. It is also indicated for the relief of pain and symptoms associated with knee OA for up to 90 days. The iovera system is not indicated for treating central nervous system tissue. On May 20, 2022, these indications were expanded to include the facilitation of target nerve location by conducting electrical nerve stimulation from a compatible nerve stimulator. Additional information can be found at:

- https://www.accessdata.fda.gov/cdrh_docs/pdf16/k161835.pdf
- https://www.accessdata.fda.gov/cdrh_docs/pdf22/K220656.pdf

Radanovich et al. (2017, included in the 2022 Hayes Evolving Evidence Review) conducted a randomized, double-blind, sham-controlled, multicenter trial to evaluate the efficacy and safety/tolerability of cryoneurolysis for reduction of pain and symptoms associated with OA. Participants were randomized 2:1 to cryoneurolysis targeting the infrapatellar branch of the saphenous nerve (IPBSN) or sham treatment. The primary endpoint was the change from baseline to Day 30 in the Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain score adjusted by the baseline score and site. Secondary endpoints, including visual analogue scale (VAS) pain score and total WOMAC score, were tested in a pre-defined order. The intent-to-treat (ITT) population consisted of 180 individuals (n = 121 active treatment, n = 59 sham treatment). Compared to the sham group, those who received active treatment had a statistically significant greater change from baseline in the WOMAC pain subscale score at Day 30 (p = 0.0004), Day 60 (p = 0.0176), and Day 90 (p = 0.0061). Participants deemed WOMAC pain responders at Day 120 continued to experience a statistically significant treatment effect at Day 150. Most expected side effects were mild in severity and resolved within 30 days. The authors concluded that cryoneurolysis of the IPBSN resulted in statistically significant decreased knee pain and improved symptoms compared to sham treatment for up to 150 days and appeared safe and well tolerated. The study is limited by a follow-up of six months only.

Prologo et al. (2017) conducted a prospective pilot study to evaluate percutaneous image-guided nerve cryoablation for treatment of refractory phantom limb pain (PLP). Twenty-one individuals underwent image-guided percutaneous cryoneurolysis procedures. Visual analog scale (VAS) scores were documented at baseline and 7, 45, and 6 months after the procedure. Responses to a modified Roland Morris Disability Questionnaire were documented at baseline and 7- and 45-days post-procedure as well. The technical success rate of the procedures was 100%. There were 6 (29%) minor procedure-related complications. Disability scores decreased from a baseline mean of 11.3 to 3.3 at 45-day follow-up. Pain intensity scores decreased from a baseline mean of 6.2 to 2.0 at 6 months. Limitations of this study include its exploratory nature (single-arm pilot cohort with no use of control, randomization, or blinding). Results will be used to design a larger, parallel-armed, RCT.

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Code	Description
0444T	Initial placement of a drug-eluting ocular insert under one or more eyelids, including fitting, training, and insertion, unilateral or bilateral
0445T	Subsequent placement of a drug-eluting ocular insert under one or more eyelids, including re-training, and removal of existing insert, unilateral or bilateral

The placement of drug eluting ocular inserts under the eyelid(s) is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Drug-eluting ocular inserts are thin, drug-impregnated, solid, or semisolid consistency devices that are designed to be placed non-invasively under the eyelid to release medication over several weeks or months. There are few published studies addressing the use of these drug-eluting ocular inserts. Therefore, it is not possible to conclude whether these inserts have a beneficial effect on health outcomes.

Rubião et al. (2021) conducted a phase II, randomized-controlled trial (RCT) of participants with primary open-angle glaucoma (OAG) and ocular hypertension (OH), comparing the safety and efficacy of bimatoprost ocular inserts to bimatoprost eye drops. The study included 13 participants with OH, and 16 participants with primary OAG. Both groups had intraocular pressure (IOP) > than 21 and ≤ to 30 mmHg. A control group of five participants with IOP ≤ 14 mmHg was also included. Participants were between the ages of 40 and 75. A chitosan-based insert of bimatoprost was placed in the upper conjunctival fornix of the right eye for each participant. Additionally, one drop of Lumigan® ophthalmic solution was used in the left eye every night for three weeks. The study results revealed IOP reduction was similar for both the insert (19.5 ±2.2 mmHg) and the eye drop (16.9 ±3.1 mmHg) during three weeks of follow-up (p = 0.165). IOP reduction in the third week was 30% for the insert and 35% for the eye drop (p = 0.165). There were no reports of intolerance or discomfort with the insert. Of note, 58% of participants preferred the insert, 25% preferred the eye drop, and 17% reported no preference. The authors concluded that both methods showed similar efficacy during follow-up, which might suggest a possible change in the daily therapeutic regimen for treatment of these two conditions. Limitations of this study are small sample size, which may not have been large enough to detect clinically significant differences and short follow-up period.

In a Preferred Practice Pattern® guideline for primary OAG, the American Academy of Ophthalmology does not specifically mention the use of ocular inserts for the treatment of glaucoma (Gedde et al., 2021).

Brandt et al. (2016) conducted a parallel-arm, multicenter, double-masked RCT of 130 participants with OAG or OH. Participants were randomized 1:1 to receive a bimatoprost ocular insert plus artificial tears twice daily (n = 64) or a placebo insert plus timolol (0.5% solution) twice daily (n = 66) for 6 months after a screening washout period. Diurnal IOP measurements at 0, 2, and 8 hours were obtained at baseline; at weeks 2, 6, and 12; and then at months 4, 5, and 6. The primary efficacy end point examined the difference in mean diurnal IOP change from baseline. Secondary end points were diurnal IOP at months 4, 5, and 6 and adverse events (AEs). The study results revealed a mean reduction from baseline IOP of -3.2 to -6.4 mmHg for the bimatoprost group compared with -4.2 to -6.4 mmHg for the timolol group over 6 months. The study met the non-inferiority definition at two of nine time points but was determined to be underpowered for the observed treatment effect. AEs were reported as consistent with bimatoprost or timolol exposure. There were no unexpected ocular AEs observed. The primary retention rate for the bimatoprost ocular insert was 88.5% at 6 months.

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The authors concluded that a clinically relevant reduction in mean IOP was observed over 6 months with the bimatoprost ocular insert. The insert appeared to be safe and well tolerated and may provide an alternative to daily eye drops, improving adherence, consistency of delivery, and reduction of elevated IOP. However, longer-term studies of a high-risk (low-adherence) population are required to demonstrate the full usefulness of the bimatoprost ocular insert system in preserving visual fields. Limitations of the study include the underpowered design and short follow-up period.

Torrón et al. (2013) compared the efficacy and safety of an ocular insert versus conventional mydriasis in cataract surgery. Seventy participants who were undergoing cataract surgery were included in the study. Thirty-five participants (Group 1) received instillation of mydriatic drops (tropicamide 1%, phenylephrine 10%, and cyclopentolate 1%) prior to surgery, and 35 participants (Group 2) had a Mydriasert® insert (Théa Pharma) (0.28 mg of tropicamide and 5.4 mg of phenylephrine hydrochloride) placed in the inferior fornix of the eye. Pupil size before and after surgery, blood pressure, and heart rate were measured. Prior to surgery, the study results revealed pupil diameter was 9.44 ±1.17 mm in Group 1 and 9.05 ±1.54 in Group 2 ($p > 0.05$). However, 24 hours after surgery, pupil diameter was 5.20 ±1.54 mm in Group 1 and 3.33 ±1.15 in Group 2 ($p < 0.001$). No statistically significant differences in blood pressure or heart rate were observed between groups. The authors concluded that the effect of the Mydriasert insert was similar to conventional mydriatic agents. Though pupil size returned to normal faster when using the Mydriasert insert compared to conventional mydriatic agents for pupil dilation. Study limitations included small sample size that may not have allowed detection of clinically significant differences and lack of clinical outcome data.

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Code	Description
0485T	Optical coherence tomography (OCT) of middle ear, with interpretation and report; unilateral
0486T	Optical coherence tomography (OCT) of middle ear, with interpretation and report; bilateral

Optical coherence tomography (OCT) for assessing and managing middle ear disorders is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Conventional diagnostic techniques for middle ear disorders include use of standard or pneumatic otoscopy, and tympanometry to evaluate the surface of the tympanic membrane. Optical coherence tomography (OCT) is a non-invasive, real-time imaging technology that uses a low-intensity light source to produce 2- and 3- dimensional structural images of the middle ear with micron-scale resolution. The image produced by the reflected light is analyzed and can be used to differentiate air from fluid, as well as characterize fluid properties due to scattering of the imaging signal from particles in the fluid (Precaido et al. 2020). There is a lack of high quality published studies that demonstrate the clinical utility of OCT on improved patient outcomes.

Zambelli-Weiner et al. (2025) evaluated a novel Optical Coherence Tomography (OCT) otoscope (Oktoeight, PhotoniCare), and how it compares to traditional otoscope for diagnosis and management of ear-related complaints. This was a planned interim analysis of the “One Year OTO-MATIC Randomized Controlled Trial (RCT), multicenter, real-world effectiveness study” (funded by Photonic are Inc.). Traditional otoscope is currently considered the Standard of Care (SOC) for these complaints. The authors’ specific intention was to see how the OCT impacted the number of antibiotic prescriptions written for pediatric patients who presented to their primary care provider with ear-related complaints. Sixteen providers from a variety of institutions were contracted for this study. The providers were assigned to employ either the new intervention or SOC, with the intention of preventing providers from switching between interventions throughout the trial. A total of 248 participants were included: 128 in the intervention arm, and 120 in the SOC arm. “Otoscopic assessments were performed at the sites for both the SOC and Intervention groups at the Baseline Visit (BV). The SOC group’s otoscopic assessment was performed using a traditional otoscope, following best practice guidelines. The Intervention group’s otoscopic assessments were performed by trained providers using the OCT device. Results demonstrate that the OCT intervention reduced the odds of antibiotic prescribing by 50% compared to the SOC (OR = 0.50, 95% CI: 0.45–0.56). Additionally, providers in the Intervention group were significantly more likely to initiate a single

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therapeutic modality versus multiple, often disparate modalities (91.6% vs. 73.8%, p < 0.001, respectively)." The authors concluded that these "Interim results suggest the OCT imaging technology (Oktoeight, PhotoniCare) improves antibiotic stewardship with clinicians in the OCT arm having a reduced likelihood of prescribing antibiotics compared to the SOC arm. Overall, changes in provider prescribing patterns and therapeutic management of the patient are consistent with increased diagnostic certainty." The authors stated that "this study is limited to measuring rates of antibiotic prescription, medical resource utilization, and economic impact, future research studies should focus on the clinical outcomes of specific treatment decisions for the various diagnoses based upon the use of OCT compared to SOC." Additionally, another limitation of this study is the financial support for the study design, data collection, and analysis by Photonic Inc.

In a 2023 guideline from the National Institute for Health and Care Excellence (NICE), there is no mention of the use of optical coherence tomography in the management of otitis media with effusion in children younger than 12 years old.

Won et al. (2023) assessed the use of optical coherence tomography (OCT) versus standard otoscopy in the diagnosis of otitis media (OM). The study's aim was that identifying middle ear effusion (MEE), and bacterial biofilms of the middle ear, which are critical in OM's management, is challenging with standard otoscopy as MEE is located behind the semi-opaque eardrum. "OCT is an optical analogue of ultrasound imaging and generates depth-resolved cross-sectional images of tissue by detecting light-echoes and does not require contact with the TM nor any impedance matching gel. OCT can provide multidimensional images at a video rate with a depth resolution of 2–10 μm." OCT images were acquired from 53 pediatric subjects (104 ears) who were undergoing ear tube surgery to aspirate the MEE and aerate the middle ear. "In vivo middle ear OCT acquired one hour prior to the surgery was compared with OCT of the freshly extracted MEEs." "Among the subjects who were identified with the presence of MEEs, 89.6% showed the presence of the TM-adherent biofilm in in vivo OCT." "Among the subjects who were identified with the presence of MEEs, 89.6% showed the presence of the TM-adherent biofilm in in vivo OCT. This study provided an atlas of middle ear OCT images exhibiting a range of depth-resolved MEE features, which can only be visualized and assessed non-invasively through OCT. Quantitative metrics of OCT images acquired prior to the surgery were statistically correlated with surgical evaluations of MEEs." The authors concluded that OCT provides new readily available information related to measurements of MEEs characteristics, which can lead to improved diagnosis and management of OM in children. However, they further acknowledge that challenges remaining for future studies include limited imaging depth of OCT may not represent the entire middle ear cavity; the presence of blood from ear tube surgery may affect the measurement of extracted MEE; and a larger patient population is needed.

In a 2022 single site study, Porter et al. collected image data from twenty-six subjects that received bilateral imaging with a commercial otoscope (OtoSight Middle Ear Scope, PhotoniCare) to assess the ability of OCT to overcome obstructions such as cerumen, hair or ear canal curvature during middle ear examination. Data were read by 12 blinded clinicians and 5 blinded OCT experts. The results showed in canals with > 75% obstruction there was 68.8% imageability compared to 37.5% using a standard otoscope. For canals with > 75% but < 100% obstruction, there was 84.6% and 46.2% imageability for OCT and otoscopy, respectively. The authors concluded that OCT provides superior views of the middle ear that standard otoscopy by the ability to direct the beam around obstructions. This study is limited by a lack of randomization and a small number of participants, as well as device manufacturer participation. Further high quality, independent research is needed to validate the superiority of OCT compared to standard otoscopy for assessing the middle ear and improve patients' outcomes.

Preciado et al. (2020) conducted a cross-sectional study to evaluate clinical usability and image readability by clinical personnel in the detection and differentiation of middle ear effusions using an OCT otoscope. Seventy pediatric participants aged seven and older undergoing tympanostomy tube placement were preoperatively imaged using an OCT otoscope. Readable images were collected in 65 ears from 45 participants. Bilateral imaging was attempted when possible. Images were sorted into three groups: no fluid, serous fluid and nonserous fluid (purulent or mucoid). The groups assigned to read OCT images included otolaryngologists, pediatricians, physician extenders and non-medical professionals. Blinded reader analysis of OCT images for identifying presence and type of fluid was then compared with intraoperative findings to determine the sensitivity, specificity, accuracy, positive/negative predictive values, and inter/intrareader agreement of OCT otoscopy. The results showed reader detection of middle ear effusions had a 90.6% accuracy, 90.9% sensitivity, 90.2% specificity, 94.5% positive predictive value, 84.2% negative predictive value, and intra/interreader agreement of 92.9% and 87.1% respectively, with no statistically significant differences between those with and without OCT experience. The authors concluded that OCT has potential to be a viable diagnostic tool in the hands of many users, regardless of experience with the technology and is at least as accurate as other diagnostic tools in terms of accuracy and specificity. This study is limited by the small number of participants, lack of standardization and does not address the clinical utility of OCT.

Monroy et al. (2018) conducted a prospective case series study to assess otitis media (OM) associated biofilm structures affixed to the mucosal surface of the TM, both in vivo and in surgically recovered in vitro samples. Forty pediatric

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participants that were scheduled for tympanostomy tube placement surgery were imaged intraoperatively under general anesthesia. Following myringotomy, a portable OCT imaging system was used to assess for the presence of any biofilm affixed to the mucosal surface of the TM. OCT was achieved for 38 participants. Samples of suspected microbial infection-related structures were collected through the myringotomy incision. The sampled site was reimaged with OCT to confirm collection from the original image site. In vitro analysis was done based on confocal laser scanning microscope (CLSM) images of fluorescence in situ hybridization-tagged samples, and polymerase chain reaction (PCR) provided microbiological characterization and verification of biofilm activity. Thirty-four samples were collected from 38 subjects. CLSM images provided evidence of clustered bacteria in 32 of 33 samples. PCR detected the presence of active bacterial DNA signatures in 20 of 31 samples. The results showed that PCR and CLSM analysis of fluorescence in situ hybridization-stained samples validates the presence of active bacteria that have formed into a middle ear biofilm that extends across the mucosal layer of the TM. The authors concluded that OCT can rapidly and noninvasively identify middle ear biofilms in subjects with severe and persistent cases of OM. This study is limited by a small number of participants, no control group, and a high risk of bias. The clinical utility of this method to diagnose OM has not been established, and large well-designed studies are required to validate these findings.

Park et al. (2018) conducted a prospective study to examine the tympanic membranes (TMs) of 120 patients with middle ear conditions using a handheld optical coherence tomography-based otoscope (860 nm central wavelength, 15 μm axial resolution, 15 μm lateral resolution, and 7 mm scanning range using relay lens). Both OCT and oto-endoscope images were compared according to the clinical characteristics such as perforation, retraction, and postoperative healing process. The objective grade about the thickness of perforation margins and the accurate information about the extent of TM retraction that was not distinguishable by oto-endoscopic exam could be identified using this system. The postoperative healing process of TMs could also be followed using the OCT device. The authors concluded that their findings suggest that the handheld OCT device would be another useful application.

Using OCT, Monroy et al. (2017) observed six pediatric participants diagnosed with chronic or recurrent OM before and following standard-of-care surgical treatment who completed a six-month period follow-up out of 25 participants initially included. At each time point, the tympanic membrane (at the light reflex region) and directly adjacent middle-ear cavity were observed in vivo with a handheld OCT probe and portable system. Imaging results were compared with clinical outcomes to correlate the clearance of symptoms in relation to changes in the image-based features of infection. OCT images of most all participants showed the presence of additional infection-related biofilm structures during their initial consultation visit and similarly for subjects imaged intraoperatively before myringotomy. Subjects with successful treatment (no recurrence of infectious symptoms) had no additional structures visible in OCT images during the postoperative visit. OCT image findings suggest surgical intervention consisting of myringotomy and tympanostomy tube placement provides a means to clear the middle ear of infection-related components, including middle-ear fluid and biofilms. Furthermore, OCT was demonstrated as a rapid diagnostic tool to prospectively monitor patients in both outpatient and surgical settings. This study is limited by the small number of participants, lack of standardization and does not address the clinical utility of OCT.

In an updated clinical practice guideline for otitis media with effusion (OME) (Rosenfeld et al, 2016), the American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) makes no mention of the use of optical coherence tomography (OCT) for diagnosing middle ear conditions. It does recommend performing standard tympanometry in children with suspected OME if diagnosis is unclear after performing pneumatic otoscopy. There is no mention of OTC in this guideline.

Cho et al. (2015) report on the application of OCT for the diagnosis and evaluation of OM. They evaluated 39 patients who were diagnosed with OM via standard otoendoscopic examination and audiological tests between July and October 2012. Six volunteers with normal TM on otoendoscopy were also included, with OCT images used as a control. Of the 39 patients, OCT images were acquired from 16 patients (41.0%). The most common cause of failure to acquire an image was a narrow or curved external auditory canal (n = 5). Other causes were the presence of obstacles, such as profuse otorrhea (n = 3), cholesteatoma material (n = 4), and cerumen (n = 7), and poor compliance (n = 4). OCT could not be obtained for the three patients with chronic OM with cholesteatomas. Despite the benefits such as noninvasiveness, lack of radiation, high resolution and ability to use outpatient, the authors report some limitations, such as, difficulty securing a light pathway for the OCT device, and the diagnostic efficiency of otoendoscopy. The authors concluded that their evaluation suggests that a handheld OCT otoscope can be applied clinically to otology, and that OCT has the potential to facilitate diagnosis of OM; however, further clinical trials are necessary.

In a study by Monroy et al. (2015), OCT was used to determine TM thickness, and the presence and thickness of any middle-ear biofilm located behind the TM in 34 pediatric patients. Participants were placed into three subgroups: normal, acute OM and chronic OM based on the clinical presentation as diagnosed by otoscope. Average TM thickness values were calculated from three representative locations for each cross-sectional OCT image. The data analysis was based on

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the optic scattering properties of the tissue, which has a direct correlation to the stage of infection. The results showed an increased thickness in the participants in the acute infection group. In chronic OM, the optic scattering appeared to return to a thickness that is similar to normal when a biofilm was present. The authors concluded that OCT offers the potential to differentiate normal, acute, and chronic OM infections in pediatric subjects. This study is limited by a small number of participants. These findings and clinical utility of the device should be validated with larger well-designed studies.

Nguyen et al. (2013) investigated the acoustic effects of bacterial biofilms, confirmed using OCT in adult ears. Biofilms have been linked to chronic OM and OM with effusion in the middle ear. Non-invasive OCT images were collected to visualize the 2D cross-sectional structure of the middle ear, verifying the presence of a biofilm behind the TM of five ears. Wideband measurements of acoustic reflectance and impedance [0.2 to 6 (kHz)] were used to study the acoustic properties of ears with confirmed bacterial biofilms. Compared to known acoustic properties of normal middle ears, each of the ears with a bacterial biofilm had an elevated power reflectance in the 1 to 3 [kHz] range, corresponding to an abnormally small resistance. The authors note that their preliminary study indicates that acoustic reflectance and impedance measurements may have utility for assessment of the presence and acoustic impact of biofilms in the middle ear; however, future study of a wide range of OM-related conditions, with definitive biofilm and non-biofilm classifications, is needed.

Several clinical trials have been completed or are in varying stages of recruitment. Further information can be found at: https://www.clinicaltrials.gov/search?term=optical%20coherence%20tomography%20for%20the%20middle%20ear&page=1.

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Code	Description
0506T	Macular pigment optical density measurement by heterochromatic flicker photometry, unilateral or bilateral, with interpretation and report

Heterochromatic flicker photometry for evaluation of age-related macular degeneration is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Sayin and Altinkaynak (2024) conducted an observational study comparing macular pigment optical density (MPOD) in first-degree relatives of patients with age-related macular degeneration (AMD) to a healthy control group. Heterochromatic

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flicker photometry (HFP) is a widely used psychophysical technique for this measurement, assuming uniform retinal spectral sensitivity from the central fovea to the surrounding parafovea. The study included 202 participants: 128 healthy individuals who were first-degree relatives of AMD patients (Group 1) and 74 healthy control subjects (Group 2). The right eyes of all participants were included. MPOD was measured using a commercially available device (MPSII®, Elektron Technology, Switzerland) based on HFP. Central foveal thickness and subfoveal choroidal thickness were measured using spectral-domain optical coherence tomography. Values were compared between the two groups. Group 1 consisted of 54 males and 74 females, while Group 2 included 32 males and 42 females. The mean ±SD ages of Group 1 and Group 2 were 49.0 ±7.6 and 41.8 ±8.6 years, respectively. The mean ±SD MPOD values for Group 1 and Group 2 were 0.43 ±0.09 and 0.47 ±0.12 (p = 0.048), respectively. The mean ±SD central foveal thicknesses were 208 ±19 µm and 216 ±8 µm (p = 0.014), and the mean ±SD subfoveal choroidal thicknesses were 232 ±29 µm and 250 ±21 µm (p = 0.002), respectively. The data challenges the assumption of HFP that retinal spectral sensitivity is uniform across the foveal and parafoveal regions without macular pigment. It appears that retinal sensitivity to red light is higher in the parafovea than in the fovea, leading to an underestimation of peak MPOD at 460 nm. Therefore, caution is needed when using HFP for MPOD measurements. Alternative techniques, such as resonance Raman spectrometry, retinal reflectometry, or autofluorescence spectrometry, which do not use the retina as the detector, might provide more accurate results. Further robust studies are needed to support the clinical utility of this technology.

Hong et al. (2020) in a retrospective study evaluated the association of macular pigment optical density (MPOD) with age in the Korean population using a device (MPSII®) that measures MPOD based on heterochromatic flicker photometry (HFP). Macular pigment (MP) is studied mainly because of the proposed link between low levels of macular pigment optical density (MPOD) and an increased risk of developing age-related macular degeneration (AMD). There were 126 eyes that were retrospectively reviewed. In the simple regression analysis, a statistically significant linear regression model was observed, and the estimated values of MPOD decreased by 0.005 as age increased by 1 year. Aged (> 50 years) showed lower MPOD than younger (30-49 years) subjects. But, in the healthy population, the estimated MPOD values exhibited a decreasing trend with age; there were no significant differences according to age, after excluding patients with AMD. MPOD was significantly lower in patients with AMD than in aged healthy controls. Furthermore, hypertension, dyslipidemia, and smoking were identified as risk factors for AMD. Study limitations included the following: the study sample was small, and further research with a larger sample is needed. Second, because the emphasis was exclusively on AMD, the relationship of this technique to other diseases remains unclear. Third, measurements of the relationship between serum or dietary carotenoid levels and MPOD were not performed. Lastly, the results did not show a significant correlation between MPOD reduction and the occurrence of AMD. Nevertheless, the author's note this was the first study to demonstrate the changes in MPOD according to age and difference in MPOD with and without AMD. The estimated values using MPSII® were measurable in all ages, especially older patients who might have dry AMD. The results of this study may lead to an increased use of MPSII® in practice and to identify the need for dietary supplementation in patients with lower MPOD. Additional studies are needed to assess the effect of MPOD on the pathologic process of AMD and MPOD levels in other diseases.

Najjar et al. (2016) studied ocular lens density and transmittance measurements of 43 subjects, obtained by an improved psychophysical scotopic heterochromatic flicker photometry (sHFP) technique. This was compared to the results obtained by three other measures: a psychophysical threshold technique, a Scheimpflug imaging technique, and a clinical assessment using a validated subjective scale. Ocular lens densities were compared for all methods by using linear regression analysis. The sHFP technique showed that transmittance decreased with age over the entire visual spectrum. Lens density obtained from sHFP highly correlated with the values obtained with the other approaches. sHFP also showed the lowest variability and the best fit with a quadratic trend of lens density increase as a function of age, compared to other objective measures. The authors concluded that the HFP technique offers a practical, reliable, and accurate method to measure lens density in vivo and predict lens transmittance over the visible spectrum. This study is limited by population size.

Reference(s)

Hong IH, Jung WH, Lee JH, et al. Macular pigment optical density in the Korean population: a cross sectional study. J Korean Med Sci. 2020 Feb 10;35(5):e30.

Najjar RP, Teikari P, Cornut PL, et al. Heterochromatic flicker photometry for objective lens density quantification. Invest Ophthalmol Vis Sci. 2016 Mar;57(3):1063-71.

Sayin O, Altinkaynak H. Macular pigment optical density in first degree relatives of age-related macular degeneration patients. Curr Eye Res. 2023 Nov;48(11):1057-1062.

Code	Description
0507T	Near-infrared dual imaging (i.e., simultaneous reflective and trans-illuminated light) of meibomian glands, unilateral or bilateral, with interpretation and report

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The use of near-infrared dual imaging of meibomian glands is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

There is a lack of evidence regarding the effectiveness of near-infrared dual imaging in the diagnosis and management of patients with meibomian gland dysfunction or blepharitis. Furthermore, professional society guidelines are lacking regarding this technology.

According to the manufacturer, the LipiScan Dynamic Meibomian Imager provides rapid high definition meibomian imaging. LipiScan offers a fast and intuitive gland imaging option allowing physician assessment of meibomian gland structure during routine workups in any practice setting. Dynamic Meibomian Imager (DMI) renders a multidimensional view of meibomian gland structure with simultaneous integration of dynamic surface illumination and adaptive transillumination technologies. Dynamic surface illumination originates from multiple light sources to minimize reflection. The adaptive transillumination technology changes light intensity across the surface of the illuminator compensates for the lid thickness variations between patients. The dual-mode DMI consists of a combination of dynamic illumination and adaptive transillumination offering an enhanced view of the meibomian gland structure.

Ophthalmic camera AC-powered devices have received FDA approval through the 510(k) process. Refer to the following website for more information (use product code HKI): https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed April 14, 2025)

Finis et al. (2015) conducted an evaluation of meibomian gland dysfunction (MGD) and local distribution of meibomian gland atrophy by non-contact infrared meibography. A retrospective analysis of 128 patients (92 women and 36 men, 57 ±17 years) from a dry eye clinic was performed. Infrared meibography was performed using the Keratograph 5 M (Oculus, Wetzlar, Germany) and evaluated with a scoring system introduced by Arita et al. The results showed a significant inverse correlation between Meibomian gland atrophy measured by meibography and expressible Meibomian glands ($r = -0.197$, $p = 0.003$) as well as between meiboscore and TBUT ($r = -0.1615$, $p = 0.012$). There also was a significant correlation between the total meiboscore and the age ($r = 0.33$, $p < 0.0001$). The authors found a strong and highly significant correlation between the total meiboscore and the individual meiboscore of the upper eyelid ($r = 0.905$, $p < 0.0001$) and the lower eyelid ($r = 0.892$, $p < 0.0001$). There was no significant difference of Meibomian gland atrophy between the individual thirds of the upper eyelid, but for the lower eyelid, a higher degree of Meibomian gland atrophy was found in the nasal third compared with the middle and the temporal third (Dunn's post hoc test, $p < 0.0001$). The authors concluded that meibomian gland atrophy seems to be not constant over the tarsal plate, but the examination of the lower tarsus might be sufficient in most of the cases. The correlation of the meiboscore with functional dry eye parameters suggest that in patients with detectable Meibomian gland atrophy there is also an impaired Meibomian gland function. However, meibography seems not to be sufficient as a single test for the diagnosis of MGD. Larger, prospective studies are needed to confirm these results and further evaluate the potential of meibography in the diagnosis of MGD.

Reference(s)

Finis D, Ackermann P, Pischel N, et al. Evaluation of meibomian gland dysfunction and local distribution of meibomian gland atrophy by non-contact infrared meibography. Curr Eye Res. 2015;40(10):982-9.

Johnson&Johnson website. Lipican Dynamic Mibomian Imager. Available at: https://www.jnjvisionpro.ca/products/lipiscan-dynamic-meibomian-imager. Accessed May 23, 2025.

Code	Description
0515T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; complete system (includes electrode and generator [transmitter and battery])
0516T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; electrode only
0517T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; both components of pulse generator (battery and transmitter) only
0518T	Removal of pulse generator for wireless cardiac stimulator for left ventricular pacing; battery component only
0519T	Removal and replacement of pulse generator for wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming; both components (battery and transmitter)

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Code	Description
0520T	Removal and replacement of pulse generator for wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming; battery component only
0521T	Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording, and disconnection per patient encounter, wireless cardiac stimulator for left ventricular pacing
0522T	Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, including review and report, wireless cardiac stimulator for left ventricular pacing
0861T	Removal of pulse generator for wireless cardiac stimulator for left ventricular pacing; both components (battery and transmitter)
0862T	Relocation of pulse generator for wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming; battery component only
0863T	Relocation of pulse generator for wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming; transmitter component only

Cardiac resynchronization therapy (CRT) with wireless left ventricular (LV) endocardial pacing is unproven and not medically necessary due to insufficient evidence of efficacy and/or safety.

Clinical Evidence

The WiSE (Wireless Stimulation Endocardially) CRT System (EBR Systems, Inc.) (formerly the WiCS-LV) is the first Food and Drug Administration (FDA)-approved wireless, endocardial LV CRT device designed for use in combination with a pacemaker. The WiSE CRT System is a wireless LV pacing system that works with a conventional pacemaker and/or defibrillator for individuals in whom CRT is indicated. The WiSE CRT system is comprised of an ultrasonic transmitter attached to a battery unit and a small wireless receiver which acts as a pacing electrode. The WiSE system allows for biventricular pacing while eliminating the need for a LV pacing wire in the coronary sinus. The system allows the provider to customize electrode placement to the optimal location for pacing, which varies among individuals; this differs significantly from conventional LV pacing leads, which are limited by coronary sinus anatomy. (Hayes, 2025).

On April 11, 2025, the FDA granted premarket approval to the WiSE CRT system. The device is intended for adult individuals who are greater than or equal to 22 years of age with an indication for CRT and who have or are eligible for an implanted right ventricle pacing system, and have failed previous coronary sinus lead implantation or who have previously implanted pacemakers or implantable cardioverter-defibrillators for which a standard CRT upgrade is not advisable. For additional information refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P240028. (Accessed April 22, 2025)

Cang et al. (2022) conducted a systematic review and meta-analysis to determine if individuals can benefit from WiSE-CRT as a way of rescue therapy for those in whom CRT failed. Five single-arm studies involving 175 individuals with heart failure (HF) and WiSE-CRT were included and evaluated for clinical outcomes including QRS duration (QRSd), ejection fraction, and LV end-systolic volume. The follow-up period was six months. The implanted success rate ranged from 76.5 to 100%. WiSE-CRT resulted in significantly narrower QRSd [mean difference (MD): −38.21 milliseconds (ms), 95% confidence interval (CI): −44.36 to −32.07, $p < 0.001$], improved LV ejection fraction (MD: 6.07%, 95% CI: 4.43 to 7.71, I2 = 0%, $p < 0.001$), reduced LV end-systolic volume [MD: −23.47 milliliter (ml), 95% CI: −37.18 to −9.13, $p < 0.001$], and reduced LV end-diastolic volume (MD: −24.02ml, 95% CI: −37.01 to −11.03, $p = 0.02$). The authors concluded that leadless endocardial LV pacing resynchronization is effective for individuals with HF who need a device upgrade or who failed conventional CRT; however, the authors note that more clinical trials are needed. Limitations include small sample sizes, lack of comparison groups, and a short follow-up period. as well as lack of patient-centered outcomes. Reddy et al. 2017, and Auricchio et al. 2014, which were previously cited in this policy, were included in this systematic review and meta-analysis.

Wijesuriya et al. (2022) conducted a systematic review and meta-analysis designed to evaluate the safety and efficacy of leadless LV pacing. Four observational studies and one prospective registry were included in the review (n = 181); all of which were multicenter and single arm. Studies were eligible for inclusion if they were related to safety and efficacy of HF treatment with leadless CRT in humans. Exclusion criteria included studies not published in English, abstracts, conference presentations, case reports, reviews, editorials/letters, expert opinions, other types of records except for original articles and articles that reported on the same cohort as another eligible study. The procedural success rate was 90.6%. Clinical response rate was 63%, with mean improvement in NYHA functional class of 0.43 (MD –0.43; 95% CI –0.76 to –0.1; $p = .01$), with high heterogeneity ($p < .001$; $I^2 = 81.1\%$). There was a mean increase in LV ejection fraction of 6.3% (MD 6.3;

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95% CI 4.35 – 8.19; p < .001, with low heterogeneity (p = 0.84; I^2 < 0.001%). The echocardiographic response rate was 54%. Procedure-related complication and mortality rates were 23.8% and 2.8%, respectively. The authors concluded that leadless LV endocardial pacing has proven effective for CRT, supporting its role as a secondary treatment option for individuals who cannot undergo standard CRT or for whom it has failed. Per the authors, enhancing the safety profile of this technology will encourage its broader adoption in treating these individuals. Okabe et al., 2022, and Sieniewicz et al., 2020, which were previously cited in this policy, are included in this systematic review and meta-analysis.

The pivotal Stimulation of the Left Ventricular Endocardium for Cardiac Resynchronization Therapy in Non-Responders and Previously Untreatable Patients (SOLVE CRT) study (NCT02922036) is currently listed as active, not recruiting participants. Initially designed as a randomized blinded sham-controlled trial, the study design was modified due to the impact of the COVID-19 pandemic on participant enrollment to a two-phase trial: a randomized phase (enrollment completed in 2019) and a single-arm phase that started in 2021 (Singh et al., 2021). In 2024, Singh et al. presented the results of the SOLVE-CRT study that included 183 participants and evaluated the safety and efficacy of the WiSE CRT System in those at high risk for a CRT upgrade or those who had failed conventional CRT. The primary safety endpoint was the absence of type one complications, while the primary efficacy endpoint was a decrease in the average left ventricular end systolic volume. The trial was terminated at an interim analysis for meeting prespecified stopping criteria. In the safety population, participants were either NYHA Class II (34.6%) or III (65.4%). The primary efficacy end point was met with a 16.4% (95% CI, −21.0% to −11.7%) reduction in mean left ventricular end systolic volume (p = .003). The primary safety end point was met with an 80.9% rate of freedom from type one complications (p < .001), which included 12 study device system events (6.6%), five vascular events (2.7%), three strokes (1.6%), and seven cardiac perforations which mostly occurred early in the study (3.8%). The authors concluded that the leadless ultrasound-based left ventricular endocardial pacing using the WiSE CRT system is linked to a reduction in left ventricular end systolic volume in those with HF who meet the standard criteria for CRT but cannot be treated with conventional CRT methods. Limitations included the revision of protocol due to the COVID-19 pandemic, lack of randomization, small sample size, short follow-up period, and lack of patient-centered outcomes.

Sidhu et al. (2020) performed a sub analysis of the WiSE-CRT, SELECT-LV and WiCS-LV studies and reported on outcomes in 22 individuals with HF who were non-responders to CRT. Six-month follow-up was available for 18 individuals. Overall, 55.6% of individuals had improvement in their clinical composite score and 66.7% had a reduction in LV end-systolic volume of at least 15% and/or absolute improvement in LV ejection fraction of at least 5%. The study is limited by lack of comparison group, and the small number of study participants limits the generalizability of these results. Further studies are required to determine the overall benefit in this patient population.

Reference(s)

Auricchio A, Delnoy PP, Butter C, et al. Feasibility, safety, and short-term outcome of leadless ultrasound-based endocardial left ventricular resynchronization in heart failure patients: results of the wireless stimulation endocardially for CRT (WiSE-CRT) study. Europace. 2014;16(5):681-688.

Cang J, Liu Y, Zhu D, et al. WiSE CRT Is beneficial for heart failure patients as a rescue therapy: evidence from a meta-analysis. Front Cardiovasc Med. 2022 Mar 15;9:823797.

EBR Systems, Inc. website. Available at: https://ebrsystemsinc.com/. Accessed April 17, 2025.

Hayes, Inc. Emerging Technology Report. WiSE Cardiac Resynchronization Therapy System (EBR Systems Inc.). Hayes, Inc. April 18, 2025.

Reddy VY, Miller MA, Neuzil P, et al. Cardiac resynchronization therapy with wireless left ventricular endocardial pacing: The SELECT-LV study. J Am Coll Cardiol. 2017;69(17):2119-2129.

Sidhu BS, Porter B, Gould J, et al. Leadless left ventricular endocardial pacing in nonresponders to conventional cardiac resynchronization therapy. Pacing Clin Electrophysiol. 2020 Sep;43(9):966-973.

Sieniewicz BJ, Betts TR, James S, et al. Real-world experience of leadless left ventricular endocardial cardiac resynchronization therapy: A multicenter international registry of the WiSE-CRT pacing system. Heart Rhythm. 2020 Aug;17(8):1291-1297.

Singh JP, Rinaldi CA, Sanders P, et al.; SOLVE-CRT Investigators. Leadless ultrasound-based cardiac resynchronization system in heart failure. JAMA Cardiol. 2024 Oct 1;9(10):871-879.

Singh JP, Walsh MN, Kubo SH, et al. Modified design of stimulation of the left ventricular endocardium for cardiac resynchronization therapy in nonresponders, previously untreatable and high-risk upgrade patients (SOLVE-CRT) trial. Am Heart J. 2021 May; 235:158-162.

Wijesuriya N, Elliott MK, Mehta V, et al. Leadless left ventricular endocardial pacing for cardiac resynchronization therapy: a systematic review and meta-analysis. Heart Rhythm. 2022 Jul;19(7):1176-1183.

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Code	Description
0525T	Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging supervision and interpretation; complete system (electrode and implantable monitor)
0526T	Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging supervision and interpretation; electrode only
0527T	Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging supervision and interpretation; implantable monitor only
0528T	Programming device evaluation (in person) of intracardiac ischemia monitoring system with iterative adjustment of programmed values, with analysis, review, and report
0529T	Interrogation device evaluation (in person) of intracardiac ischemia monitoring system with analysis, review, and report
0530T	Removal of intracardiac ischemia monitoring system, including all imaging supervision and interpretation; complete system (electrode and implantable monitor)
0531T	Removal of intracardiac ischemia monitoring system, including all imaging supervision and interpretation; electrode only
0532T	Removal of intracardiac ischemia monitoring system, including all imaging supervision and interpretation; implantable monitor only

Intracardiac ischemia monitoring systems (e.g., Guardian System) are unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

The Guardian System, formerly known as the AngelMed Guardian System is an implantable cardiac monitor with alerting capability and an external alarm device that is indicated for monitoring individuals with an acute coronary syndrome (ACS) history and who remain a high recurrence risk. The Guardian System is an adjunct to patient recognized symptoms and detects potential ongoing ACS events. It is intended to alert individuals to seek medical attention to reduce time to treatment and detect asymptomatic ACS (Avertix Guardian System website).

The Guardian System received U.S. Food and Drug Administration (FDA) premarket approval (P150009) on April 9, 2018. The Guardian System is indicated for use in individuals who have had prior ACS events and who remain at high risk for recurrent ACS events. The Guardian System is indicated as an adjunct to patient recognized symptoms. The system detects potential ongoing ACS events, characterized by sustained ST segment changes, and alerts the individual to seek medical attention for those potential ACS events. Additional FDA information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P150009. (Accessed May 2, 2025)

An ECRI product brief notes that evidence was too limited in quality and quantity to evaluate whether cardiac monitoring is beneficial to individuals. According to the product brief, the AngelMed for Early Recognition and Treatment of STEMI (ALERTS) RCT suggested the device may assist individuals to seek care promptly when the device alerts; however, the RCT was at high risk of bias from serious protocol breaches. Additionally, the device has potential to increase adverse event risks by leading some individuals not to pursue immediate care if an alert does not accompany their ACS symptoms. The authors of the report determined that the evidence was inconclusive and recommended conducting multicenter RCTs that adhere to predefined endpoints, intent-to-treat analysis, and standardized outcomes (ECRI, 2020; updated 2022).

Gibson et al. (2019) reported the results of the ALERTS (NCT00781118) trial. The ALERTS trial was a multicenter, randomized trial of an implantable cardiac monitor that alerts individuals with rapidly progressive ST-segment deviation. Subjects at high-risk of ACS (n = 907) were randomized to a control (alarms deactivated) or treatment group for six months, after which alarms were activated in all subjects. The primary safety endpoint was absence of system-related complications (> 90%). The composite primary efficacy endpoint was cardiac/unexplained death, new Q-wave myocardial infarction, or detection to presentation time greater than 2 hours. Safety was met with 96.7% freedom from system-related complications (n = 30). The efficacy endpoint for a confirmed occlusive event within seven days was not significantly reduced in the treatment compared with control group [16 of 423 (3.8%) vs. 21 of 428 (4.9%), posterior probability = 0.786]. Within a 90-day window, alarms significantly decreased detection to arrival time at a medical facility [51 min versus 30.6 hours; Pr (pt < pc) > 0.999]. In an expanded analysis using data after the randomized period, positive predictive value was higher (25.8% versus 18.2%) and false positive rate significantly lower in the ALARMS ON group (0.164 vs.

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0.678 false positives per patient-year; p < 0.001). The authors noted that although the trial did not meet its pre-specified primary efficacy endpoint, results suggest that the device may be beneficial among high-risk subjects in potentially identifying asymptomatic events. Additionally, Holmes et al. (2019) published previously unreported results from the ALERTS trial that focused on pre-hospital delays during ACS events. The study appears to include events collected after the randomization period, when all participants had the alarm on. The authors reported reduced delays, with 55% [95% confidence interval (CI): 46% to 63%] of emergency department visits for ACS events less than two hours compared with 10% (95% CI: 2% to 27%) in the Alarms OFF group (p < 0.0001) and shorter median pre-hospital delay for myocardial infarction: 12.7 hours for Alarms OFF and 1.6 hour in Alarms ON subjects (p < 0.01). The findings of this latest publication are limited by what appears to be inclusion of events outside of the randomization period, which results in breaking the randomization benefit and could introduce possible biases.

Fischell et al. (2010) combined outcomes of two first in-human case series: the Brazilian CARDIOSAVER study (n = 20) and the U.S. DETECT study (n = 17). Intracardiac monitoring was performed in 37 individuals at high risk for ACS. The implanted monitor continuously evaluated the individuals ST segments sensed from a conventional pacemaker right ventricle apical lead, and alerted individuals to detected ischemic events. During follow-up (median 1.52 years, range 126 to 974 days), four individuals had ST-segment changes of greater than or equal to three standard deviations (SDs) of their normal daily range, in the absence of an elevated heart rate. This in combination with immediate hospital monitoring led to angiogram and/or intravascular ultrasonography, which confirmed thrombotic coronary occlusion/ruptured plaque. The median alarm-to-door time was 19.5 minutes (six, 18, 21, and 60 minutes, respectively). Alerting for demand-related ischemia at elevated heart rates, reflective of flow-limiting coronary obstructions, occurred in four individuals. There were two false-positive ischemia alarms related to arrhythmias, and one alarm due to a programming error that did not prompt cardiac catheterization. The author's concluded that shifts exceeding three SD from an individual's daily intracardiac ST-segment range may be a sensitive/specific marker for thrombotic coronary occlusion. Patient alerting was associated with a median alert-to-door time of 19.5 minutes for individuals at high risk of recurrent coronary syndromes who typically present with two to three hour delays. These studies did not evaluate final clinical outcomes and is limited by lack of comparison group.

Reference(s)

Avertix Guardian System website (United States). https://avertix.com/clinical-studies. Accessed April 29, 2025.

ECRI. AngelMed Guardian System (Angel Medical Systems, Inc.) for monitoring patients at high risk of acute coronary syndrome. Plymouth meeting (PA): ECRI; 2020 Jan. (Clinical Evidence Assessment). Updated February 23, 2022.

Fischell TA, Fischell DR, Avezum A, et al. Initial clinical results using intracardiac electrogram monitoring to detect and alert patients during coronary plaque rupture and ischemia. J Am Coll Cardiol. 2010 Sep 28;56(14):1089-98.

Gibson CM, Holmes D, Mikdadi G, et al. Implantable cardiac alert system for early recognition of ST-segment elevation myocardial infarction. J Am Coll Cardiology. 2019 April 23; 73(15); 1928-1930.

Holmes DR Jr, Krucoff MW, Mullin C, et al. Implanted monitor alerting to reduce treatment delay in patients with acute coronary syndrome events. J Am Coll Cardiol. 2019 Oct 22;74(16):2047-2055.

Code	Description
0558U	Oncology (colorectal), quantitative enzyme-linked immunosorbent assay (ELISA) for secreted colorectal cancer protein marker (BF7 antigen), using serum, result reported as indicative of response/no response to therapy or disease progression/regression
0559U	Oncology (breast), quantitative enzyme-linked immunosorbent assay (ELISA) for secreted breast cancer protein marker (BF9 antigen), serum, result reported as indicative of response/no response to therapy or disease progression/regression

The use of oncology, quantitative enzyme-linked immunosorbent assay (ELISA) for protein biomarkers (e.g., IGoCheck using BF7 antigen or MammoCheck using BF9 antigen) to monitor therapy and/or disease progression/regression response is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Blood-based biomarker panels are tests to assess the expression of protein cancer biomarkers that are expressed by cancer tissues to monitor for recurrence in between imaging tests. IGoCheck and MammoCheck are manufactured by Milagen, Inc. IGoCheck is a serum-based test developed to detect early-stage colorectal cancer recurrence and monitor therapy response and MammoCheck is a serum-based test developed to detect early-stage breast cancer recurrence and monitor therapy response. https://www.milagen.com/. (Accessed May 19, 2025).

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The evidence is insufficient to support the use of these blood based protein biomarker tests for cancer recurrence and monitor therapy and/or disease progression/regression response. Further studies are needed to determine the clinical utility of these tests.

Chavany et al. (2025) study explored a promising blood-based test for early detection of colorectal cancer (CRC) and advanced adenomas (AA), aiming to improve screening adherence by offering a less invasive alternative to colonoscopies and stool-based tests. Using a proprietary ELISA to detect two CRC-specific biomarkers (BF7 and CC3), researchers analyzed 241 serum samples and found significantly elevated levels of both markers in CRC patients compared to healthy individuals. CC3 also showed a strong association with AA. The test demonstrated 80% sensitivity and 90% specificity for CRC detection, with similar performance across early and late stages, and detected 81% of AA cases. These findings suggest the test could serve as an effective triage tool for CRC screening, pending further validation in a large prospective study.

Reference(s)

Chavany C, Dea J, Guevara M. et al., A protein-based blood panel test for the early detection of colorectal cancer and advanced neoplasia. Journal of Clinical Oncology, *[s. l.]*, v. 43, p. 46, 2025.

Code	Description
0559T	Anatomic model 3D-printed from image data set(s); first individually prepared and processed component of an anatomic structure
0560T	Anatomic model 3D-printed from image data set(s); each additional individually prepared and processed component of an anatomic structure (List separately in addition to code for primary procedure)
0561T	Anatomic guide 3D-printed and designed from image data set(s); first anatomic guide
0562T	Anatomic guide 3D-printed and designed from image data set(s); each additional anatomic guide (List separately in addition to code for primary procedure)

Due to insufficient evidence of safety and/or efficacy, the use of three dimensional (3D) printed anatomic models is unproven and not medically necessary for all indications including but not limited to:

- Manufacturing of customized devices
- Surgical planning

Clinical Evidence

Three dimensional (3D) printed anatomic models are models that are created in a 3-dimensional technology using 3D printers. These 3D printed models are derived from patient imaging and can be used to plan and rehearse procedures (e.g., evaluating approaches for inserting a cardiac valve) or to manufacture customized devices. The use of 3D printed models as part of preoperative planning is thought to improve patient outcomes and reduce surgery time. Anatomic 3D models are also used for medical education, such as informing patients or training students about the surgical expertise required when performing procedures.

Orthopedics

In a systematic review and meta-analysis of Harris Hip Scores (HHS), St. John et al. (2024) aimed to determine whether traditional or 3D-printed prostheses resulted in better functional outcomes in hip arthroplasty. The analysis included three studies with a total of 195 individuals, comparing highly porous 3D-printed (3DP) acetabular cups to non-3DP acetabular cups with conventional porosity. Both the control group and the 3DP group showed substantial improvements in HHS across all three studies. The pooled mean HHS for the control group was 38.15 (+6.02) at baseline and 80.30 (+4.79) at twelve months, an improvement of 42.15. For the 3DP group, the HHS was 37.81 (+5.84) at baseline and 90.60 (+4.49) at twelve months, an improvement of 52.79. Significant improvements were observed from baseline to twelve months in both the control group [$p = 0.02$, Cohen's D = 8.57 (1.48, 15.56)] and the 3DP group [$p < 0.01$, Cohen's D = 9.18 (3.50, 14.86)], but subgroup analysis revealed no significant differences between the groups ($p = 0.89$). Two of the studies were retrospective non-randomized controlled studies, and the third was a prospective non-randomized study. The authors noted that the lack of randomization introduced an inherent risk of bias. Despite these limitations, the authors concluded that 3DP hip arthroplasty shows promise in improving short-term hip outcomes compared to conventional treatment. However, more research, including randomized controlled trials and long-term studies, is needed to confirm these findings and assess the long-term utility of 3DP acetabular cups. There were limitations identified in this analysis. All studies on 3DP hip arthroplasty were limited to revision arthroplasty, which generally has worse outcomes than primary arthroplasty. Further research is needed to determine if the benefits of 3DP arthroplasty can be extended to primary arthroplasty.

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O'Connor et al. (2024) conducted a systematic review and meta-analysis to assess the benefits of 3D printing in orthopaedic surgery, highlighting its extensive applications in the field. Sixty-five studies met the inclusion criteria. The findings indicated that 3D printing in orthopaedics significantly reduces operative time, intraoperative blood loss, and fluoroscopy time. Additionally, there was a non-significant reduction in bone fusion time and length of hospital stay. The review demonstrated that 3D printing generally leads to notable improvements in key outcomes such as operative time, blood loss, and fluoroscopy use. As 3D printing becomes more affordable and accessible, further research should focus on secondary outcomes to facilitate its integration into routine clinical practice and guidelines. The meta-analysis had limitations, including the small sample sizes of the included studies, with a total of 278 individuals treated using 3D printing and some studies involving as few as eight patients. Another limitation was the varying definitions of operative time across the studies. A consistent definition of operative time would provide a more accurate estimate of the impact of 3D printing on this measure.

Baburaj et al. (2024) performed a systematic review and meta-analysis to determine if the surgical management of intra-articular distal humerus fractures performed with 3D printing assistance was faster and resulted in fewer complications and improved clinical outcomes than conventional methods. Three randomized trials with 144 cases were selected for the final analysis. Sixty-nine cases received support with 3D printing technology. The remaining 75 cases underwent surgery without the assistance of 3D printed models. Six occurrences (8.7%) of complications were reported in the 69 cases performed with 3D printing assistance and 11 (14.7%) complications among the 75 participants that received conventional surgery. The documented complications were wound infection and ulnar neuropathy. The authors concluded that although employing 3D printing assistance for distal humerus fractures holds promise for enhancing reduction precision and postoperative functional results, this method presents certain drawbacks including additional expenses associated with the creation of 3D models, typically transferred to patients, thereby augmenting their financial strain. Moreover, intricate 3D models necessitate significant preparation and printing time, restricting their utilization in emergency scenarios or cases of open fractures. Additionally, they added further high-quality studies are imperative to establish conclusive evidence. Limitations identified in this review include the lack of adequate long-term follow-up to assess potential complications, the relatively small sample sizes may have contributed to certain findings not achieving statistical significance, the absence of blinding among participants and personnel in most studies could have introduced bias, some studies did not furnish data on blood loss, and there was a scarcity of available research on the topic.

A 2021 ECRI clinical evidence assessment was conducted on the use of 3D printed anatomic models for orthopedic surgical planning focusing on outcomes from the use of 3D printing in orthopedic surgery compared with those of conventional orthopedic surgical procedures. The evidence search dates were from January 2016 to June 2021 with a review of two systematic reviews, five clinical studies, two systematic review abstracts, two clinical studies, for a total of 2,212 patients reported on. The studies utilized reported on patients with different conditions necessitating orthopedic surgery. The studies show utilizing 3D patient-specific anatomic models for procedure planning reduces operative time, though is not a benefit over conventional surgical approaches regarding functional status, complication rates, and other patient-oriented outcomes. The limitations of the evidence consist of low-quality evidence, the need for large-sample, multicenter Randomized Controlled Trials (RCT's) which would address the evidence gap and establish 3D printing's efficacy in a clinical setting. Other limitations consist of variation in outcomes reported, surgical procedure limits comparison in studies, high risk of bias, lack of follow up, and the studies conducted were outside the United States, thus results may not be generalized to the United States healthcare system. The 3D anatomic models may benefit surgical approach in planning for complex anatomy orthopedic surgeries, but there is a lack of high-quality RCTs to define benefits in orthopedic surgery (ECRI 2021).

Hayes issued a report in 2019 on the use of three-dimensional printed orthopedic implants for knee, hip, and spinal indications which indicated that the overall quality of the body of evidence was moderate in size, but very low in quality. The Hayes report indicated that there is a need for larger, well-designed controlled trials to better determine risks and benefits over the long term and to define patient selection criteria. Hayes updated the report in 2021 and found that the evidence published since the 2019 report would not likely change their earlier conclusions (Hayes, 2019; Updated October 2022).

ECRI issued a report for the MySpine® Patient-specific Guide in 2021. The MySpine Patient-specific Guide system is comprised of a set of custom-made anatomic models intended to provide intraoperative assistance in pedicle screw placement during spinal surgery. The system uses 3D printing to create physical models of the target vertebrae and screw placement guides with tubes at each screw's preplanned position and angle. The ECRI report indicated that the evidence suggests that MySpine allows the surgeon to customize parameters such as trajectory and screw dimensions during preoperative planning and may improve pedicle screw placement accuracy over freehand implantation; however, published studies include too few patients and are at too high a risk of bias to be conclusive (ECRI 2021).

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Hasan et al. (2020) compared the migration of cementless, 3D-printed total knee arthroplasty (TKA) to cemented TKA of a similar design up to two years of follow-up using radio stereometric analysis (RSA) known for its ability to predict aseptic loosening. A total of 72 participants were randomized to either cementless 3D-printed or a cemented cruciate retaining TKA. RSA and clinical scores were evaluated at baseline and postoperatively at three, 12, and 24 months. A mixed model was used to analyze the repeated measurements. The mean maximum total point motion (MTPM) at three, 12, and 24 months was 0.33 mm [95% confidence interval (CI) 0.25 to 0.42], 0.42 mm (95% CI 0.33 to 0.51), and 0.47 mm (95% CI 0.38 to 0.57) respectively in the cemented group, versus 0.52 mm (95% CI 0.43 to 0.63), 0.62 mm (95% CI 0.52 to 0.73), and 0.64 mm (95% CI 0.53 to 0.75) in the cementless group (p = 0.003). However, using three months as baseline, no difference in mean migration between groups was found (p = 0.497). Three implants in the cemented group showed a > 0.2 mm increase in MTPM between one and two years of follow-up. In the cementless group, one implant was revised due to pain and progressive migration, and one participant had a liner-exchange due to a deep infection. The authors concluded that the cementless TKA migrated more than the cemented TKA in the first two-year period. This difference was mainly due to a higher initial migration of the cementless TKA in the first three postoperative months after which stabilization was observed in all but one maligned and early revised TKA. The authors indicated that a longer follow-up is needed to determine whether the biological fixation of the cementless implants will result in an increased long-term survivorship.

Moralidou et al. (2020) conducted a systematic review of the existing literature for the use of 3D pre-operative planning in primary total hip arthroplasty (THA). The review focused on (1) the accuracy of implant sizing, restoration of hip biomechanics and component orientation; (2) the benefits and barriers of this tool; and (3) current gaps in literature and clinical practice. A total of 43 full scientific articles were reviewed. Clinical studies have highlighted the accuracy of 3D pre-operative planning in predicting the optimal component size and orientation in primary THAs. Component size planning accuracy ranged between 34-100% and 41-100% for the stem and cup, respectively. The absolute, average difference between planned and achieved values of leg length, offset, center of rotation, stem version, cup version, inclination and abduction were 1 mm, 1 mm, 2 mm, 4°, 7°, 0.5° and 4°, respectively. The benefits of 3D pre-operative planning include 3D representation of the human anatomy for precise sizing and surgical execution. The Barriers of 3D pre-operative planning include increased radiation dose and learning curve. According to the authors, the long-term evidence investigating this technology is limited. Emphasis should be placed on understanding the health economics of an optimized implant inventory as well as long-term clinical outcomes.

In a systematic review, Burnard et al. (2020) assessed the clinical evidence for efficacy and safety of both patient-specific (PS) and Off-The-Shelf (OTS) 3DP spinal implants through review of the published literature. The aim was to evaluate the clinical utility of 3DP devices for spinal surgery. A systematic literature review of peer-reviewed papers featured on online medical databases evidencing the application of 3DP (PS and OTS) surgical spine implants was conducted in accordance with PRISMA guidelines. Twenty-two peer-reviewed articles and one book-chapter were eligible for systematic review. The published literature was limited to case reports and case series, with a predominant focus on PS designs fabricated from titanium alloys for surgical reconstruction in cases where neoplasia, infection, trauma, or degenerative processes of the spine have precipitated significant anatomical complexity. The authors concluded that PS and 3DP OTS surgical implants have demonstrated considerable utility for the surgical management of complex spine pathology. The reviewed literature indicated that 3DP spinal implants have also been used safely, with positive surgeon- and patient-reported outcomes. However, these conclusions are tentative as the follow-up periods are still relatively short and the number of high-powered studies was limited.

Malahias et al. (2020) performed a systematic review on the performance of highly coated titanium acetabular cups produced via 3D printing in primary and revision THA procedures. The aim of the study was to find the revision rate and the rate of aseptic loosening of highly porous titanium cups used in primary THA cases and in revision cases with acetabular bone loss. The authors reviewed 16 studies, all observational, which included 11,282 patients; ten studies were retrospective and six prospective. At the conclusion of the review, the authors determined there was moderate quality evidence which demonstrated that the use of highly porous titanium acetabular components in both primary and revision THA cases was associated with satisfactory clinical outcomes. The overall survival rate in primary surgical cases was 99.3% and 93.5% for revisions. While the results were positive, further research of higher quality is required to generate more evidence-based conclusions regarding the longevity of highly porous titanium acetabular implants compared with conventional titanium equivalents. Limitations included a lack of well-designed prospective studies, randomization, and blinding. Furthermore, 3D-printed cups were used in only three of the reviewed studies, limiting the implication of this study to the topic of interest for this policy.

Otorhinolaryngology

Lui et al. (2024) performed a systematic review to evaluate the prospects and applications of 3D printing in ear reconstruction education, preoperative planning and simulation, the production of intraoperative guide plates, and other related areas. A total of 24 studies were selected for qualitative analysis. The most prevalent uses of 3D printing, with

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individual counts (n) as follows were template (n = 14), training or education (n = 5), preoperative planning (n = 4), and medical device (n = 1). The authors indicated as advancements in training standards, technology and medical practice continue, 3D printing is positioned to emerge as an asset in auricular reconstruction. They added surgeons stand to gain from mastering the principles and utilization of this technology. However, to firmly establish the superiority of 3D printing, a significant body of empirical studies and rigorous testing is imperative. Limitations of this study included lack of high-quality clinical investigations, randomized controlled trials, cohort studies and research.

Omari et al (2022) conducted a systematic review on 3D printed models for patient-specific interventions in otology and auricular management with the goal of exploring present use of 3D printed patient specific otologic interventions along with state of evidence, strengths, limitations, and future possibilities. Data on the manufacturing process and interventions was identified through PubMed, EMBASE, the Cochrane Library, and Web of Science. A total of 590 studies were extracted with 63 considered eligible for inclusion. Of the studies for outer ear interventions 73% were utilized. The consensus of the reports was optimistic including increased surgical precision, quick manufacturing and operation time, reduced cost, and complications. Limitations to the report were the poor quality due to studies failing to use relevant objective outcomes, compare new interventions, and sufficiently describe manufacturing. The authors conclude that although promising, it remains unclear if 3D-Printing improves patient outcomes. Furthermore, there is insufficient reporting which makes the manufacturing and reproducibility of the 3D-printed interventions compromised.

Oral and Maxillofacial

Gernandt et al. (2023) performed a systematic review to assess the contribution of 3D printing on the management of benign jaw lesions. Thirteen studies involving 74 individuals were included in this review. 3D printing facilitated the creation of anatomical models, intraoperative surgical guides, or both, enabling the effective extraction of maxillary and mandibular bone lesions. The primary advantages reported for printed models included enhanced visualization of the lesion and its anatomical context, aiding in preoperative risk assessment. Surgical guides, designed as drilling locators or osteotomy cutting guides, played a crucial role in reducing surgical duration and enhancing surgical precision. Limited information was available regarding printing time and associated expenses across the studies. Additionally, only a small number of complications, such as nerve injury or tooth necrosis, were documented in the included literature. This review highlighted the advantages of employing 3D printing technology for the extraction of various benign jaw lesions, however, the authors concluded while the design of 3D anatomical models seems to serve as a valuable resource for preoperative simulation and training in complex surgical procedures, additional research with more robust evidence is necessary to validate these preliminary findings. This review was limited by the low prevalence of this type of bone lesion. The majority of the available data stems from case reports and case series, which often involved a limited number of patients and lack of comparative analyses, thereby diminishing the overall quality of evidence in the included studies. Another notable limitation of this study is the variation in the endpoints assessed across the studies which posed challenges in drawing conclusions.

Neurology

ECRI issued a clinical evidence assessment in 2021 on the use of 3D printed anatomic models for neurologic surgical planning. This assessment consisted of seven studies: two nonrandomized comparison studies, one pre-post treatment study, and four case series. The results suggested 3D printed models may have potential advantages in neurological surgery planning, however the studies were found to have a high risk for bias, too few patients, low quality, and quantity to be conclusive in determining the effects of patient outcomes. Larger high quality comparison studies reporting on patient outcomes are needed to define the benefits of 3D printing models in planning neurologic surgery (ECRI 2021).

Cardiovascular

An ECRI (2025) clinical evidence assessment for the Contour 3D Annuloplasty Ring suggests the available data quality is very low. Two nonrandomized comparison studies and three case series that evaluated the safety and effectiveness of Contour 3D for treating tricuspid regurgitation were reviewed. The studies available were either too biased or reported on too few relevant outcomes to determine how Contour 3D's safety and effectiveness compares to other rings and surgical techniques for tricuspid valve repair. There is a need for randomized controlled trials or other high-quality prospective studies with well-matched patient groups to compare Contour 3D with other implants.

In 2021 ECRI issued a clinical evidence assessment on the use of 3D printed anatomic models for cardiovascular surgical planning. The assessment consisted of evidence from three small studies, two comparison studies, and one case series. The studies proposed 3D-printed models may have possible advantages in the planning of cardiovascular surgery, however the evidence is too inadequate in quantity, quality, and high risk for bias. Due to these limitations, the studies cannot determine how utilizing 3D printed models affects patient outcomes compared to conventional planning. Greater sophisticated quality comparison studies that report on the results of patients with longer follow up are required to define the benefits of 3D printing models (ECRI 2021).

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Deng et al (2021) conducted an RCT on 3D printed models in preoperative ventricular septal defect repair and its utility for congenital heart disease repair. The study was accomplished at the time of consent where guardians of candidates for ventricular septal defect repair were provided comprehensive description of anatomy, purpose of surgery, complications and risks using 3D vs 2D prints. Data was composed from a questionnaire completed by participants and guardians and medical records which were statistically evaluated. The outcomes of the study display advancements in ratings of the understanding of ventricular septal defect anatomy, potential complications, and surgical procedure in the group that used the 3D model with no difference in overall ratings of consent process. Comparable in the two groups were the clinical outcomes as represented by the duration of intensive care stay and intubation duration. The conclusion of the study is that 3D printing is an effective tool for consent in congenital heart surgery, however, the impact of 3D printing used on long term outcomes remains to be defined.

Tuncay and van Ooijen (2019) performed a systematic review to evaluate the application of 3D printing to cardiac valve disease. The 29 included papers showed that the most reported application areas are preoperative planning (63%), followed by training (19%), device testing (11%), and retrospective procedure evaluation (7%). According to the authors, current technology allows for accurate printing of cardiac anatomy in materials that resemble the properties of the actual heart and vessels. The authors indicated that the actual clinical benefit of 3D printing remains to be proven.

Lau and Sun (2018) performed a systematic review to analyze the clinical applications and accuracy of 3D printing in congenital heart disease (CHD), as well as to provide an overview of the software tools, time and costs associated with the generation of 3D printed heart models. A total of 28 studies met selection criteria for inclusion in the review. More than half of the studies were based on isolated case reports with inclusion of one-12 cases (61%), while ten studies (36%) focused on the survey of opinion on the usefulness of 3D printing by healthcare professionals, patients, and others, and the remaining one involved a multicenter study about the clinical value of 3D printed models in surgical planning of CHD. According to the authors, the analysis shows that patient-specific 3D printed models accurately replicate complex cardiac anatomy, improve understanding and knowledge about congenital heart diseases and demonstrate value in preoperative planning and simulation of cardiac or interventional procedures, assist surgical decision-making and intra-operative orientation, and improve patient-doctor communication and medical education. The authors indicated that most of the studies on 3D printing of CHD are case reports so the actual clinical value of 3D technology could not be confirmed due to the potential bias in the study design. Future studies should include more cases of different types of CHD to investigate their clinical value on patients' outcomes.

Surgical Education and Evaluation

Michelutti et al. (2024) conducted a systematic review to explore the applications of 3D printing in managing orbital pathologies. By examining 12 studies, they found that 3D printing can be used to directly create implants for fracture reconstruction or to produce 3D models of the affected anatomical regions. However, they added creating 3D models is time-consuming, involving both virtual surgical planning and the printing process. Additionally, costs can be high depending on the printer and materials used. The authors concluded that 3D printing is an excellent tool for managing orbital pathologies, improving preoperative visualization, surgical preparation, precision, and outcomes. Despite these benefits, the review highlighted several limitations, including a lack of randomized clinical trials. More evidence-based studies are needed to fully understand the medical impact of 3D printing in this field.

In 2018 The Radiological Society of North America (RSNA) and 3D printing special interest group (SIG) published a document regarding medical 3D printing and suitability for clinical scenarios. The document reports on the clinical scenarios where difficulty in pathology requires a transformation of clinical imaging into a physical model. The conclusion being common clinical standards concerning proper use, information and material management, and quality control are required to safeguard the greatest possible clinical benefit from 3D printing.

Langridge et al. (2018) performed a systematic review of the uses of 3D printing within surgical training and assessment. Overall, 49 studies were identified for inclusion in the qualitative analysis. Heterogeneity in study design and outcome measures used prohibited meaningful meta-analysis. 3D printing has been used in surgical training across a broad range of specialties but most commonly in neurosurgery and otorhinolaryngology. The authors concluded that 3D printing technology has a broad range of potential applications within surgical education and training. Although the field is still in its relative infancy, several studies have already demonstrated its usage both instead of and in addition to traditional educational methods. The authors indicated that within the current literature review there is a lack of high-quality randomized control studies to assess the effectiveness of 3D printing within the preoperative planning setting. Most evidence related to the usage of 3D printing and their effect on clinical endpoints is an underexplored area with the majority of literature focusing on anecdotal case reports without assessing comparable clinical endpoints. The authors recommended that future studies should compare 3D printed models with current best surgical practice when measuring use within the preoperative planning setting. The implication of these findings on patient care is however unclear.

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Code	Description
0571T	Insertion or replacement of implantable cardioverter-defibrillator system with substernal electrode(s), including all imaging guidance and electrophysiological evaluation (includes defibrillation threshold evaluation, induction of arrhythmia, evaluation of sensing for arrhythmia termination, and programming or reprogramming of sensing or therapeutic parameters), when performed
0572T	Insertion of substernal implantable defibrillator electrode
0573T	Removal of substernal implantable defibrillator electrode
0574T	Repositioning of previously implanted substernal implantable defibrillator-pacing electrode
0575T	Programming device evaluation (in person) of implantable cardioverter-defibrillator system with substernal electrode, with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, review and report by a physician or other qualified health care professional

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Code	Description
0576T	Interrogation device evaluation (in person) of implantable cardioverter-defibrillator system with substernal electrode, with analysis, review and report by a physician or other qualified health care professional, includes connection, recording and disconnection per patient encounter
0577T	Electrophysiologic evaluation of implantable cardioverter-defibrillator system with substernal electrode (includes defibrillation threshold evaluation, induction of arrhythmia, evaluation of sensing for arrhythmia termination, and programming or reprogramming of sensing or therapeutic parameters)
0578T	Interrogation device evaluation(s) (remote), up to 90 days, substernal lead implantable cardioverter-defibrillator system with interim analysis, review(s) and report(s) by a physician or other qualified health care professional
0579T	Interrogation device evaluation(s) (remote), up to 90 days, substernal lead implantable cardioverter-defibrillator system, remote data acquisition(s), receipt of transmissions and technician review, technical support and distribution of results
0580T	Removal of substernal implantable defibrillator pulse generator only
0614T	Removal and replacement of substernal implantable defibrillator pulse generator

Insertion, repositioning, programming, interrogation, and evaluation of implantable cardioverter-defibrillator system with a substernal (extravascular) electrode are considered unproven and not medically necessary due to insufficient evidence of efficacy.

Clinical Evidence

On October 20, 2023, the FDA approved the Aurora EV-ICD™ System (Medtronic, Mounds View, MN) under its premarket approval (PMA) process. This device is indicated for the primary or secondary prevention of sudden cardia death due to life threatening ventricular tachyarrhythmias. Refer to the following website for further information: https://www.accessdata.fda.gov/cdrh_docs/pdf22/P220012A.pdf. (Accessed April 23, 2025).

In 2025, Friedman et al. reported the final results of the pivotal study conducted in 2022 (Friedman et al., 2022 below). The original study enrolled individuals with a Class I or IIa indication for a single-chamber implantable cardioverter defibrillator, and these results report the outcomes at the end of the study to (three year) assess freedom from major system or procedure related complications and appropriate and inappropriate therapy rates. Implantation was successful in 299 of the original 356 participants and results over three years show continued safety and efficacy with no major complications not seen in other types of ICD devices. There was a 77% ATP success rate with the EV ICD system preventing shocks in nearly half of spontaneous VT/ventricular fibrillation episodes. A small percentage of patients had the ATP programmed to “off” at two years, and this increased through three years, and was due to sensations related to in-office electrical testing. Conversely, the number of participants with ATP programmed “on” increased over the course of the study, indicated that perhaps in-office testing may not completely reflect patient experience. There was an 89% rate of freedom from major system or procedure related complications at three years, a slight increase from the 92.6% rate at six months. Additionally, the rate of inappropriate shocks went from 9.8% at six months to 17.5% at three years [the currently available Aurora EV-ICD system now includes a novel algorithm (Smart Sense) aimed at reducing P-wave oversensing, which was not available at any point during the Pivotal study]. More than 70% of patients who received an inappropriate shock did not experience a subsequent inappropriate shock after device interrogation, suggesting an opportunity for programming optimization. Pacing and electrical performance of the EV ICD were consistent, demonstrating the stability of leads placed substernally. R-wave amplitudes increased slightly after hospital discharge but then stabilized through the 3-year follow-up and were similarly stable regardless of body positioning or vector configuration. The authors concluded that the EV ICD system terminated spontaneous ventricular arrhythmias with a high rate of ATP and defibrillation therapy success and a low major complication rate through long-term follow-up. These results are limited by the lack of a comparator to other established approaches.

Crozier et al. (2025) reported the preliminary results of the acute periprocedural (through 30 days post discharge) outcomes of the Aurora EV-ICD System of the postmarket Enlighten registry study, which is an ongoing, global, prospective, postmarket registry study. Participants from the premarket EV-ICD studies had the option of enrolling into the Enlighten Study for continued follow-up, however, this study analysis includes only newly enrolled postmarket patients implanted with the Aurora EV-ICD system. Procedure characteristics and outcomes, defibrillation testing details, system- or procedure-related major complications, electrical measurements, and pacing therapy programming through discharge were analyzed. In the registry, 288 patients underwent an implantation attempt of an Aurora EV-ICD device, by eighteen different clinicians across nineteen countries, and this was successful in all but one. Subsequent electrical testing excluded seven participants from proceeding to follow up due to inadequate R-wave sensing. Defibrillation testing at

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implant was performed in 194 participants and although premarket studies recommended a 10-J safety margin, in this study, the safety margin was left to physician discretion. The rate of system or procedure related major complications at discharge was 3.9% and the most common were two patients with lead dislodgement and two with pneumothorax. The authors concluded that the device has a low rate of periprocedural complications and high defibrillation success in a global real-world setting. This study is limited by its registry design without a comparison group, and short-term outcomes through hospital discharge. This difference in study design and differing study protocols between this and premarket trials, and further long-term research is needed to assess the safety and efficacy of the Aurora EV-ICD system.

In a 2023 ECRI clinical evidence assessment on the Aurora Extravascular Implantable Cardioverter-Defibrillator, it was concluded that based on analysis of two studies that included 337 individuals, there is too few data to draw conclusions on the long-term safety and effectiveness of this device. It was noted that studies reported 10% of patients received inappropriate shocks through 10 month follow up, and 17% at three years. Additional studies reporting on longer-term follow-up in more patients, how it compares with other ICDs (transvenous or subcutaneous), as well as and the potential long-term benefits in patients who need to preserve venous access or who are not candidates for transvenous ICDs are needed.

In 2022, Friedman et al. (included in ECRI clinical evidence assessment) conducted a prospective, single-group, nonrandomized, premarket global clinical study on the efficacy and safety of a substernally implanted extravascular ICD system in individuals with class I or IIa indications for an implantable cardioverter defibrillator (ICD) for primary or secondary prevention. The primary efficacy endpoint was effective defibrillation at implantation. The efficacy goal would be met if the lower boundary of the one-sided 97.5% confidence interval (CI) for the percentage of those with effective defibrillation was greater than 88%. The primary safety endpoint was independence from the major system- or procedure-related complications at six months. The safety aim would be met if the lower margin of the one-sided 97.5% CI for the percentage of individuals free from such complications was more substantial than 79%. The study resulted in the enrollment of 356 participants; 316 had an implantation attempt. Amongst the 302 individuals in whom ventricular arrhythmia could be induced and who accomplished the defibrillation testing protocol, the percentage of those with effective defibrillation was 98.7% (lower boundary of the one-sided 97.5% CI, 96.6%; $p < 0.001$ for the comparison with the performance goal of 88%); 299 of 316 participants (94.6%) were discharged with an operational ICD system. The Kaplan-Meier estimate of the percentage of those without major system- or procedure-related complications at six months was 92.6% (lower boundary of the one-sided 97.5% CI, 89.0%; $p < 0.001$ for the comparison with the performance goal of 79%). No major intraprocedural complications were reported. At six months, twenty-five major complications were observed in 23 of 316 individuals (7.3%). The success rate of anti-tachycardia pacing, as calculated with general estimating equations, was 50.8% (95% CI, 23.3 to 77.8). A total of twenty-nine participants received 118 incorrect shocks for eighty-one arrhythmic episodes. Eight systems were explanted without extravascular implantable cardioverter defibrillator (EV-ICD) replacement over the 10.6-month mean follow-up period. The authors concluded that substernally implanted EV-ICDs are safe and can identify and stop induced ventricular arrhythmias at implantation. The study is limited by lack of comparison to a standard therapeutic approach.

In 2021, Swerdlow et al. studied the sensing and arrhythmia detection performance of an EV-ICD in a single-arm pilot study. To conduct the study, electrograms were post-processed from induced ventricular fibrillation (VF) at implant to uncover virtual detection times for each programmable sensitivity and the least-sensitive safe sensitivity setting. For ambulatory individuals, programmed sensitivity supplied at least a double safety margin for identifying induced VF. Noise discrimination was stress evaluated, and source, posture, and lead maturation influences were governed by electrogram amplitude. Telemetry Holter monitors were used to measure under-sensing and over-sensing. The study's results showed that for twenty individuals at implant, the least-sensitive safe sensitivity for VF recognition varied from 0.1 to 0.6 mV. Seventeen participants were followed up for a total of 16.6 patient-years. Electrogram amplitudes were even over time, but there were substantial variations between postures and sensing vectors. For the primary sensing vector, the weighted over-sensing and under-sensing rates were 1.03% and 0.40%, correspondingly, on a beat-to-beat basis. Oversensing did not trigger improper therapy for individuals with in-situ leads. Oversensing discriminators suppressed VF recognition in four out of five spontaneous, continuous over-sensed episodes. Supraventricular Tachycardia-Ventricular Tachycardia (SVT-VT) discriminators appropriately categorized 93% of 128 sustained Supraventricular Tachycardia (SVT)s in monitor zones. The authors concluded that over-sensing in the EV-ICD pilot study did not cause incorrect therapy during ambulatory follow-up of stable leads.

In the first-in-human prospective nonrandomized pilot single-arm trial, Crozier et al., 2020 (included in the ECRI clinical evidence assessment) aimed to assess the safety and performance of an EV-ICD. The study was conducted at four centers in Australia and New Zealand. Twenty- one participants were identified for ICD implantation. Participants received EV-ICD systems. Data collection involved major systemic and procedural adverse events, defibrillation testing at implantation, and sensing and pacing thresholds. The study's results showed that between 20 individuals who underwent effective implantation, the median defibrillation threshold was 15 J, and 90% passed defibrillation testing with a ≥ 10-J

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safety margin. The mean R-wave amplitude was 3.4 ±2.0 mV, the mean ventricular fibrillation amplitude was 2.8 ±1.7 mV, and the pacing was victorious in 95% at ≤ 10 V. There were no intraprocedural complications. Two individuals had undergone elective chronic system extraction since hospital discharge. In the fifteen participants implanted, the systems were steady in long-term follow-up. The authors concluded that there is the practicability of substernal lead placement, defibrillation, and pacing with a chronically implanted system. There were no major acute complications and pacing, defibrillation, and sensing performance at implantation were adequate in most people.

In 2019, Boersma et al. published results from the ASD2 (Acute Extravascular Defibrillation, Pacing, and Electrogram) study evaluating the ability to adequately sense, pace, and defibrillate persons with a novel ICD lead implanted in the substernal space. This ASD2 study was the first reported human clinical study of pacing, sensing, and defibrillation from a lead designed specifically for the substernal space. In their single-arm study, the substernal lead was implanted in 79 individuals, with a median implantation time of 12.0 ±9.0 min. Ventricular pacing was successful in at least one vector in 76 of 78 participants (97.4%), and 72 of 78 (92.3%) participants had capture in ≥ 1 vector with no extracardiac stimulation. A 30-J shock successfully terminated 104 of 128 episodes (81.3%) of ventricular fibrillation in sixty-nine individuals. There were 7 adverse events for six individuals causally (n = 5) or possibly (n = 2) related to the ASD2 procedure. The authors concluded that the ASD2 study demonstrated the ability to pace, sense, and defibrillate using a lead designed specifically for the substernal space. The proximity of the lead to the pericardium resulted in R-wave amplitudes amenable to ICD sensing, a high rate of pacing capture, and a low degree of extracardiac stimulation during pacing and defibrillation efficacy was > 80% with a single 30-J shock. The authors concluded that further investigation for individuals who are ambulatory is needed, but taken together, these results demonstrated the feasibility of a novel extravascular approach to ICD therapy delivery.

In the Substernal Pacing Acute Clinical Evaluation (SPACE) study, Sholevar et al. (2018) evaluated the feasibility of pacing from an extravascular substernal location. This primary purpose of this prospective, nonrandomized, multicenter, feasibility single-arm study was characterization of pacing from the substernal space. Evaluation of extracardiac stimulation and recording electrograms were secondary goals. A commercially available electrophysiology catheter was implanted in the substernal space via minimally invasive subxiphoid access. Eligible participants were those undergoing cardiac surgery with midline sternotomy, primary ICD system implantation, or epicardial ventricular tachycardia ablation. Catheter placement was successful in all twenty-six participants who underwent the procedure. The mean placement time was 11.7 ±10.1 minutes. Eighteen individuals (69%) had successful ventricular capture in ≥ 1 tested vector. The mean pacing threshold at a pulse width of 10 ms was 7.3 ±4.2 mA across all vectors (5.8 ±4.4 V). The mean R-wave amplitude ranged from 2.98 to 4.11 mV in the unipolar configuration and from 0.83 to 3.95 mV in the bipolar configuration. One participant with a low level of extracardiac stimulation was identified. Suboptimal catheter placement or presumed air ingression was associated with failed capture. The author's concluded pacing is feasible from the extravascular substernal location. Limitations include the small population size, and the individuals were not typical those who would receive a defibrillator. Future studies would ideally avoid the use of paralytic medications to allow the investigation of extracardiac stimulation and will need to evaluate chronic substernal therapy delivery in for individuals with indications for a permanent ICD.

In 2017, Chan et al. prospective, nonrandomized feasibility study assessed the defibrillation efficacy of the substernal-lateral electrode configuration. The study was conducted in subjects scheduled for midline sternotomy or implant of an ICD. Using a percutaneous subxiphoid method, a blunted end tunneling tool was used to insert a defibrillation lead backside of the sternum. A skin patch electrode was placed on the left mid-axillary line at the fourth to fifth intercostal space. After ventricular fibrillation induction, a single 35-J shock was delivered between the lead and skin patch. The study's results showed that of sixteen subjects (12 males, four females; mean age: 61.6 ±11.8 years) enrolled, the mean lead placement time was 11.1 ±6.6 min. Of the fourteen subjects with effectively induced ventricular fibrillation episodes, 13 (92.9%) had thriving defibrillation. The one failure was linked to high and lateral shock coil placement. The average ventricular fibrillation duration was 18.4 ±5.6 s with a shock impedance of 98.1 ±19.3 ohms. Of the 11 subjects with coil-patch electrograms, the mean R-wave amplitude during sinus rhythm was 3.0 ±1.4 mV. The authors concluded that the initial data shows that substernal defibrillation is feasible and effective defibrillation can be accomplished with the shock energy offered in current TV-ICDs. This may open new alternatives to EV-ICD therapy.

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Code	Description
0581T	Ablation, malignant breast tumor(s), percutaneous, cryotherapy, including imaging guidance when performed, unilateral
19105	Ablation, cryosurgical, of fibroadenoma, including ultrasound guidance, each fibroadenoma

Cryoablation of breast carcinoma and fibroadenoma is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

The National Comprehensive Cancer Network (NCCN) does not mention cryotherapy for the treatment of breast cancer in its clinical practice guidelines in oncology (NCCN, 2025).

The Washington University School of Medicine is sponsoring and currently recruiting for a clinical trial to study the safety and efficacy of cryoablation in individuals, at least 50 years of age, with low risk, early- stage breast cancer (COOL-IT: Cryoablation vs Lumpectomy in T1 Breast Cancers: A Randomized Controlled Trial With Safety Lead-in). Inclusion criteria for this trial, which started in April 2024, is “diagnosis of invasive ductal carcinoma of the breast of Luminal type A (ER/PR positive, Her-2 negative) that is grade 1 or 2 with intraductal component < 25%. Must be T1N0M0 (2 cm or less).” The expected enrollment is 256 individuals, with an estimated completion date of October, 2031. (clinical trials identifier number NCT05505643).

In an emerging technology report, Hayes (2024) comments specifically on the ProSense System (IceCure Medical) for low risk early-stage breast cancer. The system, which has FDA clearance for cryogenic destruction of tissue during surgical procedures, is under review by the FDA for use in treatment of early-stage low-risk breast cancer in patients who are not suitable candidates for surgical alternatives. The Hayes report identified two published studies including one with five-year outcomes of the pivotal, single arm study and one prospective single-arm trial. The report states that although there are many cryoablation systems with FDA clearance, none are currently specifically indicated for breast cancer treatment.

In a prospective pilot study by Galati et al. (2024), the efficacy, safety and patient satisfaction of ultrasound-guided cryoablation of breast cancer (BC)was evaluated. The study included 20 participants with early-stage BC, of which 10 (mean age 65, 90% menopausal, mean tumor size 9.9 mm) underwent cryoablation (cryo-group) and 10 (mean age 62,60% menopausal, mean tumor size 10.5 mm) underwent routine surgery (control group). Fifteen of the cases had one to four axillary sentinel lymph node dissection while the remaining five cases had between six to eight lymph nodes removed. Surgery was quadrantectomy in 19 cases while one participant underwent a mastectomy. The post-procedure status of the cryo-group was evaluated with MRI in five participants, with contrast-enhanced mammography (CEM) in four participants and with ultrasound in one participant who refused MRI and CEM. Participants received a satisfaction questionnaire within 10 days from surgical resection to assess their level of pain during the procedure and one week after the procedure, to assess for post-operative symptoms (such as swelling or hematoma), their need for analgesics or antibiotics the esthetic outcome and whether they would recommend the treatment to others. The authors reported that, in the cryo-group, the procedure was completed, and steatonecrosis was seen in all 10 cases with complete tumor ablation in nine (90%) and that MRI or CEM correctly predicted cryoablation technical efficacy in nine out of nine cases (complete cryoablation in eight participants and incomplete cryoablation in one participant). Participant satisfaction in the cryo-group was reported to show a median pain rating of three during the procedure with some swelling in the treated area post-procedure, with pain rated as a two one-week post-procedure in eight of the ten cases and as a one in the other two participants. Cosmetic results were reported by the authors to be scored as an eight by 50% of the participants, nine by two of the participants and ten by three of the participants. No reports of wound infection or other complications were

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reported, beyond the use of analgesics as suggested by the physician in 50% of the participants. The control group was reported to have a pain rating of three by 40% of the participants, five by one participant, six by two participants and seven by three of the participants for a median pain rating of five. The authors concluded that ultrasound-guided cryoablation of early-state BC is well accepted by patients, effective, and safe, and that MRI and CEM were able to predict the procedure's technical efficacy. Limitations of the study included the small sample size, the single center design, and the use of contrast enhancing imaging which excluded some participants.

Vogl et al. (2024) conducted a single-center retrospective study to evaluate the efficacy and safety of liquid-nitrogen based CT-guided cryoablation (CA) for the curative treatment of primary breast cancer. The study included 45 female patients (mean age 55.6 years) with 56 tumors (mean axial tumor diameter 1.6 cm with 10 above 2 cm in diameter) who had been treated by CT-guided CA in a curative intention for non-metastatic patients, as well as to achieve local tumor control in patients with metastases. Patients included 11 who had tumors that were disease recurrences of preexisting tumors and 21 patients with metastatic disease, 18 of which were axillary lymphatic metastases. The authors reported that no complications were observed in any of the 56 ablations with 100% complete ablation achieved in all cases. Four cases (8.9%) of local tumor progression were reported and six cases (13.3%) of intramammary distant recurrence were identified, while extramammary tumor progression was observed in seven patients (15.6%). The authors reported that the mean overall survival time was 4.13 years, the overall mean progression-free survival was 2.5 years, and the mean local progression-free survival was 2.9 years. The authors concluded that cryoablation was safe and effective for treatment of primary breast cancer tumors; however, potential for improvement exists and further evidence is needed. Limitations of the study include the heterogeneity of the study population, the retrospective, single-center design, the small sample size and the lack of a comparator. This study was included in the Hayes report above.

Van de Voort et al. (2021) performed a systematic review and meta-analysis of 37 articles which included 1266 patients that underwent a variety of ablations to treat small breast cancers and whether the intervention was an effective method to treat early-stage breast cancer with tumors ≤ 2 cm. Analysis included comparison of the five different ablation therapies and complication rates. Twenty-four articles were reviewed by intervention. These included 24 radiofrequency ablations (RFA), 1 microwave ablation (MWA), 5 laser ablation, 3 high intensity focused ultrasound (HIFU) and 8 cryoablation. Complete ablation and complication rates by intervention were RFA 92% and 9.4%, MWA 87% and 13%, Laser Ablation 64% and 17.7%, HIFU 61.8% and 12.1% and Cryoablation 80.3% and 5%. The authors concluded that an overall complete ablation rate for all patients was a combined 86%. Cryotherapy could be considered a promising alternative to surgical resection and potentially reduce treatment burden, morbidity and improve cosmetic outcome. However, the studies analyzed were non-comparative and small-sized therefore the results should not lead to conclusions, but a basis for larger randomized controlled trials.

Cui et al. (2021) conducted a prospective study, registered in ClinicalTrials.gov under the identifier number NCT-02860104, to evaluate the efficacy of microwave ablation (MWA) for benign breast lesions (BBLs) and explore probable factors associated with the volume reduction rate (VRR) of ablated lesions. From November 2013 to December 2017, a total of 80 patients with 104 biopsies proven BBLs larger than 2 cm in size underwent MWA. After the procedure, participants were followed up via physical and imaging examination consisting of contrast-enhanced ultrasound (CEUS) and magnetic resonance imaging (MRI). Possible factors associated with 12-month volume reduction rate (VRR) were assessed, including basic patient characteristics, index lesions and parameters of ablation technique. The mean tumor size was 2.6 ±0.6 cm (ranging 2.0-6.3 cm). Of the 104 lesions, 70 were fibroadenomas, 27 adenosis and 7 fibrocystic changes. Post-procedure CEUS or contrast-enhanced MRI showed that all lesions were completely ablated. No immediate or delayed complications were observed. All participants were followed for more than 12 months (median follow-up 12.5 months). After MWA, the ablated lesion volume decreased by 12 months ($p < 0.001$), with a mean volume reduction of 80.2 ±13.1%. Multiple linear regression analysis showed that location adjacent to areola ($\beta = 7.5$, 95%CI: 1.0-13.9, $p = 0.025$) and location adjacent to skin ($\beta = -7.4$, 95%CI: -12.7 to -13.9, $p = 0.007$) were independent factors respectively associated with the increased and decreased 12-month VRR. The authors concluded that for BBLs larger than 2 cm, US-guided MWA is a favorable treatment modality, with BBLs adjacent to the areola being associated with more 12-month VRR after MWA. Limitations of this study include the small number of individuals with BBLs larger than 3 cm. In addition, the association between VRR and vascular supply of the ablated BBLs and the influence of MWA treatment on lactation were not analyzed. Further research is needed to determine the clinical relevance of these findings.

Liu et al. (2021) conducted a prospective study to investigate the safety, efficacy, and follow-up outcomes of microwave ablation (MWA) in patients with breast fibroadenoma from October 2017 to March 2019. A total of 171 individuals with 271 lesions were enrolled. The mean lesion diameter was 1.35 ±0.47 cm. The results revealed differential lesion states, including stability, enlargement, reduction, and complete regression, at 1-6, 6-12, and > 12 months of follow-up. The size was reduced in 22.14% (31/140), 26.36% (29/110), and 36.36% (16/44) of the lesions at 1-6, 6-12, and > 12 months of follow up, respectively. The proportion of lesions with complete regression was 24.29% (34/140) at 1-6 months, 45.45% (50/110) at 6-12 months, and 40.91% (18/44) at > 12 months of follow up. There was no relationship between the curative

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effect and age, lesion location, and blood flow in patients with breast fibroadenoma after MWA ($p > .05$), but there was statistical relationship with lesion diameter (categorized as < 1.5 cm and 1.5 cm) ($p < .05$). The authors concluded that the current evidence indicates that MWA is a safe and effective method for treating breast fibroadenoma. However, further large-scale prospective trials and well-designed future studies are warranted to validate their findings. This study has limitations. At the period of > 12 months after MWA, only 10 of the 44 lesions were maintained at a stable state (7 showing enlargement and 3 showing stability), and only 18 of 44 lesions (40.91%) completely regressed. The largest diameter of the lesions included was 30 mm; thus, the feasibility and efficacy of ultrasound guided MWA should be further investigated for larger lesions. In addition, a small sample size and short duration of follow-up makes it difficult to decide whether these conclusions can be generalized to a larger population.

Pusceddu et al. (2019) performed a systematic review of the available evidence on cryoablation in the treatment of solid tumors, including breast cancer. The authors stated that although this ablation method had the advantage of being a minimally invasive procedure, due to the small sample size of the available studies, reliable and definitive conclusions on the usefulness of cryoablation in patients with breast cancer could not be drawn. They further stated that other aspects of this technology, including technical issues, indications, efficacy, imaging follow-up, and possible advantages over other percutaneous ablative methods need to be clarified.

The ASBrS Consensus Statement developed and approved on October 16, 2018, on the Use of Transcutaneous and Percutaneous Ablation for the Treatment of Benign and Malignant Tumors of the Breast states: “Cryoablation is currently approved for treatment of benign and malignant soft tissue tumors by the FDA. Currently, there are no specific technologies that have FDA approval for breast tumors. Participation in registries and clinical trials evaluating the use of these technologies with and without surgical excision of a breast malignancy is advised as early data emerges on their efficacy.”

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Code	Description
0583T	Tympanostomy (requiring insertion of ventilating tube), using an automated tube delivery system, iontophoresis local anesthesia

Myringotomy and tympanostomy tube placement under iontophoresis local anesthesia (Tula) System is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

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Clinical Evidence

The Tubes Under Local Anesthesia (Tula) System inserts tympanostomy tubes into the eardrum in children and adults, in a physician's office using local anesthesia, to treat recurrent acute otitis media or otitis media with effusion. The Tula® System consists of the Tula Iontophoresis System and the Tula Tube Delivery System. The Tula Iontophoresis System, which includes individually fitted disposable ear plugs and ear sets, delivers a local anesthetic solution, TYMBION™, (a combination of an amide local anesthetic and an alpha- and beta-adrenergic agonist) to the eardrum. The Tula Tube Delivery System is then used to place the ear tube in the eardrum, The Tula system received FDA premarket approval (P190016) on November 25, 2019. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P190016. (Accessed May 13, 2025).

Cohen et al. (2022) conducted a study to evaluate behavioral strategies to minimize in-office procedural distress associated with tympanostomy tube placement for children without general anesthesia, sedation, or papoose-board restraints. One hundred and twenty children, six months to four years old, and 102 children, 5-12 years old, were treated at 16 different practices. The in-office tube placement procedure included local anesthesia via lidocaine/epinephrine iontophoresis and tube placement using an integrated and automated myringotomy and tube delivery system. Behavioral strategies were utilized to decrease procedural distress; no anxiolytics, sedation, or papoose board were used. Pain was measured via the faces pain scale-revised (FPS-R) self-reported by the children ages five through 12 years. Independent coders supervised by a psychologist completed the face, legs, activity, cry, consolability (FLACC) behavior observational rating scale to quantify children's distress. Mean FPS-R score for tube placement was 3.30, in the "mild' pain range, and decreased to 1.69 at 5-min post-procedure. Mean tube placement FLACC score was 4.0 (out of a maximum score of ten) for children ages six months to four years and was 0.4 for children ages five to 12 years. Mean FLACC score 3-min post-tube placement was 1.3 for children ages six months to four years and was 0.2 for children ages five to 12 years. FLACC scores were inversely correlated with age, with older children displaying lower distress. The authors concluded the Tula System and behavioral program allow pediatric patients to receive in-office tympanostomy tube placement without general anesthesia, sedation, or mechanical restraints with minimal distress. Limitations included lack of a control group and two of the authors were funded for work on the project, which may introduce investigator bias. The authors recommend further studies to match intervention components and strategies to individuals.

A 2022 Hayes Evidence Analysis Research Brief identified three single-arm clinical study abstracts and one systematic review assessing automated tympanostomy tube systems for pediatric individuals. These included two articles addressing the Tula system (Tusker Medical). The Hayes Evidence Analysis Research Brief concludes there is not enough published, peer-reviewed literature to evaluate the evidence addressing the efficacy and safety of automated tympanostomy tube placement systems.

In the 2022 American Academy of Otolaryngology–Head and Neck Surgery Foundation clinical practice guideline: Tympanostomy Tubes in Children, the 2013 guideline recommendations were reevaluated and updated with evidence-based recommendations for patient selection and surgical indications for the management of tympanostomy tubes in children. The update does not contain specific recommendations regarding office insertion of tubes in children without anesthesia, however states that "Risks associated with general anesthesia can be eliminated by inserting tubes in the office setting without general anesthesia, when appropriate based on shared decision making between the clinician and family" (Rosenfeld et al. 2022).

Lustig et al (2020, included in the 2024 Hayes Evolving Evidence Review) published the results of a prospective multi-center case series evaluating the safety, technical success, and tolerability of tympanostomy tube placement under local anesthesia in an office setting (OTTER study). A total of 337 children across 18 different sites, ages six months through 12 years of age, were included in the study. Lidocaine/epinephrine iontophoresis was the method used for anesthesia and tube placement was done using the Tula integrated, automated myringotomy and Tube Delivery System (TDS). Pain was rated by participants five to 12 years old using the FPS-R tool, which is used to rate pain from zero (no pain) to 10 (very much pain). Bilateral tubes were placed successfully in 85.8% of children less than five years of age and 89.2% of children five to 12 years of age. For tube placement itself, mean FPS-R score was 3.30 [standard deviation (SD) = 3.39]. Five-minute post-procedure mean FPS-R score was1.69 (SD = 2.43). Authors note that an unexpected benefit of the in-office procedure was the avoidance of using additional medications that are often given in conjunction with general anesthesia during standard tympanostomy tube placement. 91.8% of implant tubes were still present at the six month follow up. Limitations include lack of comparison group, efficacy outcomes. Additional high-quality evidence is needed to confirm the safety and efficacy of this technology. In a follow-up study, Waldman et al. (2023), participants were followed for two years or until tube extrusion and evaluated for tube retention, patency, and safety. In this follow-up group, tubes were placed in-office for 269 patients (449 ears) and in the operating room for 68 patients (131 ears). The median and mean times to tube extrusion for the combined operating room and in-office cohorts were 15.82 and 16.79 months, respectively. Outcomes included ongoing perforation for 1.9% of ears (11/580) and medial tube displacement for 0.2% (1/580) observed at 18 months. Over a mean follow-up of 14.3 months, 30.3% (176/580) of ears had otorrhea and 14.3%

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(83/580) had occluded tubes. The authors concluded the in-office tympanostomy using lidocaine/epinephrine iontophoresis and Tula® System resulted in tube retention similar to grommet-type tubes and the complications were consistent with operating room tube placement. Limitations include lack of a control group, and the study was industry sponsored.

Yen et al. (2020) conducted a prospective, multicenter, single-arm study (ADEPT) to evaluate the safety, tolerability, and technical success of lidocaine iontophoresis and a tympanostomy tube placement system for adults in an office setting. The investigation aimed to show the system is suitable before initiating a pediatric investigation, designed with input from physician advisers to meet FDA requirements. The study evaluated 30 individuals ages 21 to 83 years receiving tympanic membrane anesthesia and tube placement recruited in eight community-based practices. The integrated myringotomy and tube delivery system was utilized for the tube placement, and tolerability of placement was measured using a patient-reported visual analog scale from 0mm-100mm; 0mm being no pain and 100mm being the worst possible pain. The participant's average pain score was compared to the performance goal of 45mm. The baseline measures included otoscopy, tympanometry, and audiometry up to 28 days preprocedural, and the technical success and safety post-procedure was evaluated for three weeks. The study resulted in twenty-nine individuals with successful placement in all indicated ears. Inadequate tympanic membrane anesthesia with no tube placement attempted occurred in one individual. The average pain score was statistically superior to the performance goal of tolerability at 9.4 (15.7) mm. Non-serious events relative to device, procedure, or drug were demonstrated in seven individuals. Limitations to the study include the risk of bias, lack of efficacy outcomes, and the lack of a control group to compare safety and tolerability. The study evaluated adults, limiting performance generalization to a pediatric population; larger, controlled studies are needed to compare the investigational system to existing options.

In 2019 The American Academy of Otolaryngology (AAO) published a Position Statement on in-office tympanostomy tube placement. The statement notes that "although insertion of tympanostomy tubes in children is generally accomplished in the operating room under general anesthesia, insertion in the clinic in appropriately selected patients using shared decision making between clinicians and families can be appropriate."

Cofer et al. (2017, included in the 2024 Hayes Evolving Evidence Review) conducted a prospective study at four U.S. centers involving 128 children and 253 tympanostomy tube placements. The outcome of the study showed an 88.3% success rate in performing the procedure under moderate sedation with adverse effects (AEs) within normal rates. The authors concluded that the feasibility of doing tympanostomy tube placement in an office setting using moderate sedation offered additional choices to physicians and parents. This study was limited by lack of a control group or efficacy outcomes.

Cohen et al. (2015) indicated that two complementary technologies have recently been developed comprising an iontophoresis system (IPS) for delivering local anesthesia and an integrated TDS subsequently eliminating the need for general anesthesia in an operating room setting. These investigators evaluated behavioral support techniques used during a clinical study of the new technology for pediatric in-office tube placement without general anesthesia or physical restraints. As part of an institutional review board (IRB)-approved, prospective, 9-center case series, pediatric patients requiring tube insertion underwent in-office treatment using the new procedure. The behavior management techniques included preparation, distraction, coaching, and reinforcement for co-operation. The entire procedure was videotaped, and two independent coders used the validated FLACC scale to code behavioral distress across five procedural phases. A total of 70 pediatric patients aged eight months to 17 years (M = 7.0 years; 51% girls) were enrolled in the study, and 68 had video recordings available for analysis. Of the 68 recordings analyzed, 63 patients completed the procedure and had tubes placed without sedation. Mean FLACC scores ranged from 0.05 to 2.38 (M = 1.25, SD = 0.82) and median (Mdn) FLACC scores ranged from zero to one (Mdn = 0), which indicated "mild" distress. During iontophoresis, eardrum tap (anesthesia assessment), and tube delivery, older children displayed lower distress and girls had higher FLACC scores during the eardrum tap procedural phase. The authors concluded that when combined with the evidence-based behavioral techniques, office-based local anesthesia and tube delivery resulted in minimal distress, suggesting that the new procedure may be a viable method of conducting tympanostomy tube placement in children without having to use general anesthesia. A randomized trial with a comparison or control group is needed to establish the efficacy of in-office tympanostomy tube placement without general anesthesia.

Zeiders et al. (2015, included in the 2024 Hayes Evolving Evidence Review) conducted a prospective, single-arm study at nine otolaryngology sites in the US. Participants included pediatric patients aged six months to less than 22 years who required tube placement. The participants were prepared for the procedure using behavioral support techniques and tube placement was attempted under local anesthesia using the IPS in conjunction with the TDS. No physical restraints were allowed nor was the use of anxiolytics, analgesics, or sedatives permitted. Safety was evaluated via the occurrence of AEs and success rates for tube placement under local anesthesia were determined. The tolerability of the procedure was evaluated using the 5-point Wong-Baker FACES Pain Rating Scale and parental satisfaction was assessed using a post-

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operative survey. A total of 70 participants (127 ears) were enrolled in the study [mean (SD) age of 7.0 (3.9) years]. No serious AEs were observed in the 70 enrolled participants. Tube placement using the TDS was successful in 96.6% (114/118) of attempted ears. A single TDS was required in 105 ears, while more than one device was required in nine ears. Of the 70 patients enrolled in study, 63 (90.0%) successfully received tubes in all indicated ears during their in-office visit. The mean (SD) change in pain score from pre-anesthesia to post-surgery was +0.9 (1.8). Favorable ratings for overall satisfaction with the in-office procedure were obtained from 96.9% (63/65) of respondents. Tube retention at two weeks was 99.1%. As only 15 patients were enrolled who were three years old or younger, the ability to generalize these results to younger patients was limited. The authors concluded that the use of the IPS and TDS technologies enabled safe, reliable, and tolerable placement of tubes in awake, unrestrained pediatric patients. This study was limited by lack of a control group or relevant efficacy outcomes.

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Code	Description
0594T	Osteotomy, humerus, with insertion of an externally controlled intramedullary lengthening device, including intraoperative imaging, initial and subsequent alignment assessments, computations of adjustment schedules, and management of the intramedullary lengthening device

Osteotomy, humerus, with insertion of an externally controlled intramedullary lengthening device, including intraoperative imaging, initial and subsequent alignment assessments, computations of adjustment schedules, and management of the intramedullary lengthening device is considered unproven and not medically necessary due to insufficient evidence of efficacy.

Clinical Evidence

In a single-center study, Laufer et al. 2022 assessed 44 individuals with severe shortening of the upper extremities and functional impairments who underwent humeral lengthening. After exclusion, the retrospective study examined the results from 28 individuals for a median follow-up time of six years. Medical charts were evaluated for improvement in function and autonomy, and a nine-item questionnaire was administered to assess the individual's functional progress in activities of daily living, physical appearance, and overall satisfaction. The results of this study showed all participants reported improvement at their most recent follow-up compared with scores obtained before treatment [median (IQR) 24 (16 to 28) before surgery versus 44 (42 to 45) at the latest follow-up, a difference of medians 20 points, $p < 0.001$]. A total of 89% (25 of 28) of those achieved the desired 8 centimeters (cm) lengthening in both arms. A total of 50% (14 of 28) of individuals experienced a significant complication. Specifically, 39% (11 of 28) had an unplanned reoperation, 39% (11 of 28) had a radial nerve palsy, 18% (five of 28) had a refracture of the regenerate, and 4% (one of 28) concluded treatment with a severe limb length discrepancy. In addition, 82% (23 of 28) of individuals experienced minor complications that were resolved without further surgery and did not involve radial nerve symptoms. Radial nerve palsy was observed

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immediately in eight of 13 segments and one to seven days postoperatively in five of 13 segments. The treatment goal was not achieved because of radial nerve palsy in 5% (three of 56) of lengthened segments, which occurred in 7% (two of 28). Complete functional recovery of the radial nerve was observed in all participants after a median (IQR) of three months (two to five). Refractures of bone regeneration were observed in 11% (six of 56) of humeri in 18% (five of 28). Of those refractures, one of six individuals were treated nonsurgically with a hanging cast, while five of six underwent revision surgery with intramedullary rodding. The authors concluded that bilateral humeral lengthening with a monolateral external fixator should only be considered for individuals with severe functional impairments because of rhizomelic shortening of the upper extremities. Internal lengthening devices are preferable, as these are generally associated with higher comfort and decreased complication rates than external fixators. Limitations include the retrospective nature of the study and small study size.

Lorange et al. (2022) conducted a systematic review designed to assess the outcome and complications of lengthening the humerus with a motorized intramedullary nail. Nine articles published between 2016 and 2021 were included in the review which resulted in a total of 20 individuals with 22 lengthened segments. The mean age of the individuals was 20.8 years-old and the mean gained length was 5.7 cm. Range of motion limitation, hardware failure, and hypertrophic bone regeneration were reported as complications. The authors concluded that a motorized intramedullary nail for humeral lengthening has favorable outcomes with low complication rates but each type of nail and surgical procedure has different risks which should be carefully examined when planning surgery. Additionally, the authors noted future high-level studies with larger patient numbers that focus on long-term outcomes are needed. Limitations included small sample size and low level of evidence (case reports or case series only).

In 2022 the National Institute for Health and Care Excellence (NICE) produced interventional procedures guidance for intramedullary distraction for upper limb lengthening. The recommendations are as follows:

- Evidence on the safety and efficacy of intramedullary distraction for upper limb lengthening needs to be improved in quantity and quality; but because this is a rare condition with limited alternative treatments, the procedure can be considered as long as special arrangements for clinical governance, consent, and audit or research are in place.
- Clinicians wanting to use intramedullary distraction for upper limb lengthening should:
  - Inform the clinical governance leads in their healthcare organization.
  - Give people (and their families and caregivers as appropriate) clear written information to support shared decision-making, including NICE's data for the public.
  - Ensure that people (and their families and caregivers as appropriate) understand the safety and efficacy and any uncertainties about the procedure.
  - Audit and review clinical outcomes of everyone having the procedure. The primary efficacy and safety outcomes identified in this guidance can be entered into NICE's interventional procedure outcomes audit tool (for use at local discretion).
  - Discuss the procedure's outcomes during their annual appraisal to reflect, learn and improve.
- Healthcare organizations should:
  - Make sure systems are in place that support clinicians to collect and report data on outcomes and safety for everyone having this procedure.
  - Regularly review data on outcomes and safety for this procedure.
- This technically challenging procedure should only be done in specialist centers using a multidisciplinary approach by surgeons with specific training and experience in upper limb lengthening techniques.
- Report any problems with a medical device using the Medicines and Healthcare Products Regulatory Agency's Yellow Card Scheme.
- Further research, which could be registry data, should report patient selection, device selection, the technique used, procedural outcomes, and long-term outcomes, including quality of life, the need for repeat interventions or surgery, and complication rates.

In 2020, ECRI produced an evidence assessment on intramedullary devices for lengthening the humerus and determined the evidence was inconclusive, had too few data, and was very low quality. Intramedullary devices were found to be effective for humeral lengthening, however, the risks and benefits for humeral distraction and how the intramedullary devices compare with external fixation for achieving humeral target-length, or quality of life and functional status improvements were not able to be determined due to the limited evidence. Moreover, these studies did not address key patient-centered outcomes, such as the intensity of pain experienced, and the duration needed to return to sports or daily activities. The assessment recommended large-scale comparative studies to determine if intramedullary devices offer advantages over external fixation devices for humeral lengthening (ECRI, 2020; updated 2024).

The FDA announced the Precice Intramedullary Limb Lengthening System (NuVasive Specialized Orthopedics, Inc) approval. The Precice Intramedullary Limb Lengthening System is indicated for limb lengthening, open and closed fracture fixation, pseudarthrosis, malunions, nonunion, or bone transport of long bones for individuals aged 18 years and

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older and indicated for limb lengthening of the femur and tibia in the pediatric population (greater than 12 years old). For use in segmental bone loss treatment. For more information, refer to the following website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K220234. (Accessed May 6, 2025)

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Code	Description
0600T	Ablation, irreversible electroporation; 1 or more tumors per organ, including imaging guidance, when performed, percutaneous
0601T	Ablation, irreversible electroporation; 1 or more tumors, including fluoroscopic and ultrasound guidance, when performed, open

Ablation, irreversible electroporation (IRE), and percutaneous are unproven because there are insufficient studies supporting the safety and efficacy of the procedure and demonstrating improvement in health outcomes compared to other standard treatments. Ablation, irreversible electroporation (IRE), open, is unproven due to insufficient clinical evidence of safety and efficacy.

Clinical Evidence

In 2025, Hayes developed an evolving evidence review for the NanoKnife (AngioDynamics Inc.) for treating localized prostate cancer. This report addressed whether full-text clinical studies, systematic reviews, and clinical practice guidelines and position statements support the use of the NanoKnife System (AngioDynamics Inc.) for treatment of localized prostate cancer. There is minimal support for using the NanoKnife System according to the reviewed clinical studies and systematic reviews. Additionally, there was no support from clinical practice guidelines and position statements for the use of the technology.

In 2025 ECRI developed an evidence analysis for irreversible electroporation (IRE) for treating colorectal cancer liver metastases (CRLM). It was determined that the available evidence is too limited in quality and quantity to determine IRE's safety and effectiveness and how it compares with other treatment modalities for CRLM. Evidence from one comparison study, three cohort studies, and four case series—all at high risk of bias—suggest IRE works as intended for unresectable CRLM tumors, but studies have reported high local recurrence and complication rates. One study compared IRE with other treatments (radiofrequency and microwave ablation), but the study was too small and at too high a risk of bias to support conclusions. Larger controlled studies are needed to determine IRE's effectiveness for survival and to assess IRE's risk-benefit profile in patients with CRLM.

In 2025, ECRI developed an evidence analysis on IRE for treating liver cancer. Evidence from two systematic reviews (SRs) with meta-analyses of low-quality single-arm studies, two additional randomized controlled trials (RCTs), and three retrospective comparison studies suggests that IRE works as intended to ablate tissue in the liver; however, whether this translates to survival benefits is unclear because none of the studies included surgery or systemic chemotherapy treatment alone as control groups. Study results suggest comparable survival outcomes between IRE and other ablation treatments [radiofrequency ablation (RFA) and microwave ablation (MWA)]; however, studies had a high risk of bias and assessed too few patients per comparison to be conclusive. Whether IRE improves patient-oriented outcomes compared with conventional treatments requires validation in larger controlled and comparison studies with long-term follow-up (i.e., up to five years).

In 2024, ECRI developed an evidence analysis for IRE for treating kidney cancer. It was determined that the available evidence is too limited in quality and quantity to enable conclusions for IRE's safety and effectiveness and how it compares with other treatment modalities for renal cancer. Evidence from eight small case series suggests IRE is technically feasible for small renal masses (SRMs), but studies reported high rates of complications, including treatment-related events. The limitations included the lack of studies that compared IRE with surgical resection, and whether IRE improves patient outcomes when used as an alternative to other ablation techniques cannot be determined from one small study that compared IRE with radiofrequency ablation. Large, prospective controlled studies are needed to determine IRE's effectiveness and assess its risk-benefit profile in early kidney cancer.

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In 2024, ECRI developed an evidence analysis on IRE for treating pancreatic cancer. Evidence from five systematic reviews (SRs) of very-low-quality studies and one small randomized controlled trial (RCT) does not permit conclusions about how well IRE works to treat pancreatic cancer. Whether IRE improves patient outcomes when used as an alternative to other ablation techniques or an adjunct to radiotherapy and chemotherapy cannot be determined from studies that provide very-low-quality comparative data. The significant rates of treatment related complications posed a safety concern. Studies reported significant rates of treatment-related complications.

In 2025, ECRI developed an Evidence Analysis for IRE for treating prostate cancer. Evidence from four systematic reviews (SRs) with overlapping data from very-low-quality single-arm studies, one additional nonrandomized comparison study, and three single-arm studies suggests IRE works as intended to ablate prostate tumors without serious adverse events in the short term; however, in the absence of a direct comparison to standard-of-care or alternative ablation techniques, patient-oriented outcomes cannot be interpretated. Larger controlled and comparison studies with long-term follow-up (i.e., up to five years) are needed to determine whether IRE improves patient-oriented outcomes, including survival, recurrence, and functional outcomes, compared with standard of care (e.g., prostatectomy) or alternative ablation techniques (high-intensity focal ultrasound, cryotherapy).

The NanoKnife System uses irreversible electroporation (IRE) for nonthermal tissue ablation of soft tissue during open, laparoscopic, or percutaneous procedures. NanoKnife uses high-voltage direct current to induce cell death by permeabilizing cell membranes. NanoKnife is not labeled explicitly for tumor ablation, but it is sometimes used for individuals to treat unresectable liver tumors. In the 2023 ECRI Clinical Evidence Assessment on the NanoKnife System (AngioDynamics, Inc) for treating liver cancer, evidence was inconclusive and very low quality. Evidence from two systematic reviews (SRs) with meta-analysis of low-quality studies, two small randomized controlled trials, and five nonrandomized comparison studies suggests NanoKnife works as intended to ablate tissue in the liver. However, how well NanoKnife works compared with other ablation modalities cannot be determined because comparative studies are at a high risk of bias and assess too few subjects per comparison. The studies also pooled outcomes for individuals with different cancer types, stages, or tumor locations, which limited generalization across studies. The SRs lack control groups, and IRE's effectiveness in improving patient-oriented outcomes cannot be interpreted without control groups.

An interventional clinical trial of the NanoKnife system for the ablation of prostate tissue (PRESERVE) is currently being conducted on 121 participants. The study is evaluating the safety and efficacy of this device in intermediate-risk prostate cancer patients. It is expected to be completed in July 2024. ClinicalTrials.gov Identifier: NCT04972097. https://classic.clinicaltrials.gov/ct2/show/NCT04972097?term=nanoknife&cond=cancer&cntry=US&draw=3&rank=9. (Accessed May 29, 2025).

In the 2023 ECRI Clinical Evidence Assessment on the NanoKnife System (AngioDynamics, Inc) For Treating Pancreatic Cancer, evidence was inconclusive and of very low quality. Evidence from five systematic reviews (SRs) of very-low-quality studies and four additional nonrandomized comparison studies do not permit conclusions about IRE's risks and benefits for treating pancreatic cancer. The SRs reported median overall survival (OS) of 6 to 27 months and OS rates of 55% at 1-year and 33.8% at 2-year follow-up, but whether IRE improves outcomes when used as an alternative to other ablation modalities or an adjunct to radiotherapy and chemotherapy remains unclear because comparative studies are of low quality and report few and inconsistent findings.

The evidence was inconclusive in the 2022 ECRI Clinical Evidence Assessment on NanoKnife System (AngioDynamics, Inc) For Treating Prostate Cancer. Two systematic reviews (SRs) that include case series and two other case series provide very low-quality evidence and do not permit conclusions on IRE's safety and effectiveness for treating prostate cancer. Reported recurrence rates varied widely (3% to 39%). Severe complication rates were low, but NanoKnife's safety is unclear because no studies compared it with other ablative treatments.

In 2022 Yu and Li conducted a meta-analysis to gauge the efficacy and safety of IRE for treating malignant hepatic tumors, with a particular interest in the damage to the gastrointestinal tract, bile ducts, and vital vessels. Twenty-six studies were uncovered, encompassing 807 participants and 1115 lesions. IRE's complete ablation rate of liver cancer was 86% (95% CI: 81%-90%). IRE-related complications were 23% (95% CI: 17%-28%); however, many were minor. The authors concluded that the meta-analysis confirmed that IRE ablation is safe and effective for treating liver cancer. This study has several limitations: the retrospective nature of the studies, differences in design and treatment methods, heterogeneity between studies, and bias. The significant differences in PLR cut-off values could affect the study results.

Through a prospective single-center, double-arm clinical trial, Liu et al. (2022) compared the efficacy, safety, and intermediate-term outcomes of IRE and radiofrequency (RF) therapy for malignant liver tumors. Included in the trial were twenty-four individuals with primary or secondary liver malignancies. In random order, participants were divided into either the IRE or RF group. Outcomes measured were efficacy (local ablation control evaluation at 90 days), safety (procedure-

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related complications at ≤ 90 days), and intermediate-term survival (at 24 months). The ablation assessment at 90 days after surgery with mRECIST for IRE compared to RF was 70%, 20%, 0%, and 10% versus 92.9%, 7.1%, 0%, and 0% (CR, PR, SD, and PD, respectively). The complication rates of IRE compared to RF with Clavien-Dindo classification were 16.7%, 25%, 0%, 8.3%, and 8.3% versus 8.3%, 50%, 0%, 0%, and 0% (Grade I, II, III, IV, and V, respectively). On average, the overall survival (OS) was 17.55 months in the IRE group (95% CI 15.13-22.37) and 18.75 months in the RF group (95% CI 12.48-22.61). Statistical differences between the IRE and RF groups in terms of efficacy (p = 0.48), safety (p = 0.887), or 24-month OS (p = 0.959) were absent. The authors concluded that IRE ablation showed comparable efficacy and safety in a short-term follow-up and similar OS in mid-term survival as RF ablation in treating malignant hepatic tumors. Follow-up was inhibited due to the COVID-19 epidemic for individuals in the later stages. Telephone follow-up was conducted, and basic information was obtained regarding follow-up.

Yaxley and colleagues (2022) steered a retrospective review of prospectively gathered data to assess histological in-field clearance of prostate cancer at ≥ 12 months for individuals post-IRE. To be considered a 'significant recurrence,' individuals would have results of ≥ 6 mm core Gleason 3 + 3 or ≥ Gleason 3 + 4 with ≥ 4 mm tumor length. Any focus of the International Society of Urological Pathology (ISUP) ≥ 2 was also investigated. For the entire cohort, the median follow-up is 23 months (range 3-39 mo). For 64 primary IRE procedures, surveillance biopsy was performed in 40/50 (80.0%) with ≥ 12 months follow-up. Significant in-field recurrence occurred in 3/40 (7.5%) or 4/40 (10.0%) with any focus of ISUP > 2. Significant out-of-field recurrence was demonstrated in 5/40 (12.5%). Three individuals (3/6, 50.0%) in salvage IRE have undetectable prostate-specific antigen levels, two have no residual cancer on biopsy, and one had an out-of-field recurrence. Erectile function was maintained in 24/28 (85.7%) primary IRE for sexually active men. For primary IRE, there was no incontinence developed (0/64). The authors concluded that primary focal IRE for prostate cancer is correlated with 90% infield ablation of any ISUP grade > two cancer with a low risk of urinary incontinence or impotence. Prostate biopsies are required to exclude progression surveillance, regardless of a standard post-IRE multiparametric magnetic resonance imaging (mpMRI). The data shows salvage IRE is an encouraging option for localized recurrence after prostate radiotherapy with low morbidity. Limitations to the study included relatively short follow-up and the retrospective review of a prospective database (which resulted in an underestimated complication rate).

In 2022, Li and associates guided a retrospective longitudinal study for individual’s ineligible for thermal ablation and underwent computed tomography-guided IRE for hepatic tumors at the hepatorenal confluence. The authors analyzed the individuals and tumor characteristics, IRE procedure details, treatment-related complications, and prognosis to carry out the analysis. Twenty-one of the 38 lesions were at the hepatorenal confluence, and complete ablation was accomplished in all cases. Of the ablated tumors, local and distant recurrence was seen in 4.8% (1/21) and 42.6% (9/21), respectively. All postcava remained perfused at follow-up, except for 1 (4.8%) hepatic vein near the lesion, found to be temporarily occluded and reestablished within one month. At 1-, 3-, and six months post-procedure, the ratio of the maximum diameter of ablation area compared to directly after IRE was 0.68 (0.50-0.84), 0.49 (0.27-0.61), and 0.38 (0.25-0.59), respectively. Progression-free survival of the individuals with recurrence was 121 (range, 25-566) days. The median OS was 451.5 (range, 25-716) days, as four (19.0%) individuals died at the end of follow-up. The authors concluded that added data is required to solidify the indications for using IRE for treating hepatic tumors at the hepatorenal confluence. When thermal ablation is inappropriate, its safety profile and sustainable rate have favored IRE as a safe and viable treatment option. The high success and low local recurrence rates indicate the efficacy of IRE, although these results are to be proven with a longer follow-up time in a more significant number of individuals. For additional benefits, Synergistic therapy may be the trend of IRE.

The FDA has cleared the NanoKnife® System (510 K number K183385) for the surgical ablation of soft tissue. Additional information can be found at:

- https://www.accessdata.fda.gov/cdrh_docs/pdf18/K183385.pdf
- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K183385

(Accessed May 29, 2025)

The National Comprehensive Cancer Network (NCCN) Guidelines for pancreatic adenocarcinoma report that irreversible electroporation (IRE) is an ablative technique in which electric pulses are used to create nanopores that induce cell death similar to apoptosis. This technique has been used for individuals with locally advanced pancreatic cancer. IRE may be safe and feasible and may improve survival outcomes. However, due to concerns about complications and technical expertise, the panel does not currently recommend IRE for treating locally advanced pancreatic cancer (V2. 2025).

The NCCN Guidelines for Hepatocellular Carcinoma report that IRE has some advantages over RFA, notably the lack of a "heat sink" effect and the ability to treat near vessels, bile ducts, and other critical structures. “However, IRE can cause cardiac arrhythmias and uncontrolled muscle contractions. Some small studies have shown that IRE treatment for unresectable HCC is safe and feasible. In a small nonrandomized trial including 30 participants with malignant liver tumors, none of the eight people with HCC experienced a recurrence through a 6-month follow-up. Recurrences have

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been reported following IRE for larger tumors. Larger studies are needed to determine the effectiveness of IRE for local HCC treatment." Although inconclusive, available evidence suggests that the choice of ablative therapy for individuals with early-stage HCC should be based on tumor size, location, underlying liver function, and available local radiologist expertise and experience. Ablative therapies are most effective for tumors less than 2 cm." (V1.2025).

The 2023 NICE guideline for irreversible electroporation for treating prostate cancer states: "There is enough evidence to suggest that the procedure works and does not raise any major safety concerns in the short- and medium term." However, NICE also states that the procedure may not be without complications, and there is uncertainty of its long-term efficacy and uncertainty of the patient population who would most benefit from this procedure. Therefore, this procedure should only be used with special arrangements, which includes knowledge of the uncertainty of the safety or efficacy, with emphasis on informed consent.

- https://www.nice.org.uk/guidance/IPG768/chapter/1-recommendations
- https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/interventional-procedures-guidance/recommendations

(Accessed May 29, 2025)

The European Network for Health Technology Assessment (EUnetHTA) reported on the Rapid Relative Effectiveness Assessment for IRE for the treatment of liver and pancreatic cancer:

- Pancreatic cancer:
  - There is insufficient evidence to establish whether IRE is more effective than, or at least as effective as, the conventional standard of care (CHEMO, CRT, or palliative therapy) for treating unresectable LAPC.
  - There is insufficient evidence to establish whether IRE is safer than, or at least as safe as, the conventional standard of care (CHEMO, CRT, or palliative therapy) for treating unresectable LAPC.
  - The existing evidence raises doubts regarding the efficacy of IRE for achieving complete ablation of unresectable LAPC.
  - The existing evidence raises doubts regarding the efficacy of IRE as the sole primary local treatment for LAPC. It is unclear whether IRE needs to be combined with CHEMO and, if so, which regimens are optimal.
  - There are uncertainties regarding severe AEs when IRE is used to treat unresectable LAPC.
- Liver cancer:
  - There is a lack of data to establish whether IRE is more effective than, or at least as effective as, the conventional standard of care (TACE, sorafenib, or palliative therapy) for treating individuals with primary or secondary unresectable liver cancer that is not suitable for thermal ablation.
  - There is a lack of evidence to establish whether IRE is safer than, or at least as safe as, the conventional standard of care (TACE, sorafenib, or palliative therapy) for treating individuals with primary or secondary unresectable liver cancer that is not suitable for thermal ablation.
  - The existing evidence raises doubts regarding the efficacy of IRE for achieving complete ablation of primary or secondary unresectable liver tumors unsuitable for thermal ablation.
  - The existing evidence raises doubts regarding the efficacy of IRE as a sole primary local treatment for primary or secondary liver tumors unsuitable for thermal ablation.
  - There are uncertainties regarding the occurrence of severe AEs when IRE is used to treat liver tumors unsuitable for thermal ablation (Zapata-Cachafeiro et al., 2019).

The German Society of Urology (Borkowitz et al., 2022) S3 Evidence-Based Guidelines on Focal Therapy in Localized Prostate Cancer states that the available data are insufficient to assess the oncological effectiveness and safety of focal irreversible electroporation (IRE), in particular, concerning long-term outcomes (evidence-based statement, level of evidence 4, overall agreement: 97%).

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ECRI. Irreversible Electroporation for treating liver cancer. Evidence Analysis. 2025 Jan.

ECRI. Irreversible Electroporation for treating pancreatic cancer. Evidence Analysis. 2024 Dec.

ECRI. Irreversible Electroporation for treating prostate cancer. Evidence Analysis. 2025 Feb.

ECRI. NanoKnife System (AngioDynamics, Inc.) for treating liver cancer. Clinical Evidence Assessment. 2023 Apr.

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Code	Description
0607T	Remote monitoring of an external continuous pulmonary fluid monitoring system, including measurement of radiofrequency-derived pulmonary fluid levels, heart rate, respiration rate, activity, posture, and cardiovascular rhythm (e.g., ECG data), transmitted to a remote 24-hour attended surveillance center; set-up and patient education on use of equipment
0608T	Remote monitoring of an external continuous pulmonary fluid monitoring system, including measurement of radiofrequency-derived pulmonary fluid levels, heart rate, respiration rate, activity, posture, and cardiovascular rhythm (e.g., ECG data), transmitted to a remote 24-hour attended surveillance center; analysis of data received and transmission of reports to the physician or other qualified health care professional

Remote monitoring of an external continuous pulmonary fluid monitoring system, including measurement of radiofrequency derived pulmonary fluid levels, heart rate, respiration rate, activity, posture, and cardiovascular rhythm (e.g., ECG data), transmitted to a remote 24 hour attended surveillance center as well as the analysis of data received and transmission of data to a qualified health care professional is unproven due to insufficient clinical evidence of safety and efficacy.

Clinical Evidence

ZOLL® µCor™ HFAMS is an FDA-cleared patch-based, wireless system that employs novel radiofrequency technology to monitor pulmonary fluid levels, an early indicator for heart failure decompensation. ZOLL® HFAMS is intended for use in patients who are 21 years of age or older requiring fluid management in outpatient clinics and home settings. The HFAMS sensor is non-invasive and can be worn by patients 24-hours a day. ZOLL® HFAMS continuously records, stores, and transmits patient data, including Thoracic Fluid Index, heart rate, respiration rate, activity, posture, and heart rhythm (ECG), and alerts physicians to signs of worsening patient condition (ZOLL® Medical Corporation, 2019). The Remote Dielectric Sensing (ReDs) Wearable System is another example of an external pulmonary fluid monitor; however, it is larger in size than the HFAMS.

Okabe et al. (2025) conducted a single-center prospective proof-of-concept study aimed to evaluate the feasibility of remote dielectric sensing (ReDS) measurements in pediatric patients and compare the diagnostic performance of chest X-ray (CXR) and ReDS in assessing pulmonary congestion in pediatric patients with a history of Fontan surgery. ReDS values and CXRs were simultaneously obtained from pediatric patients with a history of Fontan surgery at an outpatient clinic. The Congestion Severity Index (CSI) was calculated from CXRs to analyze its correlation with ReDS values. A total of 21 pediatric patients (median age: 17 years; median height: 152.7 cm; median weight: 48.6 kg; 12 male patients) were included. ReDS values were successfully measured in all participants without any measurement failure. A mild correlation was observed between ReDS values and CSIs ($r = 0.47$, $p = 0.030$). In patients with ReDS values exceeding 35% ($n = 11$), a stronger correlation was noted between ReDS values and CSIs ($r = 0.61$, $p = 0.046$). In patients with ReDS values ≤ 35% ($n = 10$), ReDS values exhibited a wide distribution (25% to 35%) despite low CSI values. The authors concluded

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that the ReDS system demonstrates potential as a feasible technology for the noninvasive quantification of pulmonary congestion in pediatric patients, irrespective of the severity of congestion. The ReDS system may have the potential to identify subclinical pulmonary congestion in pediatric patients with heart failure. This study has several limitations. As a single-center study, the findings necessitate further investigation to evaluate their scientific rigor and external validity. Participants with a body weight below 30 kg and less cooperative participants who could not understand clinicians' instructions. The applicability of the ReDS system in these cohorts requires further validation studies. The authors compared the ReDS system and CXR findings in the pediatric cohorts. This may not be sufficient to support the clinical integration of the ReDS system in this cohort. Further validation studies are essential to compare the ability to assess pulmonary congestion between the ReDS system and other modalities. In addition, future studies should explore the utility of ReDS in diverse patient populations and investigate its role within a multimodal diagnostic setting.

Alvarez-Garcia et al. (2024) conducted a randomized controlled trial (RCT) to assess whether a ReDS-guided strategy during acutely decompensated HF hospitalization is superior to routine care for improving outcomes at one month post discharge. ReDS-SAFE HF (Use of ReDS for a SAFE discharge in patients with acute Heart Failure) was an investigator-initiated, multicenter, single-blind, randomized, proof-of-concept trial in which 100 patients were randomized to a routine care strategy, with discharge criteria based on current clinical practice, or an ReDS-guided decongestion strategy, with discharge criteria requiring an ReDS value of ≤ 35%. ReDS measurements were performed daily and at a 7-day follow-up visit, with patients and treating physicians in the routine care arm blinded to the results. The primary outcome was a composite of unplanned visits for HF, HF rehospitalization, or death at one month after discharge. The mean age was 67 ±14 years, and 74% were male. On admission, the left ventricular ejection fraction was 37% ±16%, and B-type natriuretic peptide was 940 pg/L (Q1-Q3: 529-1,665 pg/L). The primary endpoint occurred in 10 (20%) patients in the routine care group and one (2%) in the ReDS-guided strategy group (log-rank p = 0.005). The ReDS-guided strategy group experienced a lower event rate, with an HR of 0.094 (95% CI: 0.012-0.731; p = 0.003), and a few patients needed to treat to avoid an event (95% CI: 3-17), mainly resulting from a decrease in HF readmissions. The median length of hospital stay was two days longer in the ReDS-guided group vs the routine care group (8 vs 6; p = 0.203). The authors concluded that the ReDS-guided strategy to treat congestion improved one month prognosis post discharge in this RCT, mainly because of a decrease in the number of HF readmissions. This study has limitations. The small sample size limits the possibility of subgroup analysis and warrants larger randomized clinical trials to confirm the efficacy and safety of the ReDS technology in acutely decompensated HF. In addition, subgroup analyses should be performed in specific populations of clinical interest, such as those with cardiorenal syndrome, diuretic resistance, diabetes, or isolated right-sided congestion.

The Journal of the American College of Cardiology released a JACC Scientific Statement on remote monitoring (internal and external) for heart failure management at home (Stevenson et al., 2023).

Regarding wearable monitoring, such as a dieletric signal system which uses two sensors embedded in a wearable chest garment, the statement discusses a randomized controlled trial (RCT) of 268 patients who showed "48% heart failure hospitalization(HFH) reduction in an analysis of patients who could be treated per protocol with the remote dielectric sensing of lung water (ReDS) system in accordance with usage and defined algorithms." The authors concluded that although this system appears promising in small studies, "combinations of structured support and telephone transmission of weights, vital signs, and symptoms consistently failed to demonstrate benefits in large, randomized trials." Also discussed, was a wearable radiofrequency-based sensor to measure lung congestion that was recently tested in the Benefits of Microcor (μCor) in the Ambulatory Decompensated (BMAD) trial (sponsored by Zoll Medical Corporation). This was a comparison of a pair of single-arm trials which suggested HFH was decreased utilizing this therapy. The authors stated, "management by the use of lung congestion measurements significantly reduced HFH compared with the study in which patch information was monitored but not used for intervention." The authors stated that algorithms need to be personalized for remote monitoring strategies, with more precision for signal thresholds and for levels of intervention, some of which should be automated for direct patient access.

Sattar et al. (2021) conducted a meta-analysis to systematically assess the utility of ReDS monitoring in reducing HF readmissions. Digital databases were searched to identify relevant articles. Pooled unadjusted odds ratio (OR) for dichotomous outcomes were calculated using a random-effects model. Findings were reported as a point estimate with its 95% confidence interval (CI). A total of 985 patients across seven studies were included in the meta-analysis. Patients with heart failure monitored with ReDS had significantly lower odds of hospital readmission compared with non-ReDS patients (OR = 0.40; 95% CI 0.29-0.56; z = 5.43 p = 0.000, I2 = 0%). Subgroup analysis based on the duration of follow-up showed a lower odd of readmission within 30 days (OR = 0.36; 95% CI 0.18-0.71; z = 2.93; p = 0.003; I2 5.7%), as well as between one and three months (OR = 0.42; 95% CI 0.29-0.61; z = 4.54; p = 0.000; I2 = 0.0%). ReDS effect of lower readmissions of HF was observed irrespective of the duration of follow-up (< 1-month vs 1-3 months). The authors concluded that ReDS monitoring lowers the odds of HF readmission within three months compared to participants not using ReDS. This meta-analysis has limitations. Data was limited by studies that did not fully explain the events or

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number, or type of medication adjusted after ReDS reading. Diuretic regimen modifications were not mentioned in all studies. The authors were also limited in their ability to examine the effect of ReDS on long-term follow-up of six months to one year because no studies examined ReDS monitoring for that length of time. Additional studies are necessary to fully understand the beneficial impact of ReDS monitoring in managing HF patients.

Bensimhon et al. (2021) conducted a prospective pilot study on 108 hospitalized individuals with acute decompensated heart failure (HF). Subjects were randomized to receive ReDS-guided therapy [Remote Dielectric Sensing (ReDs) Wearable System] or standard therapy. Based on the subject's lung congestion status after diuresis, the intent of the study was determining hospital discharge timing, and readmission rates. In this single-center study, "ReDS testing demonstrated that 32% of HF patients deemed ready for discharge have clinically significant residual lung congestion which was associated with a higher risk of readmission. ReDS-guided management was associated with significant decongestion but not a reduction in HF readmissions in this sample."

Lala et al. (2021) conducted a retrospective observational cohort study to assess whether the use of ReDS point-of-care testing would be associated with a lower rate of 30 day cardiovascular (CV) and all-cause hospital readmissions as compared with no ReDS use. The authors conducted a retrospective analysis of the use of ReDS for patients scheduled for rapid follow-up (RFU) within 10 days post-discharge for HF. Diuretics were adjusted using a pre-specified algorithm. The association between the use of ReDS and 30-day readmission was evaluated. A total of 220 patients were included. Mean age was 62.9 ±14.7 years, and 36.4% were female. ReDS was performed in 80 (36.4%) and led to medication adjustment in 52 (65%). Use of ReDS was associated with a lower rate of 30-day CV readmission [2.6% vs. 11.8%, hazard ratio (HR): 0.21; 95% confidence interval (CI): 0.05–0.89; p = 0.04] and a trend towards lower all-cause readmission (6.5% vs. 14.1%, HR: 0.43; 95% CI: 0.16–1.15; p = 0.09) as compared with patients without a ReDS assessment. The authors concluded that ReDS-guided HF therapy during RFU after HF hospitalization may be associated with lower risk of 30-day readmission. This study is limited by its retrospective observations. A small sample size makes it difficult to decide whether these conclusions can be generalized to a larger population. Also, not all patients hospitalized for HF at Mount Sinai Hospital may have been identified for RFU clinic, raising the possibility of selection bias. Further, among those presenting for RFU clinic, ReDS readings were performed in less than 40% of patients, and there was no pre-defined protocol as to which patients underwent ReDS readings. Reasons as to why ReDS readings were not performed were often not listed in the chart, which may have also introduced bias. Further research with randomized controlled trials is needed to validate these findings.

A comparison study by Wheatley-Guy et al. (2020) was conducted to validate the ability of radiofrequency (RF) to assess lung fluid via a wearable patch device compared to thoracic CT in order to characterize volume overload. A total of 120 subjects were studied: 66 acute heart failure (AHF) inpatients and 54 subjects without AHF (Control – 44 healthy and 10 stable HF). All underwent supine thoracic CT scans and supine RF readings from the wearable patch device placed on the left mid-axillary line (age = 74 ±16 vs. 57 ±15 yrs.; female = 38 vs. 44%; BMI = 33.2 ±9.0 vs. 27.3 ±5.1, AHF vs. Control respectively). Reflected RF signals and subject-specific anthropometric data were used to calculate the RF-determined lung fluid content. CT Lung fluid was reported as a percentage of lung volume. Classification analyses were used to compare RF and CT performance. AHF presented with higher lung fluid than controls by both CT and RF (CT: 20.1 ±4.2% vs. 15.4 ±2.4%; RF: 20.7 ±5.6% vs. 15.6 ±3.3%; $p < 0.05$ for all). The correlation between lung fluid measured by CT vs. RF was $r = 0.7$ ($p < 0.001$). RF determined lung fluid performed as well as CT in distinguishing AHF from control subjects: Sensitivity: 70% vs. 86%; Specificity: 82% vs. 83%; Positive Predictive Value: 82% vs. 86%; Negative Predictive Value: 69% vs. 83%, CT vs. RF, respectively. The authors concluded that noninvasive nonionizing RF determined lung fluid provides a potential alternative to other measures for diagnosing and monitoring pulmonary fluid overload. The RF technology described in the current study cannot be used to determine total body water overload or purely right sided heart failure peripheral edema as the device only looks measures at the lung fields. Furthermore, it is unclear if RF can detect intravascular congestion. The findings of this study need to be validated by well-designed studies. Further investigation is needed before clinical usefulness of this service is proven.

An ECRI Clinical Evidence Assessment (2020) Product Brief for ReDS Wearable Systems (Sensible Medical Innovations Ltd.) for Noninvasive Monitoring of Lung Fluid was published following review and evaluation of 1 non-randomized before-and-after study, and 3 diagnostic cohort studies from January 1, 2013, through February 14, 2020 (244 individuals). Evidence from 1 before-and-after study suggests that adding ReDS to standard, at-home practices for monitoring lung fluid in patients with HF may reduce hospitalization rates, but the study is at too high a risk of bias to be conclusive. 3 diagnostic cohort studies are too small and of too poor quality to determine ReDS's accuracy for monitoring lung fluid. Findings require validation in larger (n > 100) prospective cohort studies. Studies are also needed to assess inpatient monitoring with ReDS and to compare ReDS with chest impedance cardiography and manometry. Evidence is inconclusive because of too few data.

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Code	Description
0615T	Automated analysis of binocular eye movements without spatial calibration, including disconjugacy, saccades, and pupillary dynamics for the assessment of concussion, with interpretation and report

Eye-movement analysis without spatial calibration, is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

There is insufficient quality evidence to conclude that eye-movement analysis without spatial calibration is effective. Additional research involving larger, well-designed studies is needed to establish its safety, efficacy, and clinical utility as compared to conventional clinical assessment.

On October 2, 2021, the Eye-Sync® (SyncThink, Inc., San Carlos, CA) received FDA 510(k) clearance as a class II device. The Eye-Sync is a virtual reality device intended for recording, viewing and analyzing eye movements to support visual tracking impairment as an aid in the diagnosis of concussion within 3 days of injury in patients aged 17-24 in conjunction with a standardized neurological assessment. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K202927. (Accessed April 23, 2025)

On December 28, 2018. The EyeBOX was granted De Novo approval by the U.S. Food and Drug Administration (FDA) as the first non-invasive, baseline-free tool directed at diagnosing concussions (product code QEA). It is intended to measure and analyze eye movements as an aid in the diagnosis of concussion within one week of head injury in patients 5 through 67 years of age in conjunction with a standard neurological assessment. A negative EyeBOX classification may correspond to eye movement that is consistent with a lack of concussion. A positive EyeBOX classification corresponds to eye movement that may be present in both patients with or without concussion. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm?id=DEN170091. (Accessed April 11, 2025)

In a December 2023 evolving evidence review, updated in 2024, Hayes reported the findings on The EyeBox (Oculogica) as an aid for diagnosing concussion. Clinical evidence from one study suggests that the EyeBOX demonstrates high sensitivity but low specificity which may lead to false-positive results. They conclude that a minimal level of support is present and recommend monitoring the literature for further research.

Jain et al. (2022, included in the ECRI clinical evidence assessment) conducted an observational study to determine if there were differences in objective eye tracking metrics that characterize eye position, saccadic movement, and pupillary dynamics between uninjured adolescents, adolescents with acute concussion symptoms (≤ 28 days since injury), and adolescents with persistent concussion symptoms (> 28 days since injury). Uninjured adolescent athletes (n = 180) and concussed adolescent participants (n = 224), with acute or persistent symptoms, ages 13 to 17 years old were included in the study. Eye movements were recorded using EyeBOX. Two hundred fifty-six eye tracking metrics were compared. Two metrics of eye position were worse in those with concussion than uninjured adolescents, and only one metric was

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significantly different between acute cases and persistent cases. Concussed adolescents had larger left and right mean, median, minimum, and maximum pupil size than uninjured controls. Concussed adolescents had greater differences in mean, median, and variance of left and right pupil size. Twelve metrics distinguished female concussed participants from uninjured; only four were associated with concussion status in males. A logistic regression model including clinical and demographics data and transformed eye tracking metrics performed better in predicting concussion status than clinical and demographics data alone. The authors concluded that after concussion, objective eye tracking technology can identify vision and pupillary disturbances and could be used to augment existing clinical concussion assessments. The authors recommend future studies to investigate additional visual stimuli and paradigms to ascertain if other standard assessments of oculomotor function can be used to identify deficits in concussed children and modifying and consolidating these metrics with existing clinical measures to monitor recovery. Limitations include participant population of only adolescents and lack of assessment of the clinical utility above and beyond patient history and clinical findings. Furthermore, these findings need to be reproduced in an independent sample for validation.

Samadani et al. (2022, included in the Hayes evolving evidence review, and ECRI clinical evidence assessment) conducted a study to validate the sensitivity and specificity of a baseline-free eye movement tracking algorithm as a classifier for identifying concussion. The study included both adult and pediatric subjects and were separated into two groups, concussed (n = 46) and the non-concussed (n = 236). Eye tracking while watching a short film clip for 220 seconds, alteration of consciousness, and Sports Concussion Assessment Tool (SCAT3) subsets were collected then validated against a pre-specified algorithm with a cutoff for concussed vs. non-concussed. The sensitivity and specificity of eye tracking were calculated after plotting of the receiver operating characteristic curve and calculation of the AUC (area under curve). When concussion is defined by SCAT3 subsets, the sensitivity and specificity of an eye tracking algorithm was 80.4 and 66.1%, The area under the curve was 0.718. The misclassification rate (n = 282) was 31.6%. The authors concluded eye tracking has a sensitivity and specificity that is useful to aid in diagnosis of concussion. The authors recommend future, larger clinical trials to define how specific attributes or deficiency in eye-tracking ability are associated with symptoms, brain imaging, and outcomes. Limitations include small sample size, lack of assessment of the clinical utility above and beyond patient history and clinical findings, and the study was partially funded by the manufacturer.

Oldham et al. (2021, included in the ECRI clinical evidence assessment) conducted a cross-sectional study to evaluate the relationship between eye tracking, self-reported symptoms, and gait performance in both concussed participants (n = 30) and healthy controls (n = 30). Symptoms were collected using the Post-Concussion Symptom Scale (PCSS) and triaxial inertial measurement units were used to measure gait speed. The study examined the relationship between PCSS and the BOX score (a metric of pupillary disconjugacy) and a two-way mixed effects analysis of variance to examine the effect of group on single- and dual-task gait speed. There was a significant association between total PCSS score and BOX score in the concussion group but not in the control group. There were no significant associations between PCSS symptom profiles and BOX scores in the concussion or control groups. There were also no significant differences in single-task or dual-task gait speed. The authors concluded that following concussion, there appeared to be an association between eye tracking and clinical symptoms. However, it did not appear that abnormal eye tracking was influenced by a single symptom domain. The authors also note the concussion group had worse overall total symptom severity and higher scores on each of the five symptom profiles than those in the control group. The authors state that following concussion, eye tracking could be a clinically useful tool for identifying ocular and motor deficits and further research was recommended. Limitations include small sample size, predominantly female participants, and lack of blinding.

In 2020, updated in 2023, ECRI published a Clinical Evidence Assessment for EyeBOX (Oculogica, Inc). ECRI found too few data and the evidence was insufficient to determine the efficacy of the EyeBox, when added to standard diagnostic processes. No published studies provide evidence to assess the effect on patient outcomes or patient management decisions.

Samadani et al. (2015, included in the ECRI clinical evidence assessment) prospectively tracked 75 individuals with trauma with either a positive head computed tomography (CT) scan (n = 13), negative head CT (n = 39), or non-head injury (n = 23) and compared them to a normal, healthy control group (n = 64) to explore whether eye tracking would reveal the disconjugate gaze associated with both structural brain injury and concussion. Eye movements were tracked while they watched music videos on a viewing monitor of a binocular tracking device. Eye movements were recorded with an Eyelink 1000 eye tracker at a fixed distance of 55 cm from a computer monitor over a time period of 220 sec. Five out of five measures of horizontal disconjugacy were increased in positive and negative head CT patients relative to non-injured control subjects. Only one of five vertical disconjugacy measures was significantly increased in brain-injured patients relative to controls. Linear regression analysis of all 75 trauma patients demonstrated that three metrics for horizontal disconjugacy negatively correlated with SCAT3 symptom severity score and positively correlated with total Standardized Assessment of Concussion score. Abnormal eye-tracking metrics improved over time toward baseline in brain-injured subjects observed in follow-up. The authors concluded that eye tracking may help quantify the severity of

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ocular motility disruption related to concussion and structural brain injury. Limitations include small sample size, and conflicts of interest which may limit the study's conclusions.

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Code	Description
0631T	Transcutaneous visible light hyperspectral imaging measurement of oxyhemoglobin, deoxyhemoglobin, and tissue oxygenation, with interpretation and report, per extremity

Hyperspectral imaging is unproven and not medically necessary for measurement of oxyhemoglobin, deoxyhemoglobin, and tissue oxygenation in individuals with circulatory compromise due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Hyperspectral imaging (HSI) is a noninvasive assessment that provides color coded maps of oxygenated tissue, allowing qualitative and quantitative measurements with high spectral resolution (Sen, 2018). HSI technology uses transcutaneous measurements of oxyhemoglobin (HT-Oxy) and deoxyhemoglobin (HT-Deoxy) concentrations by employing wavelengths of visual light that penetrate to one to four mm below the skin. By analyzing a wide spectrum of light rather than simply assigning primary colors, a two-dimensional, color-coded "oxygen map" is created. This device can be used as a noninvasive screening tool for determining tissue oxygenation and the severity of peripheral vascular disease (PVD) and critical limb ischemia (CLI).

HyperView™ (Hypermed Imaging, Inc.) is a handheld portable diagnostic imaging device that reports an approximate value of oxygen saturation, oxyhemoglobin level and deoxyhemoglobin level in superficial tissue. OxyVu (Hypermed Imaging, Inc.) was a cart-based mobile imaging system designed to assess oxyhemoglobin, deoxyhemoglobin and oxyhemoglobin saturation in superficial tissue but is no longer produced or sold.

In a single-center, prospective, proof-of-concept observational study by Kleiss et al. (2024) the benefits of indocyanine green angiography (ICGA) (for perioperative evaluation), and HSI and thermal imaging (TI) (for postoperative monitoring) were investigated. The study included 15 adults (mean age 49.0 years, 80% White) who had undergone unilateral (n = 9) or bilateral (n = 6) deep inferior epigastric perforator (DIEP) flap breast reconstruction (n = 21 breasts). Sixteen of the DIEP flaps were judged to be uncomplicated with adequate flap perfusion both peri- and postoperatively, according to standard clinical monitoring while five DIEP flaps had impaired flap perfusion. Three of the complicated DIEP flaps were identified and addressed perioperatively while the remaining two were detected postoperatively. The ICGA perfusion curves and derived parameters, HSI extracted oxyhemoglobin (oxyHb) and deoxyhemoglobin (deoxyHb) values, and flap temperatures from TI were analyzed and correlated to the clinical outcomes. HSI and TI were done preoperatively to evaluate baseline perfusion and twice daily postoperatively starting on the first postoperative day until discharge. The authors reported that, during postoperative monitoring, HSI was used to identify impaired perfusion areas within the DIEP flap based on deoxyHb levels while ICG perfusion curves identified the lack of arterial inflow (n = 2) and occlusion of the venous outflow (n = 1) and that, overall, oxyHb showed a greater variation over time compared to deoxyHb levels as oxyHb levels were increased from the first postoperative day compared to baseline while deoxyHb levels changed negligibly. In the case complicated by venous thrombus causing venous congestion, the authors reported that there was a slight increase in oxyHb seen while deoxyHb more than doubled although no changes in skin temperature were observed. In the second complicated DIEP case found postoperatively, with a partial epidermolysis, oxyHb and deoxyHb levels evidently increased, whereas the skin temperature decreased compared to the uncomplicated flaps. Both of these cases required surgical reintervention. No additional complications were reported by the authors during the one-year follow-up. The authors also stated that the results showed a limited added value of TI. The authors concluded that HSI appeared to

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be a promising technique for postoperative flap perfusion assessment and that a diagnostic accuracy study is needed to investigate ICGA and HSI parameters in real-time and demonstrate their clinical benefit. Limitations of the study include the single-center design, the small study population, and the lack of availability of ICGA and HSI perfusion parameters in real-time.

Kleiss et al. (2023) conducted a single-center prospective cohort study aimed to detect changes in perfusion with HSI and thermal imaging peri-procedurally and determine whether these changes can identify limbs that show clinical improvement after six weeks in participants with peripheral artery disease. Participants with Rutherford class 2–6 scheduled for endovascular treatment (EVT) were included prospectively. A total of 23 individuals with 29 treated limbs were included. Hyperspectral imaging and thermal imaging were performed directly before and after EVT. Images were taken from the lateral side of the calves and the plantar side of the feet. Concentrations of (de)oxyhemoglobin, oxygen saturation, and skin temperature were recorded. Angiographic results were determined on completion angiogram. Clinical improvement six weeks after EVT was defined as a decrease of one or more Rutherford classes. Peri-procedural changes in perfusion parameters were compared between limbs with and without good angiographic results or clinical improvement. To identify limbs with clinical improvement, receiver operating characteristic (ROC) curves were used to determine cutoff values for change in HSI. Change in HSI values and temperature was not significantly different between limbs with good and poor angiographic results. Change in peri-procedural deoxyhemoglobin, determined by HSI, at the calves and feet was significantly different between limbs with and without clinical improvement at six-week follow-up ($p = 0.027$ and $p = 0.017$, respectively). The ROC curve for change in deoxyhemoglobin at the calves showed a cutoff value of ≤ 1.0, and ≤ −0.5 at the feet, which were discriminative for clinical improvement (sensitivity 77%; specificity 75% and sensitivity 62%; specificity 88%, respectively). The authors concluded HSI can detect changes in perfusion at the calves after EVT in individuals with Rutherford class 2–6. Peri-procedural deoxyhemoglobin changes at the calves and feet are significantly different between limbs with and without clinical improvement. Decrease in deoxyhemoglobin directly after EVT may identify limbs that show clinical improvement six weeks after EVT. A limitation of the study is that a small number of limbs were included. The study population was also quite heterogeneous, including individuals with Rutherford class 2–6 and patients with and without diabetes. The results and predictive value of the established cutoff values for change in perfusion should be verified in future studies with larger groups. Also, clinical outcome was only determined at six weeks of follow-up. Future studies with larger study groups could also consider other clinical outcome measures such as wound healing, pain scores, amputation-free survival, and freedom from reintervention with lengthier follow-up. The clinical utility of HSI technology to improve individuals' outcomes was not addressed in this study.

Hart et al. (2022) conducted an observational study to determine if transcutaneous oxygenation in the lower limb, as measured by HSI, changes depending on the clinical component of the Clinical-Etiological-Anatomical Pathophysiological (CEAP) classification in chronic venous disorders (CVD). This observational study consisted of individuals with CVD recruited from a vascular specialist clinic at a tertiary hospital from January 2020 to January 2021. Participants were allocated to eight groups according to the clinical component of CEAP classification of CVD. Baseline demographic and risk factor information were collected. Transcutaneous oxygenation was measured using HSI at seven sites around the foot and gaiter area in the supine and standing position. Calculations of oxyhemoglobin level [artificial unit (AU)], deoxyhemoglobin level (AU), oxygen saturation (%), and temperature (C) were obtained. There were 94 participants (164 lower limbs) included in the study. The median age was 59 years, and 59 participants (63%) were women. At all sites except the heel, deoxyhemoglobin measurements increased in the standing position compared with the supine position ($p < .001$). In the gaiter region, there was nearly a doubling in deoxy hemoglobin level at 5 cm above the medial malleolus (supine 43.88 AU vs standing 80.46 AU; $p < .001$) and 5 cm above the lateral malleolus (supine 46.33 AU vs standing 87.72 AU; $p < .001$). When measurements were stratified by clinical class of the CEAP classification, there was a greater increase in deoxyhemoglobin levels with increasing clinical class in the standing position ($p < .001$). This finding was not observed in the supine measurements. The authors concluded that in CVD, HSI shows an increase in deoxyhemoglobin in the standing compared with supine position, particularly in the gaiter region. Furthermore, standing deoxyhemoglobin increases as the CEAP clinical class increases. The authors stated this noninvasive tool may respond to venous physiology and may supplement the clinical class of the CEAP classification system. There are two major limitations of this study that could be addressed in future research. First, this was a pilot study and hence there was a relatively small number of limbs in each clinical class category. Future research with larger cohort numbers is required to validate these findings of baseline transcutaneous oxygenation values across the CEAP clinical classes in CVD. In addition, the uneven distribution of participants between the clinical classes may have impacted the statistical results, and hence future studies with greater power should particularly focus on validating the results for higher clinical classes.

Ma et al. (2022) conducted a single-center prospective cohort study to assess changes in tissue perfusion up to six weeks after endovascular therapy (EVT), in hospital and at home, and to determine differences in tissue perfusion between participants with and without clinical improvement or good angiographic results. This single center prospective cohort study included 34 individuals with 41 treated limbs undergoing EVT for Rutherford stages two to six. Hyperspectral and thermal imaging were performed at the dorsal and plantar sides of the foot. These measurements consisted of a baseline

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measurement pre-EVT, and six follow-up measurements obtained at one and four hours and six weeks in hospital, and one day, seven days, and 14 days at home. Clinical improvement was defined as a decrease of one or more Rutherford class or decrease in the wound surface area and a good angiographic result was accomplished when a Transatlantic Inter-Society Consensus for the Management of PAD II C or D lesion was treated and uninterrupted flow continued in at least one below-the-knee artery in continuation with the inframalleolar arteries. Deoxyhemoglobin values were lower at one hour post-EVT compared with baseline and increased over time up to 6 weeks post-EVT. Significant differences in deoxyhemoglobin levels at seven and 14 days post-EVT were determined between individuals with and without clinical or angiographic success. The authors concluded this prospective pilot study shows the feasibility of hyperspectral imaging and thermal imaging post-EVT at home, which may decrease the need for hospital visits. One of the study limitations is the small group of 34 participants and a substantial number of missing measurements. A major downside of all the missing data was the inability to perform mixed-model statistical analyses, which was the preferred method within longitudinal data analyses and should be used within future studies. The clinical utility of the technology to improve patients' outcomes is not addressed in this study.

Katzenschlager et al. (2022) conducted a randomized controlled trial (RCT) to assess microcirculatory alterations during trauma resuscitation care using HSI in a dedicated trauma resuscitation room of a level one trauma center. The study included 51 adults who were admitted to the trauma resuscitation room. Individuals were allocated in a 1:1 ratio to the HSI group (intervention) (n = 25) and control group (n = 26). In addition to the standard of care, participants in the intervention group had two hyperspectral recordings (HSR) of their hand palm taken using the Tivita® Tissue System (Diaspective Vision GmbH, Am Salzhaff, Germany). Primary outcomes were the treatment duration of the primary survey (until end of ABCDE-evaluation, ultrasound and evaluation by the trauma team) and the total resuscitation room care (until transport to definitive care) as well as the ability to perform measurements from all HSR. Secondary outcomes were analyses from the intervention group compared to HSI measurements of 26 healthy volunteers including an analysis based on the ISS (Injury severity score) (< 16 vs. ≥ 16). Care givers, and those assessing the outcomes were blinded to group assignment. Statistically, there was shorter median duration of the primary survey in the control group [03:22 min (Q1–Q3 03:00–03:51)] compared to the intervention group [03:59 min (Q1–Q3 03:29–04:35)] with a difference of −37 s (95% CI −66 to −12). Total resuscitation room care was longer in the control group, but without significance: 60 s (95% CI −60 to 180). From 52 HSI, the authors were able to perform hyperspectral measurements on all images, with differences noted between injured participants and healthy volunteers. A 30 day follow-up was conducted either by e-mail or a phone call. One participant was lost in the control group to 30 -day follow-up. In the control group, five (21.5%) participants had to be admitted to the ICU and three (12.5%) participants underwent surgery immediately. Another three (12.5%) participant were discharged on the same day. In the intervention group, eight (30.8%) participants were admitted to the ICU and five (19.2%) went to the OR. No participant was discharged on the same day. In both groups, all participant were alive throughout the 30 day follow up period. The authors concluded that HSI proved to be feasible during resuscitation room care and can provide valuable information on the microcirculatory state. This RCT has several limitations that should be considered for the interpretation of the results. First, it was only conducted at a single trauma center, limiting its external validity. Secondly, the study sample size was too small to analyze subgroups with severe trauma or shock. This is reflected in the non-significance when assessing HSI measurements in those with an ISS < 16 and ≥ 16. Further investigation including impact on patients' outcomes is needed before clinical usefulness of this procedure is proven.

Lopez-Moral et al. (2022) conducted a one-year prospective cohort study to compare the potential healing prognosis of the different routine noninvasive techniques implemented in the International Working Group Diabetic Foot Guidelines with the use of HSI in individuals with diabetic foot ulcers (DFUs). In 21 participants with a diabetic ulcer, HSI predicted ulcer healing with a sensitivity of 93% and a specificity of 71%. Transcutaneous oxygen pressure values showed the best diagnosis potential in 14 participants with wound healing with a sensitivity of 91% and a specificity of 100%. The authors concluded that HSI was a promising test to predict healing of diabetic ulcers, but in this study transcutaneous oxygen pressure predicted ulcer healing the best. The authors noted that the results should be interpreted with caution due to the small study size and that further studies should be pursued to verify the healing prognosis of HSI in a larger sample size and use of a control group for comparison. Furthermore, the superiority of this tool, as compared to other clinical or imaging tools, also needs to be demonstrated.

Hayes, in a 2021 Evolving Evidence Review, reported there were no clinical studies or systematic reviews addressing the clinical validity or clinical utility of HSI for the assessment of peripheral artery disease (PAD) of the lower leg, nor were there any relevant guidelines or position statements identified. While formative research was identified, it does not provide data needed to inform the clinical application of HSI in this context, and whether it performs the same, worse, or better than clinical alternatives. Hayes updated their Evolving Evidence Review in 2024, Hayes reported that there were no relevant newly published clinical studies, systematic reviews, or guidelines that may meet their inclusion criteria.

Kohler et al. (2021) performed a prospective observational study including 22 participants with soft tissue reconstruction to explore HSI as a new tool in flap monitoring to improve sensitivity compared to established monitoring tools. Flap

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perfusion was assessed by standard clinical parameters, Doppler ultrasound, and HSI on t0 (0 h), t1 (16–28 h postoperatively), and t2 (39–77 h postoperatively). HSI records light spectra from 500 to 1000 nm and provides information on tissue morphology, composition, and physiology. These parameters contain tissue oxygenation (StO2), near-infrared perfusion- (NIR PI), tissue hemoglobin- (THI), and tissue water index (TWI). Total flap loss was seen in four cases and partial loss in two cases. Every participant with StO2 or NIR PI below 40 at t1 had to be revised. No single participant with StO2 or NIR PI above 40 at t1 had to be revised. The authors reported that there were significant differences between feasible (StO2 = 49; NIR PI = 45; THI = 16; TWI = 56) and flaps with revision surgery [StO2 = 28 ($p < 0.0001$)]. The authors concluded that HSI provided valuable data in free flap monitoring. The technique seems to be superior to the gold standard of flap monitoring. StO2 and NIR PI deliver the most valuable data and 40 could be used as a future threshold in surgical decision making. The limitations of this study include its small sample size and the heterogeneity of the study's endpoint. Also, to improve selectivity in future studies with higher case numbers, the authors suggested that it may be of interest to split individual flap composition (fasciocutaneous, myocutaneous) and by the entity (e.g., ALT, latissimus dorsi, subscapular). Findings from this proof-of-concept study are however insufficient to demonstrate the validity and clinical utility of this technology.

Saiko et al. (2020) conducted a systematic review of HSI systems that have been assessed in individuals published over the past 32 years. The systematic review included 140 studies, including 10 different HSI systems. Currently in vivo HSI systems generate a tissue oxygenation map. Tissue oxygenation measurements may help to predict those individuals at risk of wound formation or delayed healing. No safety concerns were reported in any studies. A small number of studies have demonstrated the capabilities of in vivo label-free HSI, but further work is needed to fully integrate it into the current clinical workflow for different wound etiologies. The authors note that as an emerging imaging modality for medical applications, HSI offered great potential for non-invasive disease diagnosis and guidance when treating individuals with both acute and chronic wounds. They, however, concluded that they were unable to draw any firm conclusions concerning the effectiveness of the HSI techniques described. Future hyperspectral imaging studies are required to more fully quantify the tissue-oxygenation-based assessment that can provide subclinical physiological status to combine with visual clinical assessment.

Ma et al. (2019) also conducted a systematic review which provided an overview of these current diagnostic techniques to determine tissue perfusion in individuals with PAD and healthy controls. Twenty studies describing 10 different techniques were found. The authors identified two publications related to HSI, both of which are described in detail below. The authors found while using contact-free methods, such as HSI, laser speckle contrast imaging (LSCI), or MRI, may be preferable, especially when patients have foot ulcers, newer diagnostic techniques, such as HSI and LSCI require additional larger prospective cohort trials to fully assess the effectiveness.

Chiang et al. (2017, included in Saiko 2020 and Ma 2019 systematic reviews above) compared the use of OxyVu to that of established modalities such as transcutaneous oxygen measurement (TCOM) and ankle-brachial index (ABI) in individuals with peripheral vascular disease (PVD). There were 294 participants recruited and divided into three distinct groups. Participants underwent measurements of lower limbs at a standardized point using the hyperspectral device generating outputs including HT-Oxy, HT-Deoxy, HT-Sat, TCOM and skin temperature. The authors stated that HT-Sat was the most sensitive output as it took into account both the concentration of oxyhemoglobin and deoxyhemoglobin and concluded that the study demonstrated reliability of the hyperspectral device in PVD patients when compared to other established methods and it could be a useful screening tool in PVD. Limitations included lack of a standardized tool for measurement thus reliance on clinical judgement, only two target points for area assessment, and that 25% of participants were active smokers which identified slightly higher ABI recordings. These findings do not, however, demonstrate the incremental clinical utility of this approach over other established non-invasive approaches.

Chin et al. (2011, included in Saiko et al. 2020 and Ma et al. 2019 systematic reviews above) conducted a diagnostic study on 126 participants to determine if HSI could accurately assess the presence or absence of PAD and accurately predict PAD severity. All participants underwent standard noninvasive lower extremity arterial flow studies, including measurement of the ankle-brachial index (ABI); segmental pressures for the upper thigh, lower thigh, calf, dorsalis pedis, posterior tibial, metatarsal, first digit areas, and second to fifth digits if first digit pressures were < 50 mm Hg and arterial Doppler waveforms of the dorsalis pedis and posterior tibial arteries. HSI data for participants was collected using the OxyVu system and the vascular technicians were blinded to the results. The primary comparative analysis showed no significant differences in hyperspectral oxyhemoglobin values for patients with versus without PAD. In contrast, the analysis of the deoxyhemoglobin values showed statistically significant differences for non-PAD vs PAD limbs. Data also suggested a significant correlation between deoxyhemoglobin values and ABI ($p = 0.001$). The authors concluded that HSI presents an interesting new development for the diagnostic imaging and evaluation of PAD but does not provide a breakthrough to replace existing bedside technology. Future study and understanding of how this technology works may identify it as a valuable tool for the prediction of wound healing in severely ischemic patients. The findings of this study do

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not demonstrate the incremental clinical utility of this approach over other established non-invasive approaches, such as ABI.

The American College of Cardiology (ACC), American Heart Association (AHA), American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR), American Podiatric Medical Association (APMA), Association of Black Cardiologists (ABC), Society for Cardiovascular Angiography and Interventions (SCAI), Society for Vascular Medicine (SVM), Society for Vascular Nursing (SVN), Society for Vascular Surgery (SVS), Society of Interventional Radiology (SIR), and Vascular and Endovascular Surgery Society (VESS) published a guideline for the management of lower extremity peripheral artery disease (PAD) that includes diagnostic testing and imaging for lower extremity PAD; however, hyperspectral imaging is not mentioned in the guideline (Gornik et al., 2024).

The U.S. Food and Drug Administration (FDA) cleared the HyperView™ Hyperspectral Tissue Oxygenation Measurement system under its 510(k) premarket notification process as substantially equivalent to predicate devices. For additional information refer to the following website:

- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K161237
- https://www.accessdata.fda.gov/cdrh_docs/pdf16/K161237.pdf

(Accessed May 15, 2025)

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Code	Description
0640T	Noncontact near-infrared spectroscopy (e.g., for measurement of deoxyhemoglobin, oxyhemoglobin, and ratio of tissue oxygenation), other than for screening for peripheral arterial disease, image acquisition, interpretation, and report; first anatomic site
0859T	Noncontact near-infrared spectroscopy (e.g., for measurement of deoxyhemoglobin, oxyhemoglobin, and ratio of tissue oxygenation), other than for screening for peripheral arterial disease, image acquisition, interpretation, and report; each additional anatomic site (List separately in addition to code for primary procedure)

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Code	Description
93998	Unlisted noninvasive vascular diagnostic study [when used to report contact near-infrared spectroscopy studies of wounds]

Contact or non-contact near-infrared spectroscopy (NIRS) is unproven and not medically necessary for assessing tissue oxygenation in tissue flaps or wounds due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Near-infrared spectroscopy (NIRS) is a noninvasive technique using wavelengths to measure tissue oxygenation. NIRS has been proposed to be used as an indication of wound healing.

According to the FDA SnapshotNIR is intended for use by healthcare professionals as a non-invasive tissue oxygenation measurement system that reports an approximate value of: - oxygen saturation (St02), - relative oxyhemoglobin level (Hb02), and - relative deoxyhemoglobin (Hb) level in superficial tissue. SnapshotNIR displays two-dimensional color-coded images of tissue oxygenation of the scanned surface and reports multispectral tissue oxygenation measurements for selected tissue regions. SnapshotNIR is indicated for use to determine oxygenation levels in superficial tissues. Additional information is available at: https://www.accessdata.fda.gov/cdrh_docs/pdf20/K201976.pdf. (Accessed June 19, 2025).

In a single-center feasibility study by Andersen et al. 2024 made up of individuals 18 years and older with lower extremity wounds, the researchers performed serial imaging with a point–of–care, noncontact, NIR imaging device to assess the wound and surrounding skin. They evaluated the difference in time to 100% reepithelialization on visual inspection and homogeneous tissue oxygen saturation levels at the wound site and surrounding closed skin envelope. The study found an average time difference of 13.5 ±10 days between 100% reepithelialization on visual wound inspection and imaging assessment. Additionally, NIR imaging could decide when an individual was at risk for recurrent wound breakdown. Limitations of this study include that it was a single-center feasibility study with no control group or comparator, had a small sample size and short follow-up duration and required correct interpretation of the images obtained. The authors concluded that the addition of a point of care, noncontract, and NIR imaging may help guide clinical decision-making for the optimal time to transition from protective wound dressings with a gradual return to total activity and minimize wound recurrence.

Lindelauf et al. (2022) conducted a systematic review evaluating the use of NIRS versus hyperspectral Imaging (HSI) to detect flap failure in reconstructive surgery compared to standard monitoring such as clinical assessment and a handheld doppler. PubMed and Embase were searched in August 2021 with studies selected by two independent reviewers. Five HSI and 16 NIRS studies totaling 3,662 flap procedures carried out in 1,970 participants using NIRS and 90 participants using HSI were included. The flap survival of HSI was 92.5% and NIRS 99.2% with statistically significant differences observed in flap survival, flaps returned to OR, and partial flap loss rate. The literature concludes NIRS and HSI are reliable, accurate and user-friendly, however according to recent available literature, no concrete conclusions can be made regarding non-invasive monitoring techniques superiority over subjective clinical assessment, complemented with hand doppler which is the golden standard for flap monitoring.

Hill et al. (2020) conducted a cohort study to evaluate the capacity of NIR spectroscopy to detect clinically relevant differences in flap perfusion intraoperatively. Those undergoing oncologic resection of breast cancer, sarcomas, and cutaneous tumors requiring flap reconstruction (local, regional, or free) between January 2018 and January 2019 were analyzed in this study. Clinicians were blinded to device tissue oxygen saturation (StO2) measurements taken intraoperatively after closure and at follow-up appointments in the first 30 days. Measurements were categorized as (1) control areas not affected by the procedure, (2) areas at risk, and (3) areas of necrosis. These areas were retrospectively demarcated by 2 blinded assessors on follow-up images and transposed onto anatomically correlated intraoperative StO2 measurements. Forty-two participants were enrolled, and 51 images were included in the analysis. Oncologic procedures were predominantly breast (22), post-extirpative melanoma (13), and sarcoma (3) reconstructions. Flap reconstruction involved 30 regional skin flaps, 3 pedicled flaps, and 3 free flaps. Nine individuals (20.9%) and 11 surgical sites developed skin flap necrosis (SFN). Mean intraoperative StO2 measurements for control areas, areas at risk, and areas of SFN were 74.9%, 71.1%, and 58.3%, respectively. Relative to control areas, mean intraoperative StO2 measurements were lower by 17.5% ($p = 0.01$) in ultimate areas of SFN and in areas at risk by 5.8% ($p = 0.003$). Relative to areas at risk, mean StO2 measurements from areas of ultimate SFN were lower by 8.3% ($p = 0.04$). The investigators indicated that these preliminary data suggest that measuring skin flap tissue oxygenation intraoperatively, with NIR spectroscopy, can differentiate objective variations in perfusion that are associated with clinical outcomes. According to the investigators, the relatively small sample size made analysis of the sensitivity and specificity of this device limited and not applicable in a clinical context.

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Lin et al. (2020) evaluated the use wearable NIRS to determine the effect of Buerger exercises on diabetic foot ulcer (DFU) healing. Fifty consecutive individuals were enrolled in a 1-year prospective observational study of DFUs. The participants were divided into groups by their arterial statuses: group A [no peripheral arterial disease (PAD)], group B (PAD without angioplasty), and group C (PAD with angioplasty). Tissue perfusion was assessed through wireless wearable NIRS to determine the effects of Buerger exercises on wound healing. Those in group C were older, were more likely to have had an amputation, and had more severe wounds than did those in other groups. At the end of the survey, 19 people (38%) had unhealed DFUs. The NIRS revealed that most non healed individuals in groups B and C shared higher resting hemoglobin levels and tissue blood volume and lower tissue oxygen concentration, which indicated inflammation accompanied by higher blood flow and oxygen consumption. Notably, the non-healed individuals in group C showed paradoxically reduced hemoglobin and tissue blood volume after the exercises. The investigators concluded that although DFUs remain a challenge to treat, NIRS may prove valuable in predicting wound healing by identifying risk factors for poor wound prognosis, such as reduced hemoglobin and tissue blood volume after exercise. The investigators indicated that further research is needed to establish NIRS' ability to predict wound outcomes as a treatment guide. According to the investigators, the major limitation of this investigation is that it is a nonrandomized study with a small number of people.

Serena et al. (2020) conducted a study to compare measurement of tissue oxygenation of NIRS with transcutaneous oxygen measurement (TCOM) in those with acute and hard-to-heal wounds. The Shapiro-Wilk test was used to evaluate the normality of the data. The level of agreement between NIRS and TCOM was determined using Bland-Altman analysis. The relationship between TCOM and NIRS was examined using Pearson correlation. A total of 24 observations were obtained from 10 people using TCOM and NIRS. The weighted mean partial pressure of oxygen (pO2) in the study population was 39.54mmHg (8.96 standard deviation). Bland-Altman analysis showed that mean difference was positive (18.75), suggesting an overestimation of oxygen measurements using TCOM compared with NIRS. The oxygen levels measured by TCOM and NIRS showed a strong correlation (r = 0.74). The investigators indicated that the wound and hyperbaric community would benefit from a simplified procedure for measuring tissue oxygenation. According to the investigators, these findings suggest a strong trend toward correlation between NIRS and TCOM. The major limitation of this study is that it is a nonrandomized study with a small sample size. Further studies in larger populations are needed.

In a systematic review, Mortensen et al. (2019) evaluated diagnostic modalities used for acute compartment syndrome (ACS). Fifty-one pre-clinical and clinical articles were included in this study, reporting on 38 noninvasive and 35 invasive modalities. NIRS and direct intercompartmental pressure measurement were the most common diagnostic modalities. According to the authors, all modalities lacked a reliable threshold. The authors indicated that future studies on diagnostic modalities should include continuous assessment tools to better identify the earliest signs of ACS and thereby establish a reliable threshold.

Shuler et al. (2018) evaluated NIRS as a continuous, non-invasive monitor for acute compartment syndrome (ACS). NIRS sensors were placed on 86 people with, and 23 without (controls), severe leg injury. NIRS values were recorded for up to 48 hours. Longitudinal data were analyzed using summary and graphical methods, bivariate comparisons, and multivariable multilevel modelling. Mean NIRS values in the anterior, lateral, superficial posterior, and deep posterior compartments were between 72% and 78% in injured legs, between 69% and 72% in uninjured legs, and between 71% and 73% in bilaterally uninjured legs. In those without ACS, the values were typically > 3% higher in injured compartments. All seven limbs with ACS had at least one compartment where NIRS values were 3% or more below a reference uninjured control compartment. Missing data were encountered in many instances. The authors concluded that NIRS oximetry might be used to aid the assessment and management of those with ACS. However, additional interventional studies are required to validate the use of NIRS for ACS monitoring.

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Code	Description
0647T	Insertion of gastrostomy tube, percutaneous, with magnetic gastropexy, under ultrasound guidance, image documentation and report

Percutaneous gastrostomy tube insertion by ultrasound guidance is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

The percutaneous ultrasound gastrostomy is a novel procedure that has emerged as an alternative to a percutaneous endoscopic gastrostomy (PEG) or percutaneous radiological gastrostomy (PRG). It can be performed by a non-surgical provider at a patient's bedside.

In 2024, ECRI revised the 2021 clinical evidence assessment on the PUMA-G gastrostomy tube placement system. Evidence from three nonrandomized comparison studies suggests that gastrostomy using PUMA-G is comparable in safety and effectiveness to percutaneous endoscopic or radiologic gastrostomy. However, the studies include too few patients to allow definitive conclusions. The studies are all at high risk of bias due to small sample size, partially retrospective design, single-center focus, and lack of randomization. Additional controlled trials comparing PUMA-G with other devices and methods for gastrostomy tube placement are needed (Publications by Reis 2022 and Accorsi 2021 which are discussed in this policy, are included in this Clinical Evidence Assessment).

In a 2022 prospective cohort study, Reis et al. compared the safety and efficacy of percutaneous ultrasound guided gastrostomy tube placement (PUG) with traditional fluoroscopic guided percutaneous gastrostomy tube placement (PRG) and followed for thirty days. Demographic differences were not significantly different, aside from more COVID-19 individuals in the PUB group. A total of twenty-five participants were selected for each group. In the group receiving PUG, 23 were admitted to the ICU at the time of procedure request, eight procedures were performed bedside in the ICU and the remaining 17 were performed in the interventional radiology (IR) suite without fluoroscopy. The results showed that in eight individuals, there was technical success of bedside placement (the 17 individuals, in which it was not successful, underwent successful placement in the IR setting). One was stopped due to difficulty passing the orogastric balloon past the tracheostomy tube. Two major complications occurred following PUG procedure. One patient became hypotensive after being restarted on therapeutic lovenox for pulmonary embolism 24 hours post procedure, and the second had a drop in hemoglobin requiring a transfusion. In the group receiving PRG, technical success was seen in twenty-four individuals, with the one procedure unsuccessful due to lack of a safe percutaneous access window to the stomach free from intervening bowel. One major complication occurred when a tube pulled back into the subcutaneous tract resulting in an abscess and tube removal after 18 days. Another individual developed an abscess around the tube that was successfully treated. Both PUG and PRG methods of gastrostomy tube placement were similar with respect to local anesthesia and procedural sedation. The authors concluded that while both procedures were technically successful, PUG has advantages over PRG including elimination of radiation and the need to transport critically ill patients. This study is limited by differences in clinical operations, and individual underlying disease processes. Additional larger scale standardized studies are needed to evaluate the safety and efficacy and superiority of PUG over PRG.

In a prospective, single-arm clinical trial with historical matched controls, Accorsi et al. (2021) conducted a study of PUG insertion in 25 adult participants and compared its safety and efficacy to 25 who received PRG. For comparison, a retrospective cohort of 25 participants who underwent PRG were selected based on score matched criteria. The setting for PUG insertion was either beside or in the IR department. Primary outcomes included procedural success and any post -procedural adverse event (AE) at 30 days. In secondary outcomes, sedation requirements, hospital length of stay, and procedural duration were included. According to the researchers results, procedural success rate was 100% for both PUG and PRG groups. Number of AEs were not statistically significantly different between the two groups: mild AEs ($p = 0.16$), moderate AEs ($p = 0.31$) and there were no severe AEs or 30-day procedure-related mortality. Except for 8 PRG insertions as they had no sedation, the sedation requirements showed no substantial difference in the PUG versus PRG group with Midazolam ($p = 0.35$) or Fentanyl ($p = 0.14$). The hospital length of stay was not significantly different between the two groups ($p = 0.70$), but procedural duration was longer for PUG than PRG ($p < 0.001$). The researchers concluded that PUG is effective and safe in comparison to PRG. However, further prospective, randomized control trials studies are necessary to address limitations of small sample size, which may have been too small to demonstrate non-inferiority, outcomes of adverse events and operators with ultrasound experience versus non-experienced operators.

In a report by Cool et al. (2020), the authors describe the initial first-in-human experience on five participants with the PUG. Experienced interventional radiologists used the PUMA-G System kit on all patients. This kit contained a reusable

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external handheld magnet, a single use orogastric balloon catheter which contained a bar magnet within the balloon and a coil tipped guidewire. The patients received prophylactic antibiotics and moderate sedation for the procedure. All five gastrostomy insertions proved success using the PUG technique without requiring conversion to a conventional fluoroscopic insertion technique. The participants were observed over a 30-day timeframe and found no short-term adverse outcomes. The authors concluded that the PUG technique provides a feasible method for removing the need for endoscopes and fluoroscopy; however, this is a novel technique with no RCTs or long-term data.

Shukla et al. (2019) conducted a single-center, single-physician retrospective review to evaluate the safety and feasibility of ultrasound guidance gastric access for percutaneous retrograde transabdominal gastrostomy (G)-tube placement. Twenty-eight individuals (15 males and 13 females; average age: 60.7 ±15.4 years) underwent 31 ultrasound-guided antral access for transabdominal G-tube placements. Twenty-four of the individuals had head and neck malignancies and required a G-tube for enteral nutrition, and two patients had neurologic deficits and were nothing by mouth (NPO), and two patients required gastric decompression following a Whipple surgery. Average follow-up time was 125 days. Technical success was 100%. All individuals had successful placement of G-tubes with ultrasound-guided gastric access. There were no cases of aspiration or peritonitis. Average fluoroscopy time was 2.7 ±1.4 min and average radiation dose was 220 ±202 µGym2. The authors concluded that ultrasound guidance for gastric antral access is safe and effective for the placement of retrograde transabdominal gastrostomy tubes and may help reduce fluoroscopic time and radiation dose exposure. This study is limited by its retrospective observations and single-arm design. In addition, a small sample size makes it difficult to assess whether these conclusions can be generalized to a larger population. Further research with randomized controlled trials is needed to validate these findings.

The US Food and Drug Administration (FDA) approved the PUMA-G System® (CoapTech, Baltimore, MD) for gastrostomy insertions under the 510(k) pathway on April 10, 2019. It is intended to affix the stomach to the anterior abdominal wall to allow the initial percutaneous placement of a gastrostomy feeding tube in adults only. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm. (Accessed June 2, 2025)

On April 29, 2025, the FDA cleared the PUMA-G Pediatric System under the 510(k) pathway. The PUMA-G Pediatric System is intended for use in pediatric patients with a minimum weight of 15 kg, and an abdominal wall thickness between 0.6 cm and 3.0 cm. For additional information refer to the following website: https://www.accessdata.fda.gov/cdrh_docs/pdf24/K242211.pdf. (Accessed June 2, 2025)

There are currently two ongoing clinical trials for the PUMA-G system (including the PUMA-G Pediatric System). For information on these clinical trials, go to: www.clinicaltrials.gov. (Accessed June 4, 2025)

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Code	Description
0651T	Magnetically controlled capsule endoscopy, esophagus through stomach, including intraprocedural positioning of capsule, with interpretation and report

Magnetically controlled capsule endoscopy is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

On May 22, 2020, the FDA granted De Novo Clearance as a Class II device for the Navicam® Capsule Endoscope System with NaviCam Stomach Capsule (AnX Robotica, Inc. Dover, DE). This system consists of an ingestible capsule and magnetic controller, a data recorder, and a computer workstation for real-time observation and capsule navigation control. According to the FDA approval letter, it is intended for the visualization of the stomach of adults ≥ 22 years old

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with a BMI less than 38. Refer to the following website for additional information: https://www.accessdata.fda.gov/cdrh_docs/pdf22/K221590.pdf. (Accessed May 15, 2025)

Xi et al. (2022) in a prospective study, attempted to validate whether the Kyoto classification of gastritis could be applied to MCCE and if *H. pylori* infection status could be accurately assessed on MCCE. Two hundred and twenty seven participants who underwent both MCCE and urea breath tests (UBT) were recruited. Two physicians who were blinded to the UBT results independently made the diagnosis of H. pylori infection status according to ten findings listed in the Kyoto classification of gastritis after reviewing MCCE images. The author's developed two predictive models to assess *H. pylori* infection status by combining these ten findings. The MCCE overall diagnostic accuracy for *H. pylori* infection status was 80.2%. The sensitivity, specificity, and diagnostic odds ratio (DOR) for current infection were 89.4%, 90.1% and 77.1, respectively. In the two prediction models, the area under the curve (AUC) values for predicting noninfection and current infection were 84.7 and 84.9, respectively. Study limitations included a design in which approximately half of the included participants were not infected with *H. pylori* (44.5%), while the amount of past-infection participants was particularly low (15.9%); therefore, selective bias could not be avoided; the Kyoto classification system was modified because the degrees of atrophy and intestinal metaplasia on MCCE could not be rated; and lastly, the participants might have had natural eradication of *H. pylori* which would have resulted in an underestimation in diagnostic accuracy. The author's concluded that *H. pylori* infection status could be accurately assessed on MCCE according to the Kyoto classification of gastritis. Additional studies are needed to confirm these results and the clinical utility of the technology compared to usual care.

Geropoulos et al. (2021) performed a systematic review and meta-analysis assessing MCCE versus conventional gastroscopy. There were seven studies included, with a total of 916 patients and 745 gastric lesions. The mean capsule endoscopy examination time was 21.92 ±8.87 minutes. The pooled overall sensitivity of magnetically controlled capsule endoscopy was 87%. Subgroup analysis showed that the sensitivity of identifying gastric ulcers was 82% gastric polyps was 82% and gastric erosions was 95%. MCCE had minimal adverse events and was tolerated by most. The time of MCCE is also much longer than conventional gastroscopy. Authors note that the MCCE demonstrated an acceptable sensitivity of identifying gastric lesions. But well-designed randomized studies are needed to identify the risks and benefits of this new technique, as well as to determine its role as a replacement for conventional gastroscopy. The study by Liao et al (2016) described below is included in this systematic review.

A systematic review and meta-analysis by Hu et al. (2021) compared magnetically controlled capsule gastroscopy (MCCG) to conventional gastroscopy. Nine studies performed before 2020 were included in this analysis, which consisted of 1,146 individuals with gastric disorders. Results of this analysis showed "the pooled sensitivity, specificity, LR + and LR- of MCCG in detecting gastric disorders were 90%, 92%, 10.6, and 0.11, respectively. A ROC curve was drawn with Q = 0.9060 and AUG = 0.96. The diagnostic odds ratio was 93." The authors concluded that this analysis showed there was no significant difference in diagnostic accuracy comparing MCCG and conventional gastroscopy, with lower rate of adverse events.

Jiang et al. (2020) conducted a prospective single centered, blinded, randomized controlled trial comparing the clinical application of the second-generation MCCG with higher image resolution and frame rate for upper gastrointestinal tract compared with the first-generation. The first generation presented challenges including rapid transit time thru the esophagus and duodenum and longer gastric examination time. The second-generation MCCG (MCCG-2) was developed with higher image resolution and adaptive frame rate, and the authors aimed to evaluate its clinical availability for UGI examination in this study. Participants undergoing MCCG examination between May to June 2019 were prospectively enrolled and randomized to swallow the first-generation MCCG (MCCG-1) or MCCG-2 in a 1:1 ratio. The main outcomes included visualization of the esophagus and duodenum, operation-related parameters, image quality, maneuverability, detection of lesions, and safety evaluation. Eighty participants were enrolled. In the MCCG-2 group, frames captured for esophageal mucosa and Z-line were 171.00 and 2.00, significantly increased from those in the MCCG-1 group (97. and .00 .028, respectively). The gastric examination time was shortened from 7.78 ±97 minutes to 5.27 ±74 minutes, with the total running time of the capsule extended from 702.83 minutes to 1001.99. MCCG-2 also greatly improved the image quality and maneuverability. There was no statistical difference in the detection of lesions between the 2 groups, and no adverse events occurred. MCCG-2 showed better performance in mucosal visualization, examination duration, and maneuverability, making better diagnosis of UGI diseases a possibility. There are limitations to this study including the lesion detection rate was not significantly different between the 2 groups mostly because of the small sample size, necessitating further large-scale studies to test the diagnostic ability compared with conventional endoscopy. Second, the assessment of maneuverability and image quality was in some way subjective, which may skew interpretation. Larger more robust studies are needed to validate MCCG as a promising examination modality for the entire GI tract.

In a medical technology innovation briefing on NaviCam for diagnosing gastrointestinal tract conditions, the National Institute for Health and Care Excellence (NICE, 2017) reviewed five studies that were available at the time: one pilot

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study, one non-blinded comparative study, one multicenter comparative study, one feasibility study, and one poster. These five studies, in total, included 542 individuals, some of which were healthy individuals. After reviewing these five studies, NICE concluded that the evidence for NaviCam was limited in quantity, and suggested that randomized studies comparing conventional gastroscopy with NaviCam or wireless capsule endoscopy would be useful.

In a diagnostic study, Liao et al (2016) compared the performance of MCCE with conventional gastroscopy in detecting gastric lesions. A multicenter blinded study comparing MCCE with conventional gastroscopy in 350 participants (mean age, 46.6 y), with upper abdominal complaints scheduled to undergo gastroscopy. All participants underwent MCCE, followed by conventional gastroscopy two hours later, without sedation by an interventionist blinded to the findings of the MCCE. The sensitivity, specificity, positive predictive value, and negative predictive value of detection of gastric focal lesions by MCCE was calculated, using gastroscopy as the standard. MCCE detected gastric focal lesions in the whole stomach with 90.4% sensitivity [95% confidence interval (CI), 84.7%-96.1%], 94.7% specificity (95% CI, 91.9%-97.5%), a positive predictive value of 87.9% (95% CI, 81.7%-94.0%), a negative predictive value of 95.9% (95% CI, 93.4%-98.4%), and 93.4% accuracy (95% CI, 90.83%-96.02%). MCCE detected focal lesions in the upper stomach (cardia, fundus, and body) with 90.2% sensitivity (95% CI, 82.0%-98.4%) and 96.7% specificity (95% CI, 94.4%-98.9%). MCCE detected focal lesions in the lower stomach (angulus, antrum, and pylorus) with 90.6% sensitivity (95% CI, 82.7%-98.4%) and 97.9% specificity (95% CI, 96.1%-99.7%). MCCE detected 1 advanced gastric carcinoma, 2 malignant lymphomas, and 1 early-stage gastric tumor. MCCE did not miss any lesions of significance (including tumors or large ulcers). Among the 350 participants, five reported nine adverse events (1.4%) and 335 preferred MCCE over gastroscopy (95.7%). There are study limitations including, the MCCE preparation is slightly longer than conventional gastroscopy and it takes longer to perform an MCCE (approximately 30 minutes). Lastly, the preference of MCCE over gastroscopy observed in this study might be biased because the gastroscopy was performed without sedation. The author notes that this novel MCCE has a high diagnostic accuracy and is a promising alternative for patient-friendly screening for gastric diseases. Larger studies are needed to confirm the efficacy of this novel technique.

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Code	Description
0658T	Electrical impedance spectroscopy of 1 or more skin lesions for automated melanoma risk score

Electrical impedance spectroscopy for automated melanoma risk score is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Electrical impedance spectroscopy (EIS) is a device for the diagnosis of cutaneous lesions using a handheld probe with electrodes that are applied to tissue which emit alternating electric currents to measure electrical impedance differences between benign and malignant tissue. The device generates a numeric score, as well as a positive or negative result. The score is between 0 and 10 and with 0 being considered benign, and 10 malignant. This minimally invasive process does not impact future histopathological interpretation (Fried et al. 2020).

In the updated 2025 practice guideline for cutaneous melanoma, the National Comprehensive Cancer Network (NCCN) states that patients presenting with a suspicious pigmented lesion should undergo an excisional biopsy (elliptical, punch or saucerization). If excisional biopsy is inappropriate due to the location or the lesion is very large, a full thickness incisional or punch biopsy of the thickest portion is an acceptable option. In the common follow up recommendations for all patients, this guideline states that pre-diagnostic clinical modalities and other imaging technologies (e.g., reflectance

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confocal microscopy, electrical impedance spectroscopy) may aid in surveillance for new primary melanoma in patients with a high mole count and/or the presence of clinically atypical nevi.

A 2024 Hayes health technology assessment (updated 2025) evaluated the use of electrical impedance spectroscopy (EIS) with nevisense for diagnosis of cutaneous melanoma. Based on the assessment evaluating the clinical validity EIS is reasonably safe and has some capacity to diagnose cutaneous melanoma; however, there is not sufficient evidence to determine whether EIS improves melanoma diagnosis. A small body of very low-quality evidence is not sufficient to conclude that EIS as an adjunct to standard tests (clinical examination and dermoscopy) improves diagnosis or health outcomes compared with standard tests without use of EIS. No studies were identified that provided statistical analysis of the accuracy of EIS versus conventional techniques. Additional larger long-term studies are needed to evaluate the optimal clinical role of EIS in melanoma diagnosis and management, including its effects on treatment decision-making and health outcomes in patients with melanoma.

In a National Institute for Health and Care Excellence (NICE) guidance document for skin cancer, individuals with suspected melanoma are to be examined using dermoscopy. There is no mention of impedance spectroscopy (NICE, 2024).

An observational clinical trial is currently being conducted to study the Nevisense device and its usefulness in providing information about atypical moles. This information is intended to complement information from usual assessments performed during routine screening for melanoma. Forty individuals with ≥ 100 nevi on the entire cutaneous surface and at least three large, acquired nevi (LAN) > 5 mm in diameter will have electrical impedance spectroscopy scores of their nevi. The expected completion date of the study is August of 2025. To date, this study in not yet recruiting subjects. ClinicalTrials.gov. NCT04705168.

In a prospective, follow-up study, Chavez-Bourgeois et al. (2022) analyzed the performance of electrical impedance spectroscopy (EIS) and its performance in changing lesions identified during long-term (18 months) digital follow-up, in individuals at very high risk for melanoma. High-risk individuals who previously underwent total-body photography and digital dermoscopy were included in this study, which looked at changing melanocytic lesions previously detected on digital monitoring from February to December 2016. In this study, 68 lesions showing significant changes were evaluated first with an EIS device, then sent for RCM (reflectance confocal microscopy). The clinicians who decided to excise the lesions after RCM were unaware of the EIS results. “A total of 68 lesions were identified to have significant changes (11) and were included in the study. The mean TDS was 4.26 (1.51, range 1–8.8) and mean EIS 4.75 ±1.92 (range 0–9). Of the 68 lesions included, after the evaluation with RCM, 46 were considered suspicious and consequently excised. Histopathological diagnosis evaluated by 2 different dermatopathologists was melanoma in 19 lesions and naevi in the remaining 27. Of the 19 melanomas detected, 11 were *in situ* and 8 were invasive (mean Breslow thickness was 0.52 mm, range 0.16–0.94 mm). Two melanomas were detected in one patient with previous personal and familial history of melanoma. The mean ±standard deviation (SD) age of patients included in the study was 48 ±12.9 years (range 18–79); 49% were women. Sixty percent had a previous personal history of melanoma and 39% had a familiar history of melanoma. The mean age of patients with excised lesions was 46.61 years and for patients with nonexcised lesions 49.59 years. The mean age of patients with a diagnosis of melanoma was slightly higher than those with non-melanoma (48.95 ±18.5 compared with 47.04 ±10.1; p = 0.002).”In the current study, EIS was not able to detect 4 melanomas that had a relatively high total dermoscopy score (TDS), “There are several plausible explanations for the relatively low sensitivity of EIS observed in the present study compared with previous studies. First, those lesions detected during digital monitoring were incipient (3 out of 4 were *in situ*) and small in diameter. The semiology of those lesions was quite scarce in terms of malignant dermoscopic features. The suspicion of melanoma, and thus the indication of excision, was based mainly on observed changes seen through digital dermoscopy and the melanoma-specific criteria identified in RCM.” The authors concluded that the addition of RCM to digital follow-up improves accuracy. And although EIS can be useful in the detecting melanoma, it showed lower accuracy than RCM. Limitations of this study include the low number of lesions studied, and the fact that this was a single center study which could mean that different populations might produce different results.

Kolla et al. (2022) conducted a pilot study to evaluate whether clinician diagnostic confidence, sensitivity, specificity, and accuracy can be increased by adding EIS measurement scores to clinical and dermoscopic images of lesions clinically suspicious for melanoma. Three pigmented lesions specialists and three 4th year medical students completed an online survey to evaluate 34 melanocytic lesions suspicious for melanoma. For each lesion, participants provided their diagnosis, biopsy recommendation, and confidence in diagnosing a lesion as benign or malignant based on history and clinical and dermoscopic images, and again after receiving an EIS score. The authors found that the addition of EIS scores increased mean biopsy sensitivity for melanoma/severely dysplastic nevi from 70% to 84% (p = .014) and mean diagnostic accuracy from 74% to 86% (p = .005). Mean diagnostic confidence increased for all histopathologic categories for both students and dermatologists (all p < .05). In this pilot study, the authors concluded that EIS increased novice and expert

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diagnosticians' confidence regarding dermoscopically equivocal melanocytic lesions. Further studies are needed to explore how EIS can help clinicians reassure patients regarding the management of clinically dysplastic melanocytic nevi. Limitations of the study include the small sample size of participants and the number of lesions included as well as the potential for selection bias in the choice of lesions reviewed in a clinical setting.

In a National Institute for Health and Care Excellence (NICE) guidance document for assessment and management of melanoma, assessment by dermoscopy is recommended. Additionally, the guideline states: "Do not routinely use confocal microscopy or computer assisted diagnostic tools to assess pigmented skin lesions." There is no mention of impedance spectroscopy (NICE, 2022).

Pathiraja et al. (2020) conducted a systematic review including a search of Embase Classic, Embase and Medline databases for studies conducted from 1980 to February 2018 that reported on the use of electrical impedance technology in the detection of pre-malignant and malignant conditions. The ability to distinguish between tissue types was defined as the primary endpoint, and other points of interest were also reported. After a search of 731 articles identified on this technology, 51 studies reported with sufficient data for analysis; 4 of the 51 studies focused on skin melanoma and NMSC (including the Malvehy trial mentioned below). All four studies involved large-scale multicenter trials involving 2933 patients. All the trials were conducted in vivo, using a similar methodology. All the studies showed the electrical impedance technology was able to distinguish both melanomatous and non-melanomatous skin tumors with very high sensitivities > 95%. They also noted that the sensitivity of the technique increased further as the Breslow thickness of the malignant tissue increased. All the studies were also able to identify statistically significant differences between normal tissue, nonmalignant atypical lesions and non-melanomatous skin cancers. The authors concluded that electrical impedance technology provides a novel method for the detection of malignant tissue, with these large studies of skin cancer showing encouraging results. While these studies provided promising insights into the potential of this technology as an adjunct in screening, diagnosis and intra-operative margin assessment, the authors concluded that customized development as well as multi-center clinical trials need to be conducted before it can be reliably employed in the clinical detection of malignant tissue.

In a 2020 prospective study of 101 patients with 200 skin lesions, Sarac et al. evaluated the diagnostic accuracy of EIS for non- melanoma skin cancer, mainly basal cell carcinoma (BCC), and squamous cell carcinoma (SCC). However lesions with a clinical pre-diagnosis of sarcoma, melanocytic naevi, benign epithelial or dermal tumors were included. Patients had lesions excised, and EIS performed while in the operating room. Results showed a significant difference in the EIS mean scores between benign and malignant lesions. The standard deviation (SD) was significantly lower in benign lesions (6.18 ±2.1) than malignant tumors (8.02 ±1.3). There was no statistically significant difference in EIS scores between BCC and SCC. For malignant tumors, the median EIS scores ranged between 5 and 10. Nearly all epithelial malignant tumors had median EIS of 8; only invasive SCC had a median EIS of 9. In addition, the median score of cutaneous sarcomas was 10. The benign lesions (melanocytic naevi, neurofibroma, epidermal cyst and other benign lesions, including fibrous papules of the nose, syringoma and solar elastosis) had median EIS scores of 5 and lower. Although secondary excisions, seborrheic keratosis, and inflammatory reactions are categorized as benign lesions, they had median EIS scores of 6, 7.5 and 6.5, respectively. The authors concluded that while EIS showed good ability to differentiate between benign and malignant lesions, it does not replace the diagnostic gold standard which is histopathology. Instead, it can be used to support early clinical diagnosis. Additional prospective trials with larger numbers of tumors are required to test the sensitivity and specificity of this method.

In a 2019 clinical practice guideline of care for the management of primary cutaneous melanoma (CM), the American Academy of Dermatology acknowledged emerging diagnostic technologies, and stated that bedside diagnosis will continue to improve with further Investigation of existing, noninvasive imaging/electrical data acquisition and evaluation tools including electrical impedance spectroscopy combined with digital dermoscopy. Despite these emerging technologies, biopsy with histopathological examination remains the first step in establishing a definitive diagnosis of CM (Swetter et al. 2019).

Svoboda et al. (2019) conducted a comparative study reviewing clinician accuracy for diagnosing melanoma on the basis of electrical impedance spectroscopy score plus morphology versus lesion morphology alone. In total, 164 dermatology trainees completed an online survey presenting clinical images of 45 pigmented lesions (28 benign, 17 melanoma). For each image, respondents were asked if they would recommend biopsy on the basis of morphologic assessment alone, and then asked again once presented with the corresponding EIS score (along with positive and negative predictive values4). The proportion of clinical decisions for which the addition of EIS score altered the decision to biopsy was calculated. In addition, the sensitivity, specificity, and proportion of missed melanomas and benign biopsies were determined for morphologic assessment alone and for morphologic assessment plus EIS score. Significance testing was performed using McNemar test for categorical variables and paired t tests for continuous variables. Overall, 7380 clinical decisions (164 respondents 3 45 lesions) were made on the basis of morphology alone and 7380 were made on the basis

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of morphology plus EIS score. The decision to biopsy was made in 4527 of 7380 cases on the basis of morphology alone and 4553 of 7380 cases on the basis of morphology plus EIS. The EIS results altered the individual biopsy decision in 24.3% of cases (Table I). The addition of the EIS score resulted in 402 fewer missed melanomas and a net decrease of 376 benign biopsies. When including the EIS score, the mean sensitivity of respondents for ruling out melanoma increased from 80.7% to 95.2% and mean specificity from 50.4% to 58.6%. A diagnostic device is only useful if it affects clinical management and improves accuracy. In this study, EIS score led to a change in the decision to biopsy in 25% of cases and improved diagnostic accuracy, resulting in fewer biopsies of benign lesions and more biopsies of melanomas, without significantly changing the total number of biopsies. A higher specificity was seen in this study compared with the EIS pivotal trial (58.6 vs 34.4%),4,5 which measured the specificity of the device alone. This suggests that respondents utilized the EIS information synergistically with the clinical image, rather than basing decisions solely on the EIS results. The authors concluded that EIS had a meaningful impact on the decision to biopsy pigmented lesions with atypical features. When combined with morphologic assessment, EIS score led to improved accuracy without significantly changing the overall biopsy rate. A limitation of this study was that additional clinical data, such as patient history, risk factors, and dermoscopic images, were not available to participants. In addition, as this study only included trainees, the results might not extrapolate to more experienced clinicians.

In a 2018 Cochrane Systematic Review, Ferrante di Ruffano et al. reviewed the literature on the diagnostic accuracy of dermoscopy and spectroscopy-based computer- assisted (CAD) techniques for diagnosing skin cancer in adults. The objective was to determine the accuracy of CAD systems for diagnosing cutaneous invasive melanoma and atypical intraepidermal melanocytic variants, basal cell carcinoma (BCC), or cutaneous squamous cell carcinoma (cSCC) in adults, and to compare its accuracy with dermoscopy. Inclusion criteria consisted of studies of any design that evaluated CAD alone, or in comparison with dermoscopy, in adults with lesions suspicious for melanoma or BCC or cSCC and compared with a reference standard of either histological confirmation or clinical follow-up. Out of 42 studies that met the inclusion criteria, only two used EIS. The results showed across all CAD systems (including EIS) there was considerable variation in the hardware and software technologies used, the types of classification algorithms employed, methods used to train the algorithms, and which lesion morphological features were extracted and analyzed. This was true even between studies evaluating CAD systems. Meta-analysis found CAD systems had high sensitivity for correct identification of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants in highly selected populations, but with low and very variable specificity. Regarding EIS specifically, Nevisense was the only system used in the two large prospective studies. These studies had overlapping recruitment periods and study centers, so there may have been overlap of participants. The results showed in a total of 2389 lesions with a finding of 368 melanomas, summary sensitivity of 97.0% (95% CI 94.7% to 98.3%) and specificity of 33.6% (95% CI 31.6% to 35.7%). Accuracy data for 226 invasive melanomas, showed a summary sensitivity of 98.2% (95% CI 95.4% to 99.3%) and specificity of 38.0% (95% CI 36.0% to 40.1%). 644 malignancies or highly dysplastic lesions, had a summary sensitivity of 93.5% (95% CI 91.3% to 95.1%) and specificity of 32.6% (95% CI 30.4% to 34.8%), including one Merkel cell carcinoma. Some benign lesions are more difficult to distinguish from malignancy using both Derm-CAD and Spectro-CAD systems, particularly seborrheic keratoses which proved problematic for the Nevisense system, however the reporting of benign diagnoses by CAD result was very poor. The authors concluded that in highly selected patient populations, all CAD types demonstrate high sensitivity and could prove useful as a back-up for specialist diagnosis to assist in minimizing the risk of missing melanomas. However, the evidence base is currently too poor to understand whether CAD system outputs translate to different clinical decision-making in practice. Insufficient data are available on the use of CAD in community settings, or for the detection of keratinocyte cancers. The evidence base for individual systems is too limited to draw conclusions on which might be preferred for practice.

Malvehy et al. (2014, included in the Pathiraja systematic review above) conducted an international, multicenter, prospective, and blinded clinical trial on the efficacy and safety of the Nevisense system in distinguishing benign lesions of the skin from melanoma compared to the histopathological gold standard (HSG). This took place at five sites in America, and 17 in Europe. Patients with an even distribution of low, medium, and high-risk skin lesions selected for total excision (to rule out melanoma) were asked to participate in the study. A total of 1,951 patients with 2,416 lesions were enrolled. 1,943 lesions were eligible for evaluation with the primary efficacy endpoint. All eligible skin lesions in the study were examined with the EIS-based Nevisense system, photographed, removed by excisional biopsy, and subjected to histopathological evaluation. The results showed of the 1,942 eligible lesions, 265 were cutaneous melanoma, 55 were non melanoma skin cancer (NMSC) including basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs). Nevisense correctly identified 256 melanomas, and all of the NMCs resulting in observed sensitivity of 96.6% and 100%, respectively. Of 157 naevi with severe dysplasia, Nevisense gave a positive reading for 132 of them, seven out of eight actinic keratoses had a positive reading, and one Merkel cell carcinoma was correctly identified. Of the remaining 1457 lesions, 501 were diagnosed as negative, yielding an observed specificity of 34 4%. The positive predictive value (PPV) of Nevisense was 21 1% and the negative predictive value (NPV) was 98 2%. Only 3 adverse events were defined as definitely related to the device and were mild. The authors concluded that Nevisense has been shown to be an accurate

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and safe device that should be used in conjunction with the clinical risk assessment for patients with suspicion of melanoma in the intended use population.

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Code	Description
0659T	Transcatheter intracoronary infusion of supersaturated oxygen in conjunction with percutaneous coronary revascularization during acute myocardial infarction, including catheter placement, imaging guidance (e.g., fluoroscopy), angiography, and radiologic supervision and interpretation

Transcatheter intracoronary infusion of supersaturated oxygen in conjunction with percutaneous coronary revascularization during acute myocardial infarction is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

The ZOLL Medical Corporation website states they have developed a proprietary medical technology called SuperSaturated Oxygen (SSO_2) Therapy (TherOx®). The system includes three device components: a console, cartridge, and SSO_2 catheter, which are intended to create and deliver SuperSaturated Oxygen (SSO2) Therapy following an acute heart attack. The premise is that "SSO_2 Therapy creates a highly oxygenated saline solution and combines it with the patient's arterial blood to provide focal hyperoxemic oxygen therapy to ischemic (oxygen-deprived) tissue."

Clinical Evidence

A clinical trial sponsored by TherOx, to evaluate the safety and feasibility of supersaturated oxygen (SSO2) delivery in individuals with ST elevation myocardial infarction and cardiogenic shock (STEMI-CS), was withdrawn in January 2024 due to lack of enrollment. ClinicalTrials.gov identifier: NCT04876040.

Falah et al. (2024), contended that two previously published studies which assessed SSO_2 delivered after percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI), [the optimized SSO_2 pilot study (20 participants), and the IC-HOT study mentioned below (100 participants)], showed reduction in infarct size. However, these studies did not assess the effects of SSO_2 on microvascular obstruction (MVO). Therefore, in this data pooled analysis, Falah et al. aimed to compare MVO in individuals with anterior STEMI after successful PCI with and without SSO_2 treatment. Seven randomized trials with a total of 874 individuals were included in this comparison. Ninety individuals

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were treated with SSO_2, while the remaining 784 individuals did not receive SSO_2 treatment. The result of this study showed "SSO_2 therapy was independently associated with a lower extent of MVO compared with no SSO_2 therapy (coefficient, _1.35; 95% CI, _2.58 to_0.11; p = .03). SSO_2 therapy was also associated with a borderline lower risk of any MVO (adjusted odds ratio, 0.56; 95% CI, 0.31-1.00; p = .051)." The authors concluded that "an appropriately powered randomized trial is warranted to definitively determine whether SSO_2 treatment improves long-term clinical outcomes in patients with anterior STEMI who undergo primary PCI." Limitations of this study include the nonrandomized comparison of the seven different trials and lack of patient-centered outcomes. Additionally, the studies were limited to anterior STEMI individuals with successful PCI, and without cardiogenic shock. These results may not be applicable to individuals with non-anterior STEMI, with cardiogenic shock, or those in whom PCI was unsuccessful.

In January 2023, Zoll Medical Corporation announced the start of the REAL SSO_2 post-market observational study, assessing the clinical utility and cost-effectiveness of the TherOx® system. They expect to enroll 750 individuals, consisting of SSO_2-treated and control subjects. As of March 2024, this trial was still recruiting subjects. This trial has subsequently been terminated. ClinicalTrials.gov Identifier: NCT05156996.

In a clinical evidence assessment of TherOx DownStream SuperSaturated Oxygen Therapy System, ECRI (2021) assessed two multicenter randomized controlled trials (RCTs), and one prospective, nonrandomized comparison study of this system/procedure. Among the limitations of these RCTs were only short-term results, and too few patients. Additionally, it was felt that the comparison study was at high risk of bias because of the retrospective design and lack of randomization. ECRI concluded that there were too few data to come to a conclusion on this system and that the evidence is inconclusive.

In a clinical practice guideline by the American College of Cardiology/American Heart Association for coronary artery revascularization, there is no mention of using SuperSaturated Oxygen (SSO_2) therapy in conjunction with percutaneous coronary revascularization during acute myocardial infarction (Lawton et al, 2021).

In 2019, Hayes published an update to their Emerging Technology Report for DownStream System for SuperSaturated Oxygen Therapy (TherOx), which included review of the IC-HOT trial (David et al, 2019), and the AMIHOTII trial (Stone et al, 2009), both listed below. Hayes concluded that "while results from the IC-HOT trial are promising, further evidence is needed to confirm these findings." Additionally, no guidelines were identified that include recommendations for the use of SSO2 therapy after PCI.

In the IC-HOT study, David et al. (2019) (referenced in the ECRI and Hayes report listed above), evaluated the safety of SSO2 used in acute anterior MI. SSO2 therapy was administered to 100 individuals with anterior ST-segment elevation myocardial infarction (STEM in a single-arm study design. SSO2 use was successful in 98% of patients. At 30 days, NACE occurred in 7.1% of individuals, with no deaths, one stent thrombosis, and one case of severe heart failure. The authors concluded that SSO2 infusion following primary percutaneous coronary intervention in acute anterior STEMI showed a favorable early safety profile. The findings are limited by the single arm design. In the IC-HOT study follow-up report, Chen et al. (2021) report, (referenced in the ECRI report listed above), on 1-year clinical outcomes of supersaturated oxygen therapy (SSO_2) after successful percutaneous coronary intervention (pPCI) in individuals with anterior STEMI. One hundred individuals were evaluated in this prospective open-label, single -arm study. These individuals were compared with a control group of similar patients enrolled in the INFUSE-AMI trial (which evaluated the effect of myocardial infarction on the heart tissue and function). The authors found that treatment with SSO_2 was associated with a lower 1-year rate of the composite endpoint of all-cause death or new-onset heart failure (HF) or hospitalization for HF (0.0% vs. 12.3%, p = .001). All-cause mortality, driven by cardiovascular mortality, and new-onset HF or HF hospitalization were each individually lower in SSO_2 -treated patients. "There were no significant differences between groups in the 1-year rates of reinfarction or clinically driven target vessel revascularization." The authors concluded that SSO_2 Infusion following pPCI in patients with anterior STEMI was associated with improved 1-year clinical outcomes including lower rates of death and new-onset HF or HF hospitalizations and that study is required to examine the salutary benefits of SSO2 delivery following pPCI in individuals with anterior STEMI. The findings are limited by lack of contemporary comparison group and lack of randomization.

In 2009, Stone et al. (referenced in the ECRI and Hayes report listed above), conducted a prospective, multicenter trial (AMIHOT II) to investigate SSO2's role in reducing infarct size in early use in individuals with large STEMIs undergoing PCI within 6 hours of symptom onset. Three hundred and one individuals were randomized to SSO (2) infusion in the left anterior descending artery infarct territory (n = 222) or control (n = 79). Among 281 randomized individuals with tc-99m-sestamibi single-photon emission computed tomography data in AMIHOT II, median (interquartile range) infarct size was 26.5% (8.5%, 44%) with control compared with 20% (6%, 37%) after SSO (2). The pooled adjusted infarct size was 25% (7%, 42%) with control compared with 18.5% (3.5%, 34.5%) after SSO (2) [P (Wilcoxon) = 0.02; Bayesian posterior probability of superiority, 96.9%] The Bayesian pooled 30-day mean (+/-SE) rates of major adverse cardiovascular events

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were 5.0+/-1.4% for control and 5.9+/-1.4% for SSO(2) by intention-to-treat, and 5.1+/-1.5% for control and 4.7+/-1.5% for SSO(2) by per-protocol analysis (posterior probability of noninferiority, 99.5% and 99.9%, respectively). The authors concluded that at 30 days, SSO2 infusion into the left anterior descending artery infarct territory resulted in a significant reduction in infarct size with noninferior rates of major adverse cardiovascular events. The findings are limited by lack of blinding or sham control and the clinical significance of the findings is unclear.

The TherOx DownStream System (Product Code MWG) received U.S. Food and Drug Administration (FDA) premarket approval on April 2, 2019 for the preparation and delivery of SuperSaturated Oxygen Therapy (SSO2 Therapy) to targeted ischemic regions perfused by the patient's left anterior descending coronary artery immediately following revascularization by means of percutaneous coronary intervention (PCI) with stenting that has been completed within 6 hours after the onset of anterior acute myocardial infarction (AMI) symptoms caused by a left anterior descending artery infarct lesion. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P170027. (Accessed April 1, 2025).

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Zoll Medical Corporation, Corporate Headquarters, 269 Mill Road, Chelmsford, MA 01824-4105.

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Code	Description
0664T	Donor hysterectomy (including cold preservation); open, from cadaver donor
0665T	Donor hysterectomy (including cold preservation); open, from living donor
0666T	Donor hysterectomy (including cold preservation); laparoscopic or robotic, from living donor
0667T	Donor hysterectomy (including cold preservation); recipient uterus allograft transplantation from cadaver or living donor
0668T	Backbench standard preparation of cadaver or living donor uterine allograft prior to transplantation, including dissection and removal of surrounding soft tissues and preparation of uterine vein(s) and uterine artery(ies), as necessary
0669T	Backbench reconstruction of cadaver or living donor uterus allograft prior to transplantation; venous anastomosis, each

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Code	Description
0670T	Backbench reconstruction of cadaver or living donor uterus allograft prior to transplantation; arterial anastomosis, each

Uterus transplantation is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Uterus transplantation (UTx) is under clinical investigation as a treatment for absolute uterine factor infertility (AUFI). Future studies are needed to further evaluate the safety and efficacy of UTx as well as to better define suitable donors and recipients.

Brännström et al. (2025) systematically reviewed maternal and neonatal outcomes in the pregnancies of women who underwent UTx. The systematic review included 24 articles containing data on 40 unique live births. All deliveries were cesarean section, of which 47.5% were considered emergent. Of the elective cesarean sections, 52.4% were performed before 37 weeks' gestation. A markedly increased risk for both the mother and child following cesarean section after UTx was noted using historical comparison to population data. Rates of specific maternal outcomes determined to be comparatively high included gestational hypertension (7.5%), preeclampsia (15.0%), premature rupture of membranes (15.0%), placenta previa (10.0%), gestational diabetes (7.5%), placenta accreta spectrum (5.0%), and intrahepatic cholestasis of pregnancy (5.0%). Median maternal length of hospital stay was 4 days (range: 2-48). (Although this data was only reported for 12 live births.) Rates of specific perinatal outcomes determined to be comparatively high included prematurity (70.0%), respiratory distress syndrome (35.0%), continuous positive airway pressure treatment (32.5%), weight deviation < 10th percentile (20.0%), weight deviation < 2 standard deviation percentile (7.5%), and congenital malformation (2.5%). Sixteen infants required the neonatal intensive care unit (NICU). The median NICU time was 2.5 days (range: 1-79). The authors concluded that the maternal and perinatal outcomes observed for these 40 live births after UTx indicated that these pregnancies may be at a high risk for complications. However, delaying elective cesarean section beyond 37 weeks' gestation may potentially reduce some risks. The registration of maternal and perinatal outcomes after UTx through quality registries are necessary to help establish specific obstetrical care guidelines. The systematic review is limited by the very low certainty of evidence available. All of the included studies were either case reports (n = 15) or case series (n = 9). (Fronek et al., 2021, which was previously cited in this policy, is included in this systematic review).

Testa et al. (2024) conducted a case series to determine if UTx was feasible and safe and resulted in births of healthy infants. The prospective Dallas Uterus Transplant Study (DUETS) included 20 participants with AUFI and at least one functioning ovary. The median age was 30 years (range: 20-36). The primary outcome for the study was procedure efficacy, defined as graft survival and at least one live birth following UTx. Secondary outcomes were procedure safety, including survival and complications occurring in all participants. Participants underwent in vitro fertilization prior to UTx from 18 living donors and two deceased donors. An immunosuppression protocol was followed until the transplanted uterus was removed, following one or two live births, or after graft failure. The median time interval from UTx to first embryo transfer was 4.1 months (range: 2.1-7.7). The study results revealed 14 (70%) participants had a successful uterus allograft and gave birth to at least one live-born infant. Maternal and/or obstetrical complications occurred in 50% of the successful pregnancies. The most common complication was gestational hypertension (14%), cervical insufficiency (14%), and preterm labor (14%). The median gestational age at live birth was 36 weeks 1 day (range: 30 weeks 6 days to 38 weeks 1 day). No congenital malformations were noted among the 16 live-born infants. One child did not meet his communicative milestones at the 12-month examination and was later diagnosed with autism at 24 months. At the 18-month examination, two additional children showed transient cognitive deviations, but improved at subsequent follow-up visits. Four of the 18 living donors experienced Clavien-Dindo (CD) grade 3 complications. The authors concluded UTx was technically feasible and associated with a high live birth rate following successful graft survival. However, adverse events were common. Medical and surgical risks affected recipients and donors. Congenital abnormalities and development delays were not observed in live-born children. The DUETS study is limited by the single center design and small sample size.

Hayes published an evolving evidence review on UTx for the treatment of AUFI. A review of three clinical studies and one systematic review suggested minimal support for the procedure. The three clinical studies appeared to demonstrate that after UTx, the transplanted uterus remained intact for embryo transfer in 70-78% of recipients. The rate of clinical pregnancy ranged from 50-78% regardless of transplant viability. However, the rate of clinical pregnancy ranged from 71-100% for individuals with a viable graft. Live birth occurred at a rate > 60% with children exhibiting typical development. Recipient complications were described as frequent, but few affected birth outcomes. Preeclampsia occurred in some individuals. Rejection reactions were reported as common. Adverse events caused by immunosuppressive treatment also

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occurred, but without significant sequelae. Other complications included vaginal stenosis, urinary tract infections, leukopenia, kidney disease, hematoma, and blood loss requiring transfusion. Limitations of the three clinical studies include small sample size and the duration of follow-up. The systematic review appeared to demonstrate that UTx may result in clinical pregnancy and the successful delivery of healthy infants. However, there is uncertainty whether clinical outcomes are better for recipients receiving a uterus from a live donor versus a deceased donor. Limitations of the systematic review include that most studies were case reports or small case series. A review of clinical practice guidelines and position statements suggested no or unclear support on UTx for the treatment of AUFI. Hayes noted that the two guidelines included in the review are expert opinion based, without a formal process (Hayes, 2023; annual review 2024).

American College of Obstetricians and Gynecologists (ACOG) committee opinion on the diagnosis, management, and treatment of Müllerian agenesis states: "Uterine transplantation has resulted in live births, but given limited data, this procedure currently is considered experimental and is not widely available" (ACOG, 2018; Reaffirmed 2024).

Using International Society of Uterus Transplantation registry data, Brännström et al. (2023) reported on 45 UTx procedures. Performed between 2012 and 2020 at 13 centers, the procedures included 35 live donors and 10 deceased donors. The median age of the live donors, deceased donors, and recipients were 50 years (range 32-62), 38.5 years (19-57), and 29 years (22-38), respectively. Recipients had AUFI due to Mayer-Rokitansky-Küster-Hauser syndrome, except for one recipient with history of a hysterectomy due to cervical cancer. The duration of surgery for the majority of live donors was > 8 hours. The duration of surgery for most recipients was 2-6 hours. The total ischemic time for grafts was around 2-fold longer in deceased donors when compared to live donors. However, rewarming ischemia times were similar. A CD classification score was used to grade postoperative complications within 30 days of surgery. Postoperative complications were reported for 20% of live donors. Three live donors experienced complications exceeding CD grade 2. Postoperative complications were reported in 24% of recipients. Eight recipients experienced complications exceeding CD grade 2. Acute rejection was observed in 33% of recipients 1-5 months after transplantation and in 21% of recipients 6-10 months after transplantation. There were 19 healthy neonates delivered after in vitro fertilization from 16 recipients (14 from live donors and two from deceased donors). Three women gave birth to singletons twice. The total live birth rate per embryo transfer was 35.8%. The median length of pregnancy was 35 gestational weeks. A much higher than expected rate of pregnancy complications (47%) was reported to have motivated delivery. There were 21 transplant hysterectomies reported (9 after live births and 12 without childbirth). The authors concluded that while the registry provides a detailed analysis of outcomes and complications, a mandatory registry is necessary to better determine quality and process improvement. UTx should still be regarded as an experimental procedure. A limitation of the report includes missing data from more than 25 UTx procedures at centers not participating in the registry.

A clinical evidence assessment from ECRI revealed the evidence for treating AUFI with UTx is inconclusive. Only one systematic review was found, and current available evidence lacked the volume of patients to conclusively characterized the risks and successes for the procedure. Additional robust studies are needed to further evaluate the safety and efficacy of this technology (ECRI, 2017; updated 2022).

Johannesson et al. (2022) reviewed transplant and birth outcomes of UTx recipients in the United States since 2016. The study included data from three centers and 33 recipients with AUFI. The primary recipient outcomes were survival, allograft survival, and live birth. The primary living donor outcome was survival. The primary offspring outcomes were gestational age and weight percentile at delivery. The study results revealed 64% of UTx recipients received organs from living donors. The mean follow-up was 36 months (range: 1-67) months. There was no donor or recipient mortality reported. One-year graft survival was 74% and 84% of these recipients delivered a live-born child. Overall, 58% of recipients delivered a live-born child (n = 21). The median gestational age at birth was 36 weeks 6 days (range: 30 weeks 1 day to 38 weeks). The median birth weight was 2,860 grams (range: 1,310-3,940). The median weight percentile at delivery was 58th percentile (range: 6th-98th). There were no congenital malformations reported. The authors concluded UTx enabled women with AUFI to successfully gestate and deliver children. Aggregate data from U.S. centers demonstrated safety for the recipient, living donor, and child. These data may be used to counsel women on the treatment options with AUFI. The study is limited by the small sample size and short follow-up time.

American Society for Reproductive Medicine (ASRM) committee opinion (2018) states:

- "Uterus transplantation is an experimental procedure for the treatment of absolute uterus-factor infertility (UFI)."
- "Uterus transplantation should be performed within an Institutional Review Board (IRB)–approved research protocol."

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Code	Description
0672T	Endovaginal cryogen-cooled, monopolar radiofrequency remodeling of the tissues surrounding the female bladder neck and proximal urethra for urinary incontinence
53860	Transurethral radiofrequency micro-remodeling of the female bladder neck and proximal urethra for stress urinary incontinence
53899	Unlisted procedure, urinary system

Radiofrequency (RF) therapy, including but not limited to cryogen-cooled monopolar radiofrequency (CMRF), monopolar RF, multipolar RF, RF-lifting, and temperature controlled RF therapies for the treatment of stress urinary incontinence (SUI) is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Cryogen-cooled monopolar radiofrequency (CMRF) combines heat and cryogen cooling to stimulate collagen production. Transurethral and transvaginal RF therapy involves the use of non- ablative thermal levels of RF energy for tissue remodeling by shrinking and stabilizing the endopelvic fascia, thus improving the support for the urethra and bladder neck. RF therapies are proposed to treat SUI, however, there is insufficient published evidence from well-conducted, randomized, controlled trials that these treatments improve outcomes compared to other available treatments for SUI.

Er-Rabiai et al. (2024) evaluated the effect of adding transvaginal monopolar non-ablative RF to pelvic floor muscle training (PFMT) on leakage severity, quality of life and urinary incontinence-related symptoms in women with SUI. A double-blind randomized controlled trial (RCT) was conducted, with a 6-week intervention and a 6-month follow-up. Participants were randomly assigned to the experimental group (PFMT plus RF; n = 18) or the control group (PFMT plus placebo; n = 20). The primary outcome was the International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF). Secondary outcomes included the Pelvic Floor Distress Inventory-20 (PFDI-20) and the Pelvic Floor Impact Questionnaire-7 (PFIQ-7), self-efficacy, female sexual function, pelvic floor muscle dynamometry, 1-h pad test and number of SUI episodes per week. Both groups achieved a statistically significant improvement in ICIQ-SF over time. However, the differences observed in the experimental group exceeded the minimal clinically important differences by 4 points (MD = -9.4, 95% CI = -12.6 to -6.3), which was not observed in the control group (MD = -3.9, 95% CI = -6.9 to -1.0). This was maintained at the 6-month follow-up with a significant time x group interaction ($p < 0.001$, $\eta p2 = 0.150$). There was no time x group interaction in the other variables ($p > 0.05$). Additionally, a significant difference in favor of the experimental group was observed in the 1-h pad test and episodes of SUI per week ($p < 0.05$). While this study highlights the effects of adding transvaginal RF to PFMT on the severity and amount of leakage, as well as on the quality of life and urinary incontinence-related symptoms in women with moderate SUI, the study is limited by small sample size, short-term follow-up, and multiple comparisons.

In a 2024 single-arm pilot study, Franić et al. evaluated RF as a new option for treating overactive bladder (OAB) with or without urge urinary incontinence (UUI). Nineteen women aged 38-71, and BMI of 21-35 were included. Outcomes were assessed subjectively using the International Consultation on Incontinence Questionnaire Overactive Bladder Module

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(ICIQ-OAB) which measures the impact of urinary frequency, urgency, urge incontinence and nocturia symptoms. RF was applied four times for 20 minutes each once per week and follow up occurred at 2 weeks post treatment. Five of the 19 patients did not return for follow up, three because they were completely satisfied, and two because they were not. The results showed statistically significant improvements in all four domains of the ICIQ-OAB at two weeks, with the best results shown regarding urgency. The authors concluded this study shows RF is a promising treatment for reducing symptoms of OAB and UUI and acknowledges higher quality research is needed. This study is limited by a small number of participants with a very short follow up time, lack of objective outcomes assessment and lack of a comparator group.

Zhang et al. (2023) conducted a systematic review and meta-analysis of RCTs to evaluate the efficacy and safety of vaginal energy-based therapies, including CO2 laser, RF and Er: YAG laser, in comparison to placebo intervention in treating SUI. The primary outcome was ICIQ-SF score, and the secondary outcomes included the 1-hour pad test and cure rate. A total of 577 patients from 6 studies (including two studies comparing RF to sham) were included in the meta-analysis. The results showed that energy-based therapies did not significantly improve the ICIQ-SF score at all visits (1,3 and 6 months). The subgroup analysis showed that there was no significant improvement in ICIQ-SF score in the CO2 laser group compared to the placebo group at all visits (1, 3 and 6 months). A meta-analysis was not performed in Er: YAG laser and RF therapy due to insufficient trials, but the report of the two RF RCTs provided mixed findings with favorable findings on the ICIQ-SF score, but unfavorable or inconclusive findings on pad weight. The authors concluded that based on limited clinical evidence, and heterogeneity among the included studies, there is no efficacy of energy-based therapy over placebo interventions. Furthermore, risks of complications of these interventions are acknowledged by the authors. Further research is needed and should address safety, clarification, and consistency in terms of intervention sessions, intervals, and parameters of device use, as well as the impact of population characteristics such as age, body mass index (BMI) and severity of SUI. (Publication by Leibaschoff 2016 et al., which was previously cited in this policy is included in this systematic review and meta-analysis).

In a 2022 prospective double blind randomized controlled trial, Seki et al. (included in the Zhang et al. systematic review above) compared the efficacy of CO2 laser and RF compared to sham control (SCT) for the treatment of SUI. One hundred and thirty-nine women were randomized to have CO2 laser (42), RF (47) or to SCT (50). A total of 114 women, 38 in each group, reached the 12-month follow-up. Treatment consisted of three consecutive monthly sessions of 15 minutes and follow up occurred at 1,6 and 12 months. The primary outcomes were the participants subjective observation of improved SUI on the Linkert Scale, and an objective cure which was evaluated by three negative tests for the following: stress test (tested with comfortably full bladder in a gynecological and standing position), pad test and an absence of any urinary leakage in the 7-day voiding diary. Secondary outcomes assessed included the impact on quality of life, sexual function, urinary loss during intercourse and associated symptoms such as urgency and nocturia. Subjective improvement and objective cure results were reported by intention-to-treat (ITT) and per protocol (PP) analysis, with significant improvements seen in QOL scores, and no significant difference in sexual function among any groups before or after treatment. The results showed at 12 month follow up, the subjective outcomes showed significant improved in the laser and RF treatment groups compared to the SCT. Objective incontinence measurements also showed better results in the groups that received energy -based therapies, and results were significantly better in mild cases of SUI in premenopausal women with pure SUI. No major complications were identified. The authors concluded that CO2 laser and RF are effective outpatient treatment options compared to sham treatment, especially in premenopausal women with pure SUI. This study is limited by a lack of comparison to established treatments for SUI; further research is needed.

In an evidence- based clinical consensus statement on vaginal energy -based devices (EBD), the American Urogynecologic Society (AUGS) was unable to reach consensus due to a lack of evidence, and it is unknown if EBD therapy offers better success rates than pelvic floor exercise or midurethral slings for treatment of SUI (Alshiek et al., 2022).

The National Institute for Health and Care Excellence (NICE) transvaginal laser therapy for stress urinary incontinence Interventional procedures guidance indicates that the evidence on long-term safety and efficacy is inadequate in quality and quantity. Therefore, this procedure should only be used in the context of research. Further research should report long-term safety and efficacy outcomes, the type of laser and energy used, treatment protocols, and patient selection including age, menopausal status and severity of stress urinary incontinence (2021).

The American College of Obstetricians and Gynecologists (ACOG) Committee Opinion (2020) states that the FDA's 2018 Safety Communication warns against the use of energy-based devices (commonly radiofrequency or laser) to perform vaginal “rejuvenation,” cosmetic vaginal procedures, or nonsurgical vaginal procedures to treat symptoms related to menopause, urinary incontinence, or sexual function and prospective studies that use validated measures of quality of life, body image, and sexual function are needed to understand the true benefits and harms of these procedures, noting that the FDA has not cleared or approved any energy-based medical device for the treatment of vaginal symptoms related to menopause, urinary incontinence or sexual function. They recommend prospective studies that use validated measures of

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quality of life, body image and sexual function to understand the true benefits and harms of these procedures be done by those without a financial interest in the outcomes.

Allan et al. (2020) conducted a twelve-month single site, randomized, unblinded feasibility study investigating the effectiveness of CMRF (Viveve) as a treatment for female SUI. The study included 35 women with 21 of them receiving one treatment and 14 receiving two treatments. Twenty-five women completed the 12-month follow-up, with nine women dropping out of the first group and three women dropping out of the second group. The authors concluded that this feasibility study indicates there is promising efficacy and safety of CMRF therapy for treating SUI although there was a decrease in efficacy noted between six months and 12 months post-procedure; however, this study did not show benefit from a second CMRF treatment at six weeks. The percentage of women showing a > 50% reduction from baseline in leakage volume at 12 months was similar between groups. Limitations that the authors noted include the age and weight disparity between the groups in that the first group had a mean age of 41.0 years and a lower BMI (24.5) while the second group was older with a mean age of 46.1 years and an average BMI of 26.0. They also noted that there were three women in group two who were post-menopausal while group one had none. The authors recommend additional studies with a larger number of women, inclusion of a sham treatment group, longer time between treatments and a longer follow-up period. The study is further limited by lack of comparison to treatments other than CMRF.

Lalji and Lozanova (2017) conducted a prospective, multi-center, single arm study evaluating the safety and efficacy of monopolar RF treatment for addressing mild to moderate SUI as well as vulvo-vaginal laxity. The study included 27 women who were treated with three once-weekly sessions that included intra-vaginal treatment then treatment of labia majora and the perineum. The authors noted that the treatments were well tolerated with no adverse events observed. Improvement in the SUI condition was evaluated weekly and at a 1-month follow-up visit. Sixteen women (59.3%) reported a decrease in the amount of leakage with 15 women (55.6%) becoming leak free at the 1-month visit. Data assessing vulvo-vaginal laxity were collected before the first treatment and at the 1-month follow-up visit with 100% of the women reporting improvement on the non- standardized subjective vulvo-vaginal laxity questionnaire (VVQL). The authors reported that one month after the last treatment, all participants (100%) evaluated their vulvo-vaginal sensation to be slightly, moderately, or very tight. They stated that future studies with longer follow-up are needed to understand how the results develop over time as the collagen remodeling process takes up to 90 days to fully complete and that further controlled study is needed to confirm the data. Limitations of the study include the small sample size, the short follow-up period and the lack of a control group.

Kang et al. (2015) conducted a systematic review of randomized and quasi-randomized trials comparing transurethral RF collagen denaturation (TRCD) versus no treatment/sham treatment, conservative physical treatment, mechanical devices, drug treatment, injectable treatment for urinary incontinence (UI) or other surgery for UI in women. The review included one small sham-controlled randomized trial of 173 women performed in the United States. Participants enrolled in this study had been diagnosed with SUI and were randomly assigned to TRCD (treatment) or a sham surgery using a non-functioning catheter (no treatment). Mean age of participants in the 12-month multi-center trial was 50 years (range 22 to 76 years). Of three patient-important primary outcomes selected for this systematic review, the number of women reporting UI symptoms after intervention was not reported. No serious adverse events were reported for the TRCD arm or the sham treatment arm during the 12-month trial. Owing to high risk of bias and imprecision, the authors downgraded the quality of evidence for this outcome to low. The effect of TRCD on the number of women with an incontinence quality of life (I-QOL) score improvement ≥ 10 points at 12 months was as follows: RR 1.11, 95% CI 0.77 to 1.62; participants = 142, but the confidence interval was wide. For this outcome, the quality of evidence was also low as the result of high risk of bias and imprecision. The authors found no evidence on the number of women undergoing repeat continence surgery. The risk of other adverse events [pain/dysuria (RR 5.73, 95% CI 0.75 to 43.70; participants = 173)]; new detrusor overactivity (RR 1.36, 95% CI 0.63 to 2.93; participants = 173); and urinary tract infection (RR 0.95, 95% CI 0.24 to 3.86; participants = 173) could not be established reliably as the trial was small. Evidence was insufficient for assessment of whether use of TRCD was associated with an increased rate of urinary retention, hematuria and hesitancy compared with sham treatment in 173 participants. The GRADE quality of evidence for all other adverse events with available evidence was low as the result of high risk of bias and imprecision. The authors found no evidence to inform comparisons of TRCD with conservative physical treatment, mechanical devices, drug treatment, injectable treatment for UI or other surgery for UI. The authors concluded it is unknown whether TRCD, as compared with sham treatment, improves patient-reported symptoms of UI. Evidence is insufficient to show whether the procedure improves disease-specific quality of life. Evidence is also insufficient to show whether the procedure causes serious adverse events or other adverse events in comparison with sham treatment, and no evidence was found for comparison with any other method of treatment for UI.

To assess treatment efficacy and quality of life in women with SUI 3 years after treatment with nonsurgical TRCD (Renessa), Elser et al. performed a prospective study including 139 women with SUI due to bladder outlet hypermobility. Radiofrequency collagen denaturation was performed using local anesthesia in an office setting. Assessments included incontinence quality of life (I-QOL) and urogenital distress inventory (UDI6) instruments. In total, 139 women were

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enrolled, and 136 women were treated (mean age, 47 years). At 12 months, significant reductions existed from baseline in the median number of daily (-0.61) and weekly (-4.0) leaks caused by activity, and 50% of the subjects experienced at least 50% fewer leaks compared with baseline (52% of evaluable participants) (Elser et al., 2009). At the 18-month follow-up, data were available on 60 women (44%). The study found incontinent episodes decreased whereas quality of life and participant satisfaction with the procedure increased (Elser 2010). At 36 months, 63 patients were lost to follow-up and 76 patients remained. With the intent-to-treat analysis (n = 139) revealed significant improvements in quality of life at 36 months. Mean I-QOL score improved 17 points from baseline (p = .0004), while mean UDI-6 score improved (decreased) 19 points (p = .0005). The authors concluded that transurethral collagen denaturation is a low-risk, office-based procedure that results in durable quality-of-life improvements in a significant proportion of women for as long as three years. The long-term durability of this minimally invasive procedure in women with SUI may be a beneficial intervention for women with this condition who wish to avoid or postpone surgery. The results also confirm that the treatment has a good safety profile, with no serious adverse events reported at any time during this or previous trials. Limitations of this study include the dropout rate with regard to patients completing all of the in-office assessments and a lack of a control group (Elser et al., 2011).

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Code	Description
0686T	Histotripsy (i.e., non-thermal ablation via acoustic energy delivery) of malignant hepatocellular tissue, including image guidance
0888T	Histotripsy (i.e., non-thermal ablation via acoustic energy delivery) of malignant renal tissue, including imaging guidance

Histotripsy is unproven and not medically necessary for treating malignant liver and renal tumors due to insufficient evidence of safety and/or efficacy.

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Clinical Evidence

Histotripsy is a novel, non-invasive therapeutic technique that uses focused ultrasound waves to mechanically disrupt targeted tissues. Initial studies have shown that histotripsy is technically feasible and can achieve precise targeting and destruction of affected liver tissue and unresectable tumors, however there is a lack of well-designed randomized controlled trials that conclusively demonstrate efficacy and safety compared to other standard treatments. Furthermore, oncologic outcomes are not reported in the published literature.

On March 13, 2024, the Edison System (HistoSonics, Inc., Plymouth, Minnesota) received FDA clearance under the 510(k) pathway. It is indicated for the non-invasive destruction of hepatocellular tumors, including unresectable tumors, using a non-thermal mechanical process of focused ultrasound. Refer to the following website for additional information: https://www.accessdata.fda.gov/cdrh_docs/pdf23/K233466.pdf. (Accessed May 22, 2025).

The Real-world Evaluation of the HistoSonics Edison System for Treatment of Liver Tumors Across Multidisciplinary Users (BOOMBOX: Master Study) is a clinical trial that is currently in the recruitment stage. This trial will aim to understand how different patient characteristics and procedural characteristics may affect histotripsy technical success at 36 hours post-histotripsy procedure. Full information can be found at: https://clinicaltrials.gov/study/NCT06486454. (Accessed May 22, 2025).

In 2024, Mendiratta-Lala et al. presented the interim results of the #HOPE4LIVER trials which were prospective, multicenter, single-arm studies conducted in Europe and the United States. Forty-four participants with 49 tumors smaller than three centimeters were enrolled. CT or MRI and clinic visits were conducted at one week or less before the procedure, at index procedure, and 36 hours or less postprocedure, and 30 days postprocedure. Primary end points were technical success and lack of major complications. Complete baseline and post-procedure imaging assessment could not be performed due to poor image quality in three tumors in three participants, and lack of contrast administration for two tumors in one participant. The results showed the technical success endpoint was reached in forty-two of the forty-four tumors treated. Technical success on the participant level was performed as a sensitivity analysis assuming total correlation, choosing the worst outcome if multiple lesions were treated and was achieved in 38 of 40 participants (95%; 95% CI: 84, 99). In the tumors without technical success, it was determined that they were not fully covered by the histotripsy treatment zone due to mistargeting, and one of the two treatment zones was also volumetrically smaller than the tumor volume. Technique efficacy at 30 days was 83% (95% CI: 68, 92) and was achieved in 30 of 36 lesions. Major complications at the index procedure was reported in three of the forty-four participants. These were classified as primary safety end-point failures and included sepsis in a participant with a pre-existing indwelling biliary stent, pleuritic pain, and hepatic failure on day twelve in a participant with innumerable breast primary metastatic lesions. Within the first 30 days, there were a total of 101 adverse events, of which 94 were considered not serious and included abdominal pain, procedural pain, fever, back pain, atelectasis and anemia. The remaining serious adverse events were splenic hematoma, melena, procedural pain, and metastatic colorectal cancer. The authors concluded that this study met the primary endpoints, and that histotripsy can treat liver tissue successfully and safely. Participants will be followed for five years, with results reported. This trial is limited by a small sample size and short term follow up. Further research comparing histotripsy to established ablative therapies, and that assess oncological outcomes is needed.

The NCCN guidelines on Hepatocellular Carcinoma do not mention histotripsy as a locoregional therapy ablation technique (NCCN, 2025).

Vidal-Jove et al. (2022) conducted a phase I feasibility trial to provide the initial safety and efficacy data on the use of histotripsy in individuals with hepatocellular carcinoma and hepatic metastasis feasibility study, the THERESA trial, as the first-in-human use of a prototype histotripsy system (HistoSonics) in eight participants with unresectable end-stage multifocal liver tumors from colorectal, breast and cholangiocarcinoma metastases and hepatocellular carcinoma. Participants were followed for eight weeks and the results showed that the procedure was technically successful in all eight participants and there were no significant procedure-related events. According to the authors, the study did not provide data on oncologic outcomes due to the short follow up time required to evaluate the technology in end stage individuals. Additional research with larger numbers of participants and a longer follow up, that includes oncologic outcomes are needed.

In a 2022 ECRI Evidence Analysis, revised in 2024, it was concluded that there are too few data to draw conclusions on the efficacy of the Edison Histotripsy System for ablating hepatic tumors. Two small case series with a high risk of bias do not report on overall survival and do not compare the system with other treatments. Further research is needed.

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Code	Description
0692T	Therapeutic ultrafiltration
90999	Unlisted dialysis procedure, inpatient or outpatient (when used to report aquapheresis (ultrafiltration))

The use of ultrafiltration (aquapheresis) is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Ultrafiltration (aquapheresis) is an alternative therapy for removing excess sodium and water for individuals with fluid overload unresponsive to medical management.

Guerrero Cervera et al. (2025) conducted a systematic review and meta-analysis to compare the safety and efficacy of ultrafiltration (UF) versus conventional diuretic treatment. The systematic review included 13 studies of 1,100 individuals with decompensated heart failure (HF) requiring hospital admission. Of these individuals, 568 received standard drug treatment and 532 received UF therapy. The study results revealed that UF showed a non-statistically significant lower creatinine at discharge [standardized measurement error (SME) = -0.68; 95% confidence interval (CI) -1.50 to 0.13; I2 = 97%] with no difference in glomerular filtration rate (SME = 0.05; 95% CI -0.17 to 0.27; I2 = 0%). There was also a non-statistically significant greater weight loss with UF (SME = 1.82; 95% CI -0.79 to 4.42; I2 = 99.7%) and greater volume removed (SME = 3.04; 95% CI -2.13 to 8.20; I2 = 99.8%). There was no difference in length of hospital stay (LogOR = -0.14; 95% CI -0.52 to 0.23; I2 = 66.9%) or mortality at 1 month (LogOR = -0.04; 95% CI -0.34 to 0.44; I2 = 0%). Though, there was a reduction in readmissions for UF (LogOR = -0.60; 95% CI -0.94 to -0.26; I2 = 40.5%). The authors concluded that UF versus diuretic intensification is a safe and effective option for individuals with decompensated HF and cardiorenal syndrome (CRS) with inadequate diuretic response. UF reduced readmissions, and the data suggests a non-statistically significant decreased weight and creatinine levels, and increased volume depletion without affecting mortality. However, prospective, randomized studies with a sufficient sample size, careful matching of diuretics, clear definition of diuretic resistance, UF strategy, endpoints, and other key clinical variables are needed to validate these findings. The results of the systematic review are limited by mostly findings that are not statistically significant, heterogeneity between studies with different designs, objectives, and follow-up. (López-Vilella et al., 2023, Costanzo et al., 2016, and Bart et al., 2012, which were previously cited in this policy, are included in this systematic review).

Terpos et al. (2024) performed a systematic review and meta-analysis to determine if there was a benefit in using UF versus diuretics to reduce mortality or hospital readmissions. The systematic review included 10 randomized controlled trials (RCTs) and 941 individuals. Of these individuals, there were 455 in the UF group and 486 in the diuretics group. The study results revealed that UF was associated with a reduction in HF hospitalizations [risk ratio (RR): 0.72; 95% CI: 0.55 to 0.96, p = 0.02]. UF was also associated with weight loss [mean difference (MD): -1.55, CI: -2.36 to -0.74, p = 0.0002] and net fluid loss (MD: -2.10, CI: -3.32 to -0.89, p = 0.0007). There were no significant differences observed between treatments for the duration of hospitalization, increase in serum creatinine levels, and mortality. The authors concluded that among individuals with decompensated HF, UF was associated with reduced rehospitalizations, increased weight loss, and increased net fluid loss, when compared to diuretics. The systematic review was limited due to the overall low quality of evidence and heterogeneity between studies. (Costanzo et al., 2016, and Bart et al., 2012, which were previously cited in this policy, are included in this systematic review).

An ECRI clinical evidence assessment compared the efficacy and safety of the Aquadex SmartFlow® System (Nuwellis, Inc.) with other hypervolemia treatments for individuals with HF. The assessment included five publications describing four RCTs and one post hoc analysis. Comparable effectiveness was reported between the Aquadex and diuretics. Mortality and decongestion rates appeared similar between the Aquadex and diuretics. The results were mixed on short-term HF-related rehospitalization rates. There were two studies that reported fewer rehospitalizations with the Aquadex. But other studies reported no statistical difference between treatments. However, the Aquadex was associated with a higher number of treatment-related and serious adverse events. The authors concluded that the Aquadex is a treatment option for individuals whose symptoms do not respond to diuretics. Individuals should be carefully selected for treatment with the

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Aquadex. ECRI noted there were some evidence limitations including one RCT at a moderate risk of bias as it was conducted at a single center. Additionally, some studies were limited by a small sample size. The evidence base overall was limited by the use of different metrics, instruments, and follow-up durations. The longest follow-up was limited to 90 days. Longer-term effectiveness and the effectiveness of repeated treatments was unclear (ECRI, 2023).

Chen et al. (2023) performed a systematic review and meta-analysis to investigate the efficacy and safety of early UF for individuals with acute decompensated HF. The systematic review included eight RCTs that compared the effectiveness of early UF and traditional diuretics. The primary outcomes of interest were changes in body weight, serum creatinine levels, 30-day hospital readmission rate, and 30-day mortality rate. The results of the meta-analysis revealed early UF was effective in reducing body weight (RR = 1.45, 95% CI: 0.54 to 2.35, p = 0.002). However, UF also increased serum creatinine (RR = 0.1, 95% CI: 0.03 to 0.17, p = 0.003). UF did not reduce the 30-day rehospitalization rate (RR = 0.84, 95% CI: 0.62 to 1.14, p = 0.28) or mortality rate (RR = 0.90, 95% CI: 0.57 to 1.44, p = 0.67). The authors concluded early UF was more effective than traditional diuretics in reducing body weight for individuals with acute decompensated HF. However, early UF was also associated with increased serum creatinine levels and did not reduce the 30-day hospital readmission and mortality rates. Additional higher-quality studies are needed to confirm these results. Limitations of the systematic review include the small sample size of eight studies and the heterogeneity of results between studies. (Costanzo et al., 2016 and Bart et al., 2012, which were previously cited in this policy, are included in this systematic review).

Tay et al. (2023) conducted a systematic review and meta-analysis to investigate the impact of UF compared to diuretics on prognostic cardiac and renal biomarkers for individuals with acute decompensated HF. The systematic review included ten RCTs and a total of 917 individuals randomized to UF (n = 443) or diuretics (n = 474). Outcome measures included cardiac and renal biomarkers. The results of an inverse-variance random effects meta-analysis of the pooled results demonstrated no significant difference between UF and diuretics for brain natriuretic peptide, N-terminal pro-brain natriuretic peptide, serum creatinine, serum sodium, and long-term (after hospital discharge) blood urea nitrogen (BUN). However, UF produced statistically greater increases in BUN in the short-term (before hospital discharge). The authors concluded that overall, for individuals with acute decompensated HF, UF produces a similar impact on prognostic cardiac and renal biomarkers when compared to diuretic therapy. Citing the significant impact of UF on short-term BUN, further research to investigate more optimal protocols of UF administration was recommended. The meta-analysis was limited due to the large variability found between studies for UF (flow rate and duration) and diuretic treatment protocols. Additionally, the incomplete reporting of study protocols and individual data was noted to have prevented sub-group analysis or analysis of covariance. (Costanzo et al., 2016 and Bart et al., 2012, which were previously cited in this policy, are included in this systematic review).

Joint HF guidelines from the American Heart Association, American College of Cardiology, and the Heart Failure Society of America do not provide specific recommendations for UF, but note “Many aspects of ultrafiltration including patient selection, fluid removal rates, venous access, prevention of therapy-related complications, and cost require further investigation.” (Heidenreich et al., 2022).

In a Cochrane systematic review, Srivastava et al. (2022) assessed the effects of UF compared to diuretic therapy on clinical outcomes such as mortality and hospital readmission rates for individuals with acute HF. The systematic review included 14 RCTs and 1,190 individuals with clinical signs of hypervolemia. The results of the systematic review revealed uncertainty about the effect of UF on all-cause mortality at 30 days or less (very low-certainty evidence) (RR = 0.61, 95% CI 0.13 to 2.85). UF may have little to no effect on all-cause mortality at the longest available follow-up (low-certainty evidence) (RR = 1.00, 95% CI 0.73 to 1.36). UF may reduce all-cause hospital readmission at 30 days or less and at the longest available follow-up (low-certainty evidence) (RR = 0.76, 95% CI 0.53 to 1.09). UF may also reduce HF-related hospital readmission at 30 days or less (low-certainty evidence) (RR = 0.62, 95% CI 0.37 to 1.04). UF probably reduces HF-related hospital readmission at longest available follow-up (moderate-certainty evidence) (RR = 0.69, 95% CI 0.53 to 0.90). UF may have little or no effect on serum creatinine change at 30 days since discharge (low-certainty evidence) (MD 14%, 95% CI −12% to 40%). UF may increase the risk of new initiation of renal replacement therapy (RRT) at longest available follow-up (low-certainty evidence) (RR = 1.42, 95% CI 0.42 to 4.75). There was an uncertain effect of UF on the risk of complications from central line insertion (very low-certainty evidence) (RR = 4.16, 95% CI 1.30 to 13.30). The authors concluded that there was insufficient evidence to determine the impact of UF on acute HF. Limitations of the systematic review included low-certainty evidence from the included studies, variability in the study settings, conflicting results between studies, limitations in how the studies were designed, deviations from the intended protocols from high cross-overs, a high risk of bias in some studies, and missing outcome data for long-term follow-up. Future research should consider evaluating UF in conjunction with current therapies and focus on outcomes such as HF-related rehospitalization, cardiac mortality, and renal outcomes at medium to long-term follow-up. (Wobbe et al., 2021, Costanzo et al., 2016, Bart et al., 2012, and Costanzo et al., 2010, which were previously cited in this policy, are included in this systematic review).

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In a systematic review and meta-analysis, Ullah et al. (2022) compared UF with diuretics in HF with reduced ejection fraction (HFrEF). The systematic review included 10 clinical trials and 838 individuals. Of these individuals, 413 were treated with UF and 425 were treated with diuretics. The primary endpoint was a composite of all-cause mortality and all-cause re-hospitalizations: major adverse cardiovascular events (MACE) The study results revealed there was no significant difference between UF and diuretics for MACE [odds ratio (OR) 0.71, 95% CI 0.47–1.07] and all-cause mortality (OR 1.08, 95% CI 0.77 to 1.52) at a median follow-up of 90 days. There was also no statistically significantly difference between the two groups for emergency department visits (OR 1.05, 95% CI 0.38 to 2.90), all-cause admissions (OR 0.97, 95% CI 0.72 to 1.30), HF-related re-hospitalization (OR 0.47, 95% CI 0.21 to 1.02), and In-hospital risk for hypotension (OR 0.49, 0.23 to 1.04) and post-therapy creatinine rise > 0.3 mg/dL (OR 1.18, 95% CI 0.74 to 1.89). Sensitivity analysis showed no influence of any individual study on the pooled estimates of MACE and all-cause mortality. The authors concluded that UF appears to be safe for individuals with HFrEF. However, UF may not provide significant benefits for reducing the risk of mortality or readmission rates compared with diuretics. Limitations of the systematic review include heterogeneity between trials and lack of some data, including dosage of diuretics, compliance, UF treatment details, and long-term follow-up. (Wobbe et al., 2021, Costanzo et al., 2016, and Bart et al. 2012, which were previously cited in this policy, are included in this systematic review).

European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of HF state "In patients who fail to respond to diuretic-based strategies, renal replacement therapies should be considered. Ultrafiltration is one of the most common approaches. It may be considered in those with diuretic resistance even if data about its effects on outcomes are unsettled." This is a Class IIb ESC recommendation, the usefulness/efficacy of UF is considered less well established by evidence/opinion and based on data derived from a single RCT or large non-randomized studies (McDonagh et al., 2022).

Wang et al. (2021) conducted a systematic review and meta-analysis to assess the safety and efficacy of UF for the treatment of acute decompensated HF. The systematic review included 12 RCTs and 1,197 individuals. Of these individuals, 584 were in the UF group and 613 were in the diuretics group. HF rehospitalization, all-cause hospitalization, adverse events, and mortality were the primary outcomes assessed. The study results revealed a reduction in HF rehospitalization (RR 0.67, 95% CI: 0.52 to 0.87, p = .003) and all-cause rehospitalization (RR 0.62, 95% CI: 0.42 to 0.92) for UF. Though, there was no difference in mortality (RR 1.09, 95% CI: 0.78 to 1.51; p = .62). There was an increase observed in fluid loss (1.47 L, 95% CI: 0.95 to 1.99 L, p < .001) and weight loss (1.65 kg, 95% CI: 0.90 to 2.41 kg; p < .001) for UF. Additionally, a subgroup analysis showed that a larger mean fluid-remove rate (≥ 200 mL/h) removed more fluid, caused more weight loss, and further decreased heart failure rehospitalization. A meta-analysis for adverse events was not performed due to heterogeneity between studies. There were inconsistent agreements about total adverse events. The authors were unable to conclude UF was superior to diuretics for the treatment of acute decompensated HF. UF was more effective at removing fluid than diuretics and decreased rehospitalizations especially with mean fluid-removal rates set to ≥ 200 mL/h. However, there was not enough evidence to show that UF was superior with regards to mortality. Agreements about total adverse events were also inconsistent. High-quality RCTs are needed to support the safety and effectiveness of UF, as well as the type of individuals most likely to benefit. Limitations of the systemic review include high heterogeneity between studies for some outcomes of interest and a lack of sufficient information to assess for bias. (Costanzo et al., 2016 and Bart et al., 2012, which were previously cited in this policy, are included in this systematic review).

An ECRI clinical evidence assessment analyzed the safety and effectiveness of the Aquadex SmartFlow System for RRT in children, including off-label use in infants and neonates < 20 kilograms. The assessment included two retrospective case series using the Aquadex FlexFlow®, a functionally equivalent, but earlier version of the Aquadex SmartFlow. The studies included children diagnosed with fluid overload, acute kidney injury, end-stage kidney disease, or congenital chronic kidney disease. ECRI concluded the study results were inconclusive and insufficient to draw conclusions. There was 97% RRT survival observed in children > 20 kg and 58% to 66% survival in low-weight (< 20 kg) critically ill neonates and small infants with renal failure treated off-label. No data was available comparing the Aquadex with other treatment options. While the Aquadex is not cleared for use in children < 20 kg, its low extracorporeal fluid volume is likely to improve safety over UF devices that require various adaptations for use with low-weight, critically ill neonates, and small infants with renal failure. ECRI noted the evidence for RRT in children was limited. One of the case series reported on a very small subject group at a single center. The larger case series included children with different weight, etiology, and RRT regimens. This prevented generalizing findings because the groups varied in prognosis, complication risks, and technical RRT complexity (ECRI, 2021).

National Institute of Health and Care Excellence (NICE) guidelines on the diagnosis and management of acute HF state that UF should not be used routinely for people with acute HF. However, UF can be considered for people with confirmed diuretic resistance. (Diuretic resistance is defined as dose escalation beyond a person's previously recognized dose ceiling or a dose approaching the maximum recommended daily dose without incremental improvement in diuresis) (NICE, 2014; updated 2021).

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UF devices with an indication for fluid overload have received U.S. Food & Drug Administration clearance through the 510(k) premarket notification process. Refer to the following website for more information (use product code KDI): https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed May 7, 2025)

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Code	Description
0694T	3-dimensional volumetric imaging and reconstruction of breast or axillary lymph node tissue, each excised specimen, 3-dimensional automatic specimen reorientation, interpretation and report, real-time intraoperative

Three-dimensional volumetric imaging and reconstruction of breast or axillary lymph node tissue is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

There are no widely accepted techniques for breast volume measurement due to a lack of information regarding the accuracy and comparability of each method. Many have not met the requirements of reproducibility, patient compliance, and cost efficiency, which has limited the use of breast volume measurement methods in routine clinical practice.

The manufacturer of the Vectra H2 3D imaging system (Canfield Scientific, 2025) states on its website in relation to breast implant surgery that this technology “generates actual 3D models of the implants you select and calculates a realistic outcome based upon gravity, the shape and placement of the selected implant.” In relation to breast revision surgery, they

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state the Vectra system “provides sliders to simulate replacement of current implants with new larger implants. Adjust volume independently for each breast, or linked for matching changes.” https://www.canfieldsci.com/imaging-systems/vectra-h2-3d-imaging-system/.

In a prospective controlled study, Wang et al (2025) aimed to evaluate breast measurement by the use of AI-based 3D scanning in women scheduled to undergo breast reconstruction. Fifty-eight participants (116 breasts) were measured with 3D scanning as well as manual measurements. “For the left breasts, AI and manual measurements showed excellent consistency [intra-class correlation coefficients (ICC) = 0.81] in width measurements, moderate consistency (ICC = 0.59) in height measurements, excellent consistency (ICC = 0.87) in convexity measurements, and good consistency (ICC = 0.74) in volume measurements. For the right breasts, the width consistency was excellent (ICC = 0.93), height consistency was good (ICC = 0.65), convexity consistency was excellent (ICC = 0.94), and volume consistency was excellent (ICC = 0.85). The Bland–Altman curves also showed that the measurement results were comparable, and few outliers were detected. AI average measurement time (compared to manual measurements) was significantly shorter (40.65 ±1.51 s vs. 610.47 ±18.74 s; $p < 0.001$).” The authors stated this study has shown the accuracy and reproducibility of this technology in measuring breast volume and parameters. Even with 3D imaging hardware and software scanning being limited by high prices and complicated operations, the authors concluded that they believe 3D scanning for breast surgery has great potential due to its high accuracy and better reproducibility and suggest that further research is needed to develop standardized procedures.

Loucas et al. (2023) conducted a retrospective review of 103 individuals who underwent breast surgery where 3D volumetric evaluation was performed three months postoperatively using the VECTRA H2 3D imaging system. These evaluations were compared to the volumetric assessments that were done on all of these individuals intraoperatively. “All of the study participants were women with a mean age of 48.3 ±14.7 years (range: 20–89). The mean time for intraoperative volumetric assessment was 8.7 ±2.6 min. The postoperative 3D volumetric assessment, with a mean volume of 507.11 ±206.29 cc, showed no significant difference from the intraoperative volumetric measurements of 504.24 ±276.61 cc ($p = 0.68$). The mean absolute volume difference between the intraoperative simulations and postoperative results was 27.1 cc. Intraoperative 3D volumetric assessment using the VECTRA H2 imaging system seems to be a feasible, reliable, and accurate method for measuring breast volume.” The authors conclude that based on these results, the VECTRA H2 3D system appears to be a feasible method for measuring breast volume, and 3D imaging systems for the intraoperative 3D volumetric assessment of breast volume will play an important role in the evaluation of breast symmetry in the future.

Killaars et al. (2020) conducted a clinical assessment comparison study. In this study the investigators evaluated whether the Vectra XT 3D imaging system is a reliable tool for determination of breast volume in clinical practice. It was compared with the current gold standard in literature, magnetic resonance imaging (MRI) and current clinical practice. Breast volumes of 29 patients (53 breasts) were evaluated. 3D images were acquired by Vectra XT 3D imaging system. Pre-existing breast MRI images were collected. Both imaging techniques were used for volume analyses, calculated by two independent investigators. Breast volume estimations were done by plastic surgeons during outpatient consultations. All volume measurements were compared using paired samples t-test, intra-class correlation coefficient, Pearson’s correlation, and Bland–Altman analysis. The authors concluded that the 3D imaging system measures lower volumes for breasts than MRI. However, 3D measurements show a linear association with MRI and had excellent reliability, making them an objective and reproducible measuring methods suitable for clinical practice. The study did not aim to investigate the reproducibility of plastic surgeon’s estimation. The answers obtained were limited to this study design. Future research should focus on reproducibility of plastic surgeon’s estimation of breast parameters to see if 3D breast volumes are superior in the clinical assessment of breasts. This could increase the clinical utility of 3D imaging for breast assessment and could represent an important step toward a more standardized approach to breast surgery.

Lee et al. (2016) conducted a retrospective review on 25 patients to determine the validity of 3D scanning technology and software for evaluating breast volume. Bilateral breast volumes were obtained preoperatively by three methods: the water-displacement technique, MRI-based volumetry, and 3D scanning using the Axis Three scanner. Due to a lack of MRI performance on some patients, 7 specimens were not recorded, leaving only 18 specimens of the removed breast tissue for comparison to the 3D scan. The authors analyzed the various methods used noting the cost effectiveness of each, the length of each procedure, the impact for the patient and sensitivity of the equipment. The authors found the 3D scan to have excellent reliability when compared to the water-displaced and MRI methods. Limitations of the study included a small number of patients, retrospective review, lack of standardization in the points for the 3D scan, and potential errors in calculation of breast weight. Future studies of the 3D scan are warranted and should include verification and validation of the use of the 3D scan, more robust RCTs and long-term outcomes.

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- https://doi.org/10.1016/j.jpra.2025.01.023
- https://www.sciencedirect.com/science/article/pii/S2352587825000221

Code	Description
0695T	Body surface-activation mapping of pacemaker or pacing cardioverter-defibrillator lead(s) to optimize electrical synchrony, cardiac resynchronization therapy device, including connection, recording, disconnection, review, and report; at time of implant or replacement
0696T	Body surface-activation mapping of pacemaker or pacing cardioverter-defibrillator lead(s) to optimize electrical synchrony, cardiac resynchronization therapy device, including connection, recording, disconnection, review, and report; at time of follow-up interrogation or programming device evaluation

Electrocardiographic body surface mapping is unproven and not medically necessary for the evaluation or treatment of cardiac disorders.

Clinical Evidence

Sedova et al. (2023) conducted a comparative study of the 12 lead EKG compared to PaceView, a 99-lead body surface potential maps (BSPM) used during cardiac resynchronization therapy (CRT). There were 19 participants with dilated cardiomyopathy and left bundle branch block (LBBB) that had prior CRT implantation. All participants underwent BSPM using the 99-lead system ProCardio-811. After the initial recording of a sinus rhythm, the device was programmed to the sequential LV pacing and sequential RV pacing (atrial pacing at 10 bpm above the sinus rate, AV-delay 120 ms). The author indicates the results are as follows: (1) the novel noninvasive inverse ECG method, PaceView, is able to estimate ventricular activation sequence from different number of ECG leads, either 99-lead BSPM or the standard 12-lead ECG, (2) the accuracy of PaceView was determined by localizing the pacing lead in patients with implanted CRT devices, either to the right ventricular cavity or the left ventricular epicardium—the typical CRT lead implant sites, (3) the PaceView algorithm showed high agreement between the results obtained from 99-lead BSPM or the 12-lead ECG, (4) for paced rhythm, the localization errors were comparable (median localization error less than 10 mm), while for the intrinsic activation, a correlation above 96% was reached for the initial estimated activation sequences. The localization error for the RV/LV lead was 9.0 [IQR 4.8–13.6] /7.7 [IQR 0.0–10.3] mm using the 12-lead ECG and 9.1 [IQR 5.4–15.7] /9.8 [IQR 8.6–13.1] mm for the BSPM. Thus, the noninvasive lead localization using the 12-lead ECG was accurate enough and comparable to 99-lead BSPM. They concluded that PaceView could be a clinically relevant tool to support the CRT patient selection process (intrinsic activation) and the implantation procedure to verify the optimal localization of the CRT pacemaker leads. This study limitations include, a small cohort, limited to participants with nonischemic cardiomyopathy and an LBBB and the location of leads V1-V6 varied. In conclusion, the authors note this novel device may be helpful in CRT implants and/or programming. Further robust studies are needed to confirm the findings of this new device.

In a multi-center, prospective, randomized trial of patients with heart failure, Rickard et al. (2023) evaluated the efficacy of the ECG Belt System (EBS) a novel surface mapping system in patients who were less likely to respond to CRT and whether EBS use in lead placement guidance and device programming was superior to standard CRT. The study included 408 participants (79.2% male and 65.9% had an American College of Cardiology/American Heart Association class II indication for CRT) from 43 centers in Europe and North America who were implanted with a CRT device and LV lead. Participants were randomized into either the ECG Belt arm (n = 200) or a control arm (n = 208). For patients in the ECG Belt arm, the EBS was applied to the patient's chest and back to be worn during the CRT implant procedure to guide left ventricular (LV) lead placement while patients in the control arm had their leads implanted per standard of care. The authors reported that both groups had an improvement in left ventricular end-systolic volume and that there was no significant statistical difference in relative change from baseline. The authors noted that patients with a higher baseline standard deviation of the activation times derived greater left ventricular reverse modeling but that improvement in

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electrical dyssynchrony did not correlate with the extent of reverse modeling. The authors concluded that their study did not support the use of EBS-guided therapy for CRT management of heart failure with reduced ejection fraction. Study limitations include some patient dropout, and the use of AdaptivCRT in 22% of the EBS arm but not in any of the control arm (as per protocol) and the open-label design, which could have introduced biases.

Bank et al (2018) used a body-surface activation mapping (BSAM) system in a study to quantify changes in electrical synchrony and the potential for optimization with CRT. The study included 94 patients with a history of heart failure with ejection fraction ≤ 40% (mean 25.7 ±7%) who were at least four months post-CRT and were clinically stable. The authors reported that CRT programmed clinically at baseline settings reduced electrical dyssynchrony by 20% and that this improvement was greater in left patients with LBBB but similar in patients with and without QRS ≥ 150 milliseconds (ms). The authors also reported that, at individualized optimal device settings based on BSAM, there was a further 26% improvement in standard deviation of activation times (SDAT) as compared to current programming. Limitations of the study include the study design (single-center, retrospective, observational), and the lack of evaluating other atrio-ventricular, ventricular-ventricular delays, and/or pacing vectors or patient-centered outcomes. The authors concluded that BSAM can noninvasively quantify electrical dyssynchrony at multiple device settings and identify the setting in an individual patient that provides the lowest electrical dyssynchrony.

In a single-arm, single-center feasibility study to characterize changes in electrical heterogeneity during biventricular (BiV) pacing from different LV pacing sites during device implantation, Johnson et al (2017) computed two EH metrics-standard deviation of activation times and mean left thorax activation times from isochronal maps that were based on 53-electrode body surface mapping. The body surface mapping was done during baseline AAI pacing and biventricular (BiV) pacing from different pacing sites in coronary veins in 40 patients that cardiac resynchronization was indicated. The authors reported that the greatest combined reduction in standard deviation of activation times and left thorax activation times from baseline to BiV pacing was hemodynamically optimal in 35 of the 40 patients (88%) and that sites with the longest right ventricle-left ventricle (RV-LV) and narrowest paced QRS were hemodynamically optimal in 26 of the 40 patients (65%) and 28 of the 40 patients (70%) respectively. Limitations of the study include the study design (single center, single arm), lack of long-term follow-up, and the lack of clarity regarding the degree of acute hemodynamic improvements that correlates with the degree of chronic improvement in symptoms in patients using CRT. The authors concluded that changes in EH from baseline to BiV pacing more accurately identified hemodynamically optimal sites than RV-LV delays or paced QRS shortening and that optimization of LV lead location by minimizing EH during BiV pacing with the use of body surface mapping may improve cardiac resynchronization therapy response.

Revishvili et al. (2015) performed a single-arm, single-center study to validate the mapping accuracy of an epi- and endocardial electrophysiology system (NEEES). Their study included 29 patients (79% male, mean age 62 ±11 years) with previously implanted devices who were being seen for regular check-up at a pacemaker clinic. Study participants included 21 (72%) with a history of ischemic cardiomyopathy, 7 (24%) with a history of dilated cardiomyopathy and one (4%) with a history of restrictive cardiomyopathy. Each patient received pacing from a total of 76 pacing sites (21 in the right atrium, 29 in the right ventricle and 26 in the left ventricle). The authors reported that the mean distance from the non-invasively predicted pacing site to the anatomic reference site was 10.8 ±5.4 mm for the right atrium, 7.7 ±5.8 mm for the right ventricle, and 7.9 ±5.7 mm for the left ventricle activated via the coronary sinus lead and that there was no significant difference in accuracy for the left vs. right ventricular sites, while the difference in accuracy was significant when they compared the ventricular and atrial sites. The authors stated that the NEEES is capable of mapping both the endo- and epicardial surface when compared with other non-invasive mapping systems that rely on epicardial surface information. Limitations included the use of different systems with inherent differences in the geometries created, the small study size and the single-center study design. The authors concluded that the NEEES was able to correctly identify the site of pacing from various endo- and epicardial sites with high accuracy and they recommended future studies to assess the feasibility of the NEEES to correctly diagnose the origin of focal or re-entry arrhythmia within the human heart.

The U.S. Food and Drug Administration (FDA) has cleared several body surface mapping systems under its 510(k) premarket notification process as substantially equivalent to predicate devices. Refer to the following website for more information (use product code DQK): https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed April 14, 2025)

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Code	Description
0735T	Preparation of tumor cavity, with placement of a radiation therapy applicator for intraoperative radiation therapy (IORT) concurrent with primary craniotomy (List separately in addition to code for primary procedure)
19294	Preparation of tumor cavity, with placement of a radiation therapy applicator for intraoperative radiation therapy (IORT) concurrent with partial mastectomy (List separately in addition to code for primary procedure)
77424	Intraoperative radiation treatment delivery, x-ray, single treatment session
77425	Intraoperative radiation treatment delivery, electrons, single treatment session
77469	Intraoperative radiation treatment management

Intraoperative radiation therapy, using low-energy x-rays or electrons, is unproven and not medically necessary for treating all indications due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Intraoperative radiotherapy (IORT) is a technique that involves the delivery of a large dose of ionizing radiation to the tumor or tumor bed during surgery. This allows maximization of the dose to surgical site and minimizes the dose to normal surrounding tissues. Different methods of IORT include electrons, low-kV X-rays and HDR brachytherapy (Pilar et al., 2017). Currently there is a paucity of high-quality evidence that demonstrates improved outcomes over standard radiotherapy treatment modalities. The National Cancer Care Network (NCCN) recommendations for colon cancer, rectal cancer and retroperitoneal and intra-abdominal site soft tissue sarcomas state that based on lower level evidence, there is uniform consensus that IORT may be appropriate. However, other conformal radiation techniques are likely to be more suitable for these indications.

Breast Cancer

In a 2024 practice guideline entitled Partial Breast Irradiation for Patients with Early-Stage Invasive Breast Cancer or Ductal Carcinoma In Situ, the American Society for Radiation Oncology (ASTRO) states the following regarding IORT:

- For patients with early-stage invasive breast cancer receiving PBI, electron IORT is not recommended, unless part of a clinical trial or multi-institutional registry (strong recommendation, moderate level of evidence).
- For patients with early-stage invasive breast cancer receiving PBI, kV IORT alone (without WBI) is not recommended, unless part of a clinical trial or multi-institutional registry (Strong recommendation, low level of evidence).
- IORT alone is not recommended as treatment for early-stage invasive breast cancer or DCIS.

ASTRO states further, that it remains to be defined if more optimized patient selection criteria and treatment techniques will make IORT a recommended option. Given the increased patient convenience of completing RT at the time of surgery, investigation into a preferable IORT approach warrants further study. How best to weigh the potential higher local recurrence risk of IOERT and kV IORT with its increased efficiency and low toxicity when delivered without the addition of WBI remains to be defined.

In a 2023 systematic review and meta-analysis, Fan et al. (2023) assessed the efficacy of low-kV IORT as a boost in individuals receiving breast conserving surgery. Twelve studies comprised of 3006 patients were included in the final analysis, with a median follow-up of 55 months. Tumor size stages were T1-T2 in six studies, four studies included T2+ tumors and one included pathologic complete response (pCR) and carcinoma in situ (Tis) tumor. Lymph node statuses ranged from N0 to N3 in eight studies, N0-1 in two studies, and only N0 patients in one study. Tumor grades were available in eight studies and ranged from grade 1 to grade 3. Most individuals had undergone breast-conserving surgery and received similar systemic treatments, including endocrine therapy (if HR-positive), and chemotherapy Seven studies excluded neoadjuvant treatment (NAT), one included only patients receiving NAT, with one study including a very small number of individuals that received NAT. Due to these variations, the local recurrence rate (LRR) of IORT as boost in non-NAT patients and NAT patients in this study is pooled into different subgroups for analysis. The results showed for patients that received NAT, two studies reported a pooled LRR of 0.39%, with the predicted 5-year LRR of low-kV IORT boost estimated by the Poisson regression model is 3.45%. In individuals that did not receive NAT, the pooled LRR of

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low-kV IORT boost is 0.41%, and the predicted 5-year LRR of low-kV IORT boost in non-NAT patients is 2.66%. These differences were not clinically significant. The authors concluded that low-kV is an effective boost in breast cancer patients and may be a promising alternative to EBRT. Limitations of this systematic review include a lack of availability of randomized controlled trials, single arm design and heterogeneity among clinical protocols. Additional high quality research is needed to validate these findings.

He et al. (2023) conducted a systematic review and meta-analysis of 1 RCT and 8 comparative studies with control groups to assess the efficacy and safety of IORT combined with whole breast irradiation (WBI) compared to conventional radiotherapy in women with early stage breast cancer undergoing breast conserving surgery. There was a total of 3219 patients, 1832 in the IORT group and 1387 in the EBRT group, and outcomes assessed included local recurrence rates [LRRs] (including ipsilateral intramammary, Cutaneous, and chest wall recurrences), distant metastases rate (DMR), disease free survival (DFS) outcomes, cosmetic outcomes and toxicity. The results showed that for LRRs, cosmetic outcomes, fibrosis and hyperpigmentation, there was no statistically significant differences between patients treated with IORT and those receiving conventional radiotherapy. The DMR was significantly lower in the IORT boost + WBI group, and DFS was significantly better in the IORT boost + WBI group than in the conventional radiotherapy group. Four of the five studies that provided overall survival (OS) data showed no benefit in OS or breast cancer-specific OS in the IORT boost + WBI group. The authors concluded that patients with early stage breast cancer who receive IORT boost + WBI show significantly better outcomes in DMR and DFS than those who receive conventional radiotherapy, and this meta-analysis provides important evidence for the use of IORT as a tumor bed boost. These results are limited by heterogeneity among quality scores, patient population, treatment protocols and follow up periods. No studies were blinded and only one was an RCT. Further high quality research is needed to validate these findings.

In a 2023 AHRQ comparative effectiveness review on partial breast irradiation (PBI) for breast cancer, Shumway et al., evaluated the effectiveness and harms of PBI compared to whole breast irradiation (WBI) for early-stage breast cancer, and how differences in effectiveness and harms may be influenced by the patient, the tumor, and treatment factors, including treatment modality, target volume, dose, and fractionation. Six modalities were evaluated. For IORT it was concluded that compared to WBI, IORT is associated with a significantly higher ipsilateral breast recurrence (IBR) rate at 5,10 and over 10 years (high strength of evidence) with no difference in overall survival, cancer-free survival, or mastectomy-free survival (low to high strength of evidence). There were significantly fewer acute AEs and late AEs grade ≥ 2 with IORT.

A 2023 ECRI clinical evidence assessment regarding intraoperative radiotherapy for breast cancer concluded that based on a large body of evidence that included six systematic reviews and meta-analyses, IORT is equally effective as whole breast irradiation (WBI) and achieves a long term survival rate of 95%. Local recurrence can occur after either intervention but is more likely with IORT, therefore it may be best for select low-risk patients. Additional high-quality studies focusing on specific patient groups (e.g., patients with specific cancer etiology and grade), comparing electron and photon IORT, and further assessing IORT in locally advanced cancer would be useful.

The National Comprehensive Cancer Network (NCCN) guidelines on breast cancer do not specifically address IORT using low-energy x-rays or electrons. The guidelines state that boost treatment in the setting of breast conservation in patients with higher risk for recurrence, and can be given sequentially after whole breast RT, or as a simultaneous integrated boost. When addressing accelerated partial breast irradiation (APBI) and Partial Breast Irradiation (PBI), the guidelines state that APBI offers comparable local control and comparable or improved cosmesis to whole dose regimes when delivered with specified doses. (NCCN, Breast Cancer v3, 2025).

A meta-analysis by Wang et al. (2021, included in ECRI clinical evidence assessment) was conducted to compare the efficacy and safety of IORT to whole breast radiotherapy (WBRT) for early-stage breast cancer patients. Ten randomized control trials (RCT) involving 5,698 patients were included in this meta-analysis. “This meta-analysis showed that the IORT group was associated with a higher local recurrence risk (RR = 2.111, 95% CI, 1.130–3.943, p = 0.0191), especially in the long-term follow-up subgroup or published after 2020 subgroup or Caucasian subgroup (RR = 2.404, 95% CI, 1.183–4.885, p = 0.0154). Subgroup analysis showed that the IORT group had a higher recurrence risk than the WBRT group in the polycentric randomized controlled trial subgroup (RR = 1.213, 95% CI, 1.030–1.428, p = 0.0204). Pooled analysis showed that there was no statistically significant difference in overall survival, recurrence-free survival, distant metastasis-free survival, and cancer-specific survival between IORT and WBRT groups. Additionally, the risk of skin toxicity was reduced, but the incidences of fat toxicity, edema, and scar calcification were significantly increased in the patients who underwent IORT in comparison to those who underwent WBRT.” The authors concluded that IORT was not a better alternative to WBRT, and that large-scale, well-designed clinical trials with longer follow-up are needed.

Valente and Shah (2021) reviewed the results of the TARGIT-A and ELIOIT randomized trials mentioned below. Their review found that breast cancer patients treated with IORT had a higher risk of local recurrence (LR). However, patients

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with low-risk features and IORT performed at the time of surgery had similar rates of LR at 5 years. The authors concluded that further studies, with longer follow-up are needed to validate the role of IORT, including assessing which patients are appropriate for this therapy.

He et al. (2021, included in ECRI clinical evidence assessment) conducted a meta-analysis of 38 studies (30,225 participants), to investigate the 5-year oncological efficacy of IORT compared to whole-breast irradiation (WBI). "A non-comparative binary meta-analysis was performed to calculate the weighted average 5-year local recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), and overall survival (OS) in the two cohorts, respectively. The LRFS, DMFS, and OS (without restriction on the 5-year outcomes) between the two cohorts were further investigated by a comparative binary meta-analysis. The weighted average 5-year LRFS, DMFS, and OS in the IORT cohort were 96.3, 96.6, and 94.1%, respectively, and in the WBI cohort were 98.0, 94.9, and 94.9%, respectively. Our pooled results indicated that the LRFS in the IORT cohort was significantly lower than that in the WBI cohort [pooled odds ratio (OR) = 2.36; 95% confidential interval (CI), 1.66–3.36]. Nevertheless, the comparisons of DMFS (pooled OR = 1.00; 95% CI, 0.76–1.31), and OS (pooled OR = 0.95; 95% CI, 0.79–1.14) between the IORT cohort with the WBI cohort were both not statistically significant." The authors concluded that although both cohorts had a very high 5-year oncological efficacy, and the DMFS and OS did not differ between groups, the LRFS was significantly poorer in the IORT cohort than in the WBI cohort.

In 2019, the American Brachytherapy Society (ABS) published an evidence based consensus statement on IORT. It states that as monotherapy, after breast-conserving surgery, it should not be offered to patients outside of prospective clinical trials, regardless of IORT technique. Patients who are interested in IORT should have an informed discussion with their treatment team regarding the differences in local recurrence between techniques (Tom et al.). In a 2022 consensus statement on partial breast irradiation, the ABS refers to this consensus statement and concluded that there has not been enough additional data published since that time to justify changing this recommendation (Anderson et al.).

TARGIT-A

In 2023, Vaidya et al. reported the long term local control and survival rates in participants of the TARGIT-A RCT. The results showed that participants free of local recurrence at 10 years, were as follows: TARGIT arm (those who received supplemental EBRT), 82.6%, those who did not receive supplemental EBRT 84.5%, and EBRT arm 85.5%. Overall survival was higher in the TARGIT-IORT arm by 4.4% at 12 years in patients with grade 1 and grade 2 cancers which make up the majority of cases. Deaths from other causes were fewer in the TARGITIORT arm by 41%, which is statistically and clinically significant. The prognosis after rare local recurrence after TARGIT-IORT was much better than after EBRT. The authors concluded that long-term follow-up (maximum 19 years, median 8.6 years) shows that there was no statistically significant difference between TARGIT-IORT and EBRT in terms of being free of local recurrence, remaining mastectomy free, remaining distant disease free, or of breast cancer related mortality.

TARGIT-R

TARGIT-R is a multi-institutional retrospective registry of patients who underwent lumpectomy with IORT between 2007 and 2013. Valente et al.(2021) retrospectively evaluated 667 individuals who underwent lumpectomy with IORT, primarily looking for ipsilateral breast tumor recurrence (IBTR) at 5-year follow-up. "Primary IORT (IORT at the time of lumpectomy) was performed for 72%, delayed IORT (after lumpectomy) for 3%, intended boost for 8%, and unintended boost (primary IORT followed by whole-breast radiation) for 17% of the patients. At 5 years, IBTR was 6.6% for all the patients, with 8% for the primary IORT cohort and 1.7% for the unintended-boost cohort. No recurrences were identified in the delayed IORT or intended-boost cohorts. Noncompliance with endocrine therapy (ET) was associated with higher IBTR risk [hazard ratio (HR), 3.67]. Patients treated with primary IORT who were compliant with ET had a 5-year IBTR rate of 3.9%." Because the local recurrence rates in this review are notably higher than in previous studies in similar patients, the authors concluded that "understanding differences in this retrospective series and the prospective trials will be critical to optimizing patient selection and outcomes going forward."

TARGIT-US

An interventional, open label, phase IV trial: Targeted Intraoperative Radiotherapy United States (TARGIT-US) Phase IV Registry Trial: A Registry Trial of Targeted Intraoperative Radiation Therapy Following Breast-conserving Surgery (NCT01570998) is currently active and no longer recruiting. The authors hypothesize that delivering radiation one time to the area where the tumor was removed while the patient is still in the operating room may kill any residual tumor cells and may be as effective as standard radiation therapy in patients with early-stage breast cancer. The study will investigate how well IORT works, and any associated side effects in this patient population. For more information, refer to the following website: https://www.clinicaltrials.gov/study/NCT01570998?term=TARGIT-US&rank=2 With Breast Cancer Undergoing Breast-Conserving Surgery | ClinicalTrials.gov. (Accessed April 14, 2025).

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ELIOT

Orecchia et al. (2021) examined the planned long-term recurrence and survival outcomes from the ELIOT trial. In the ELIOT group, the 10-year rate was 8.1% (6.1–10.3), and the 15-year rate was 12.6% (9.8–15.9). In the WBI group, the 10-year rate was 1.1% (0.5–2.2), and the 15-year rate was 2.4% (1.4–4.0). At final follow-up on March 11, 2019, 193 (15%) women had died from any cause, with no difference between the two groups (98 deaths in the ELIOT group versus 95 in the WBI group; HR 1.03, 95% CI 0.77–1.36, p = 0.85). In the ELIOT group, the overall survival rate was 96.8% (95% CI 95.1–97.9) at 5 years, 90.7% (88.2–92.7) at 10 years, and 83.4% (79.7–86.4) at 15 years; and in the WBI group, the overall survival rate was 96.8% (95.1–97.9) at 5 years, 92.7% (90.4–94.4) at 10 years, and 82.4% (78.5–85.6) at 15 years. The authors confirmed there was a higher rate of IBTR in the ELIOT group compared to the WBI group, without any differences in overall survival. Limitations include absence of long-term toxicity data, especially cardiac toxicity and difficultly gathering long-term outcome data.

Veronesi et al. (2013) conducted ELIOT, a single-institution randomized trial among women with early breast cancer to determine whether intraoperative radiotherapy (IORT) was non-interior to postoperative external radiotherapy (EBRT) in local recurrence and overall survival (OS). Eligible patients were women aged 48–75 years with early breast cancer with a maximum tumor diameter up to 2.5 cm and suitable for breast-conserving therapy. After undergoing standard breast-conserving surgery, patients were randomly assigned to receive a single dose of intraoperative radiotherapy of 21 Gy to the tumor bed during surgery or conventional radiation therapy consisting of a 50-Gy postoperative external-beam dose to the whole breast with conventional fractionation plus a 10-Gy boost. Equivalence was prespecified and defined as a 5-year local recurrence rate that did not exceed 7.5% in the IORT group. The primary endpoint was occurrence of ipsilateral breast tumor recurrence (IBTR); overall survival was a secondary outcome. A total of 1,305 patients were randomized, with 654 patients in the EBRT group and 651 in IORT group and a median follow-up of 5.8 years. The 5-year IBTR rate was higher in the IORT group compared with the EBRT group (4.4% versus. 0.4%; p < 0.0001). OS did not differ between the groups. Based on the increased harm with IORT, the authors concluded that improved selection of patients may reduce the rate of recurrence with IORT with electrons and that the advantage of not having to undergo radiation therapy over many weeks must be weighed against the possibility of an increased risk of local recurrence. Additional randomized trials are still needed to further clarify the subgroup of breast cancer patients who may benefit from IORT.

Gynecological Cancers

The NCCN guidelines for uterine neoplasms makes the following recommendations:
For the treatment of recurrent or metastatic disease:

- Patients with no previous RT exposure at the recurrence site or previous vaginal brachytherapy, the panel recommends surgery with or without IORT and systemic therapy (category 3 recommendation for IORT*).
- For patients previously treated with brachytherapy only at the recurrence site, surgery with or without IORT is recommended. (category 3 recommendation for IORT*).
- For patients previously treated with EBRT at the recurrence site, surgery with or without IORT (category 3 recommendation for IORT*) plus or minus systemic therapy for isolated relapse is recommended.

*A Category 3 recommendation from NCCN indicates this recommendation is based on any level of evidence and that there is major NCCN disagreement that the intervention is appropriate.

Sprave et al. (2024) conducted a retrospective cohort study on forty patients to analyze outcomes and determine prognostic factors in forty patients who were diagnosed with recurrent gynecologic cancer (RGC) and underwent surgical treatment combined with high dose radiotherapy (HDR)-IORT or IORT using electrons (IOERT) alone. The criteria included patients with potentially resectable locally recurrent gynecological cancer (RGC), radical surgery, and negative or microscopic residual tumour on frozen section specimen. Outcomes measured were locoregional control (LRC), overall survival (OS), and survival without distant metastases (DMFS) Cervical carcinoma was the most common diagnosis in eleven patients, endometrial carcinoma in ten patients, and vulvar carcinoma in ten patients. Twenty-one individuals received HDR-IORT and nineteen received IOERT and the median follow up time was 22 months. Following surgery with IORT, histopathologic results showed no residual tumor in twenty-four patients, microscopic residual disease in five patients, could not be determined in three patients, and was unknown in eight patients. Following IORT, 65% of patients experienced recurrence and these were localized: in-field 32.5%, out-of-field 22.5% and margin-of-field 12.5%. At the median follow-up, the 5-year OS was 55%, the LRC was 56% and the DMFS was 49%. Acute radiotherapy toxicity were Grades 1-3 with no Grade 4 reported and included lymphedema, bleeding, wound infection, and enterocutaneous and vesicovaginal fistula. No Grade 4 events were associated with late toxicity and these included lymphedema, cystitis, would healing disorder, infected urinoma and vesicovaginal fistula. The authors concluded that IORT combined with radical surgery is well tolerated, but not associated with improved survival rates. Limitations of this study include a heterogeneous cohort from one institution which limits transferability to other patient groups.

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Chen et al. (2022) conducted a case series to evaluate the safety and feasibility of low energy photon IORT as adjuvant therapy for recurrent gynecological cancer. Five women who underwent surgical resection plus IORT for cervical cancer (2) endometrial cancer (2) and uterine leiomyosarcoma (1) were included. The overall local control rate and OS was 40%. The median recurrence-free survival was 13.8 months. For endometrial cancer, the results showed no evidence of recurrence after treatment, however one patient died due to lung and liver metastases. Repeat IORT was performed on one patient with cervical cancer and the single patient with uterine leiomyosarcoma. The cervical cancer patient experienced vaginal stump recurrence 17 months after exenteration and the patient with leiomyosarcoma experienced repeat recurrence and passed away. No Clavien -Dindo grade III-IV were seen. This study is limited due to its retrospective nature, small sample size, and heterogeneous cancer type. Future large-scale studies are needed to validate these findings.

In a 2021 institutional review, Delara et al. reported survival outcomes in patients with locally recurrent gynecological malignancies who received extirpative surgical treatment with or without IORT. 44 patients were treated at a single tertiary-care center over a 15-year period. The results showed for all cancer types, complete tumor resection had improved 3 year PFS and OS rates compared with patients who had suboptimal resection regardless of IORT administration. The authors concluded that complete tumor resection is imperative for central control, PFS and OS, and that IORT may improve these if optimal surgical resection is achieved.

Arians et al. (2016) conducted a study of patients with recurrent gynecologic malignancies who underwent resection including IOERT (intraoperative electron radiation therapy) to assess the clinical outcomes and potential predictive factors or subgroups and which benefit the most from this treatment regimen. A total of 36 patients with recurrent gynecologic malignancies (cervical-18, endometrial -12 or vulvar cancer - 6) with no other curative options left and were eligible for resection and IOERT with expected reasonable morbidity and toxicity were retrospectively identified through hospital databases. There were no restrictions to prior treatment. Follow up time ranged from 0.1–154 months with a median of 14 months. The results showed during follow up, 20 of the 36 patients had an extensive tumor recurrence with infiltration of either the bladder and/or rectum. Thirteen patients showed positive lymph nodes and 7 patients a lymphangiosis carcinomatosa. In 15 cases R0 resection was achieved, R1 resection in 14 patients and 1 R2 resection. 6 patients had complete gross but microscopically unclear margins. Death was documented in 25 patients - 15 with cervical, 5 with endometrial, and 5 with vulvar cancer. Median OS was 0.1–153.5 months with a median of 14 months (24.5 months for endometrial, 10.3 months for cervical, 16 months for vulvar cancer). For the entire cohort 1, 2 and 5-year OS was 65.3%, 36.2% and 21.7%, respectively. The authors concluded that resection with IORT is a curative option in patients with recurrent endometrial cancer. For patients with recurrent cervical and vulvular cancer, this is a palliative option as survival rates are much lower.

Colorectal Cancer

Tiwari et al. (2025) conducted a systematic review of the techniques, outcomes and complications of intraoperative electron radiotherapy (IOERT) as part of multimodal treatment for locally advanced and locally recurrent colorectal cancer (LACC/LRCC). The primary outcomes were overall survival (OS), disease free survival (DFS) and local control (LC) at 5 years. Secondary outcomes included post-operative complications. (This is an update the systematic review and meta-analysis by Mirnezami, 2013 which was previously included in this policy). Sixteen new studies were included in this update; two were prospective, including one randomised controlled trial, with the remainder retrospective. Eight studies reported the oncological outcomes for patients with LACC. There was a wide variety of T stages in these articles and included T4, T3/T4, T1-2, T2/T3 which negates the potential utility of IOERT, as many of these participants would be expected to have clear resection margins. Comparative studies showed one RCT from Japan that showed T1-T4 rectal cancer patients randomized to receive IOERT and nerve sparing total mesorectal excision (TME), or TME with lateral lymph node dissection with limited pelvic autonomic nerve preservation. This trial was stopped early due to the IOERT group showing significantly worse distant metastasis free survival. One nonrandomized study compared HDR-IORT with IOERT in patients with LACC and LRCC R1 resection. These results showed no statistically significant differences in 5 year OS between the groups, but HDR-IORT was associated with significantly improved local recurrence-free survival. Another study compared outcomes of patients with pT4N0/T1-4N LARCC treated with IOERT and adjuvant chemoradiotherapy compared with adjuvant chemoradiotherapy alone. These results showed that the 5-year OS, DFS and LC were better in the IOERT group, however the difference was not statistically significant. Over 93% of patients in both groups had an R0 resection. Another study by the same authors only included patients with T3N0M0 rectal cancer. This also showed no statistically significant differences in 5-year OS, DFS and LC. Four non-comparative studies consisted mainly of patients with predominantly R0 resections, though no study reported oncological outcomes separately by resection margin. The largest was a multi-center study comprised of 417 patients with T4b rectal cancer that underwent multi-modality treatment, including IOERT. 78% had chemoradiotherapy, 19% had radiotherapy and 73% had an R0 resection and 27% had an R1/R2 resection. The 5-year OS and 5-year DFS was 56% and 55% respectively. Another large single-center study included 335 patients with T2-4 rectal cancer who underwent multi-modality treatment including IOERT and neoadjuvant chemoradiotherapy. These results showed 5-year OS, DFS and LRC of 75%, 72% and

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92% respectively. The 10-year IOERT in-field and out-of-field control were both 96%. With regard to LRCC, a multi-centre non-randomised study compared patients who received carbon-ion radiotherapy (CIRT) with or without surgery to IOERT and multi-modality treatment with neoadjuvant therapy. There were 85 and 86 patients in the CIRT and IOERT group, respectively. The 5-year OS was 47% in the CIRT group compared to 26% in IOERT group. In the large multicenter study above for LACC, the oncological outcomes were also measured for LRCC. These results showed 5-year local recurrence-free survival (LRFS) was significantly higher in the HDR-IORT group, but the 5-year OS which was low in both cohorts. Commonly reported complications were related to the wound and included infection, dehiscence, and healing problems. Other complications included GI such as abscess, and anastomotic leak, fistula, and urological complications. The authors concluded that despite a lack of randomized studies, the addition of IOERT to multi-modality treatment may improve oncological outcomes in patients with LACC and LRCC, with R1 resection margins. Further research in the form of randomized controlled trials are needed to validate these findings.

The NCCN guidelines for colon cancer states that if IORT is available, it may be considered for patients with T4 or recurrent cancers as an additional boost (Category 2A recommendation*).

The NCCN guidelines for rectal cancer states that IORT, if available and can be delivered safely may be considered for very close or positive margins after resection as an additional boost, especially for patients with T4 or recurrent cancers (Category 2A recommendation*).

*A Category 2A recommendation from NCCN indicates this recommendation is based upon lower- level of evidence, and there is uniform consensus that the intervention is appropriate.

Fadel et al. (2022) conducted a systematic review of neoadjuvant treatment modalities in patients undergoing surgery for locally recurrent rectal cancer. Modalities included radiotherapy or chemoradiotherapy (CRT), adjuvant CRT, surgery only, or surgery and intraoperative radiotherapy (IORT). Fifteen studies comprised of 974 patients were included and of these, one included surgery and IORT. For surgery and IORT, the results showed limited data on outcomes and the use of IORT for LRRC remains controversial. CRT followed by surgery, in cases where the intention is curative, provides the best oncological outcomes.

In a single-institution, prospective, single arm, phase II trial, Cho et al. (2022) evaluated the safety, feasibility, and early outcomes of IORT using a low energy source in patients with resectable pancreatic cancer. The primary outcome was acute postoperative complications (within 3 months), and oncologic outcomes. Forty-one patients were treated by curative resection, and IORT. The target volume (including the tumor bed, the celiac and superior mesenteric arteries, the mesenteric root, and the portal vein as well as other areas determined to be high risk) was irradiated with a single dose of 10Gy at 5mm depth into the tumor bed. Eight to 12 weeks following surgery and IORT, patients received 6 cycles of adjuvant gemcitabine- based chemotherapy 3 times a week, every 4 weeks. The results showed that 10 patients experienced post operative complications, the most common being delayed gastric emptying. Other postoperative complications included pancreatic fistula, chyle leakage, and duodenal ulcer perforation which were tolerable with conservative management, however, one patient required drainage for pancreatic fistula and one patient experienced duodenal ulcer perforation (G3b). Oncologic outcomes showed the first recurrence local only failure in 4 patients, distant only failure in 9, and 2 experienced both local and distant failure. The 1-year local control and distant control rates were 76.4% and 55.7%, respectively. The authors concluded that IORT was well tolerated for this cohort and found that high CA19-9 levels, lymph node metastasis, and narrow R0/R1 resection were significantly associated with local recurrence even after IORT. This study is limited by short term follow up which impacts assessment of toxicity and treatment outcomes. Furthermore, since there was not a control comparing IORT with surgery alone, and patients received adjuvant chemotherapy, superiority cannot be determined. More randomized trials comparing IORT to the current standard of care are required.

Liu et al. (2021) conducted a systematic review and meta-analysis on the clinical outcomes and safety of IORT for the treatment of rectal cancer. Three randomized controlled studies and 12 observational studies comparing IORT and non-IORT treatment comprising 1460 patients (687 in the IORT group, 773 in the non-IORT) were included. The results showed that 9 studies included 5 year overall survival, and the meta-analysis showed no statistical differences in those receiving IORT and those who did not. In 6 studies, the 5-year disease free survival was reported and there were also no statistically significant differences. No statistical differences were found with regard to abscess, fistula, wound complications, anastomotic leak or neurogenic bladder dysfunction. Five year local control showed statistically significant differences favoring the patients that received IORT. When compared with patients who did not receive adjuvant therapy (preoperative radiotherapy, postoperative radiotherapy, chemotherapy), patients who received adjuvant therapy clearly showed beneficial effects of IORT, indicating the importance of adjuvant therapy with IORT. The authors concluded that the use of IORT during rectal cancer surgery may improve LC with a moderate impact on disease prognosis and survival. This study is limited by a lack of available randomized studies, with irregular sample sizes, mixed inclusion criteria and

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different comparator procedures. Well-designed RCTs are needed to better define the treatment effects of IORT for the treatment of rectal cancer.

In the 2012 American College of Radiology Appropriateness Criteria on recurrent rectal cancer, it was concluded that the treatment of patients with recurrent rectal cancer is complex and dependent upon many factors including, but not limited to, a history of previous radiotherapy to the pelvis. Newer systemic treatments have improved response rates and given physicians more options in the treatment of patients in this clinically challenging population. Specialized treatment modalities such as IORT should be used at institutions with experience in these techniques and preferably in patients enrolled in clinical trials.

Sarcoma

The NCCN guidelines for Soft Tissue Sarcoma state that for the retroperitoneal/intra-abdominal sites, IORT can be considered a boost for known or suspected positive margins at the time of surgery. For soft tissue sarcomas of the extremities, superficial trunk, or the head and neck in patients who received preoperative EBRT, IORT can be delivered immediately after resection to the area at risk avoiding the uninvolved organs. (Category 2A recommendation). The guideline also states that while IORT has shown excellent clinical outcomes, efficacy needs to be confirmed in larger cohorts of patients with longer follow-up.

Sarria et al. (2020) conducted a retrospective chart review of 31 patients (15 female, 16 male, aged 15-77) treated for primary and recurrent soft tissue sarcoma (STS). Outcomes assessed were progression -free survival (PFS), overall survival (OS) and local PFS (L-PFS). Toxicity was assessed according to the Common Terminology Criteria for Adverse Events. Patients were followed at 1, 3, 6, 12, 18, 24 months and annually thereafter. Six-month MRI and thorax CT was done during the first 2 years and then annually. Median follow up ranged from 1-9 years. Tumor specifics included 16 patients with extremity sarcoma, 14 with pelvic and abdominal tumors, 3 with thoracic sarcoma, and 1 had head and neck primary sarcoma. Twenty-five had recurrent disease and had previously been treated with surgery and/or EBRT. Four patients with previously un-irradiated recurrences received neoadjuvant EBRT. The post-recurrence surgical margin status was found to be R0 in 18 patients, R1 in 8 patients, R2 in 2 patients and not clear in 3 patients. The results showed the overall PFS for both primary and recurrent disease was 11 months, and 5- year O-PFS was 42.6%. Distant metastasis was seen in 7 patients with recurrent and 1 patient with primary STS patient after 10 months. Only one local recurrence occurred in patients with primary STS after 22 months and 8 in the recurrent group. The median L-PFS in the group with recurrent STS was 12.5 months and the estimated 5-year L-PFS was 65.5%. The 5-year OS estimated rate was 94.7%. There was no statistically significant difference amongst anatomical location in terms of O-PFS. The toxicity profile shows that no G3 or wound related toxicity occurred. The authors concluded that within the limitations of a retrospective study and heterogeneity of patient cohort, IORT shows a benefit for L-PFS for patients with STS.

In 2020, the European Society for Radiotherapy and Oncology (ESTRO) Task Force on IORT (Roeder et al.) convened a panel of experts to conduct a systematic literature review, combined with clinical expertise to develop the following recommendations for the use of IORT for STS. The authors state that all patients diagnosed with soft-tissue sarcoma should be discussed within a multidisciplinary tumour board prior to treatment initiation to define the optimal treatment.

- For extremity STS, if preoperative radiation therapy (RT) is planned, IORT may be added if close or positive margins are found or assumed intraoperatively.
- For retroperitoneal STS, EBRT should be done preoperatively and can be combined with IORT boost if close or positive margins are found or anticipated intraoperatively.

Other Indications

Chen et al. (2025) completed an interim evaluation of an ongoing prospective phase II study on the safety and efficacy of IORT using a low energy x-ray source (50 kV) in the treatment of patients undergoing radical pancreatectomy for pancreatic cancer. The primary endpoint was time to treatment failure (TTF) survival. Secondary endpoints were safety and OS. Patients were followed up every 3 months for the first 2 years after treatment, followed by evaluations every 6 months for an additional 3 years. Thirty five patients were treated, with thirty one completing at least one-year of follow up, and almost half were followed up for more than 2 years. All patients underwent R0 resection. Four patients did not undergo adjuvant chemotherapy: 2 declined 1 was lost to follow-up, and another died in the hospital because of abdominal infection and grade C pancreatic fistula. Two patients with Stage III disease were included. The results showed seven individuals experienced local recurrence, 23 had distant metastasis, and five showed both. The median time to local failure was 9.8 months, and TTF was 11.68 months. This was dependent on dose with median TTF in patients the received a IORT dose of ≤ 15 Gy. Patients that received > 15 Gy showed a median TTF of 7.6 months. Median TTF for patients with Stage I disease was 20.89 months, Stage II disease was 9.2 months, and Stage III, 2.1 months. A univariate analysis showed a significantly elevated risk of recurrence in patients with elevated carcinoembryonic antigen (CEA) and D-dimer. Twenty patients did not survive and for the majority it was due to cancer progression. The median OS for the

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entire cohort was 22.2 months. Pancreatic fistula was the most common complication, and occurred in 33 individuals. Other complications included delayed gastric emptying and intra-abdominal abscess. The authors concluded that IORT can safely be integrated into the multimodal treatment of resectable pancreatic cancer, and has acceptable morbidity and mortality. This trial is limited by a single arm design, as well as limited enrollment affecting the study progress. This trial protocol did not specify post operative adjuvant chemotherapy, which could influence these findings.

In a 2024 systematic review and meta-analysis, Palavani et al. to evaluate the efficacy and safety of IORT for the treatment of high-grade glioma. Sixteen studies comprised of 436 patients were included. Tumor types were predominantly glioblastoma multiforme (GBM), and anaplastic astrocytoma (AA). The results showed survival rates of 74% at twelve months and 24% at twenty four months. IORT failure was seen is 77% of the cases (which was not significantly superior to the isolated progression rate reported in a previous meta-analysis involving 73 studies and over 3,700 patients). The mortality rate was 61%, and complications occurred in 17% of individuals. The authors concluded that IORT shows comparable or even improved survival outcomes compared to other treatment modalities. Specifically, survival rates are consistent with or slightly higher than those achieved by a combination of therapy with interferon and temozolomide (70.2% at 12 months and 37.2% at 24 months), as well as conventional treatments (68.2% at 12 months and 37.8% at 24 months). The authors concluded that IORT is a promising treatment for select individuals with high-grade gliomas. The absence of a control group is a limitation of these findings, as well as significant heterogeneity among the included studies. Further research is needed to compare IORT to other treatment modalities. A currently active clinical trial (INTRAGO II) may contribute to the body of research in this area.

de Castro et al. (2023) reported the first results of a single arm open label phase 2 trial that evaluated LC and brain disease control (BDC) after IORT for resected brain metastases. Ten patients were included that met inclusion criteria of symptomatic adults 18 or over with one completely resected supratentorial BM in the presence of up to 10 lesions (which was suggestive of BM from different primary sites). The primary endpoints were actuarial LC and BDC. Local failure (LF) and distant brain failure (BDF), with death as a competing risk, were estimated. DBF was characterized if any new BM developed more than 5 mm from the border of the surgical cavity. The median clinical and imaging follow up occurred at 11.2 and 9.7 months, respectively. The results showed 6-month and 12-month LC was 87.5%. The 6 and 12-month BDC was 39% and 13%, respectively. One patient had local failure (LF) 3 months after IORT, and 3 patients died due to disease progression during the follow up period. Median local control was not reached, and median brain disease control was 5 months. The authors concluded that these first stage results suggest IORT for completely resected BM shows potential for local control with a low risk of toxicity and further research is warranted.

In a 2023 randomized single center prospective study, Li et al. evaluated the efficacy and safety of IORT for the treatment of recurrent high-grade glioma in adults with a with a Karnofsky Performance Status > 50. Twenty-two patients were allocated to the IORT group and 21 to receive surgery only. The results showed progression-free survival of the IORT group was 9.6 months and of the surgery only group was 7.3 months (P0.018), and the overall survival of the 2 groups was 13.5 months and 10.2 months, respectively. The authors concluded that IORT can improve survival in patients with recurrent glioma, but further study is needed to validate these findings.

In a 2022 systematic review, Villafuerte et al. (2022) evaluated and consolidate the published literature on IORT for head and neck malignancies. Fifty-two studies composed of observational cohorts and case series and comprised of 2389 patients were included. Subsites included neck (20.4%), oropharynx (17.7%), oral cavity (14.4%), nasal cavity and paranasal sinuses (9.8%), hypopharynx (8.1%), parotid (8.1%), larynx (4.2%), other salivary glands (3.0%), skull base (2.9%), scalp or skin (2.5%), nasopharynx (1.4%), temporal bone (1.1%), orbit (0.9%), thyroid (0.3%) and others (4.96%). The majority of the cases were locally advanced squamous cell carcinomas (SCCs). The studies were considered homogenous or heterogenous and each had 3 subclassifications. Homogenous studies (treatment settings were well defined) were classified as follows; treatment in the primary setting using both IORT and EBRT, treatment in the recurrent setting treated with IORT alone and treatment in the recurrent setting using IORT alone in patients with a history of irradiation. Heterogenous studies included both primary and recurrent cases, primary and reirradiation treatments, or IORT with and without EBRT were classified as follows; treatment in the recurrent setting with or without prior irradiation using IORT and EBRT, treatment in the primary or recurrent setting with no prior irradiation using IORT and EBRT, and treatment in the primary or recurrent setting with or without prior irradiation using IORT with or without EBRT. The results showed that IORT has shown local control (LC) benefits in patients with a high risk of locoregional recurrence of approximately 69%. The effectiveness of IORT shows the highest effectiveness in R0 and R1 surgical margins. OS averaged 53% at 2-3 years follow up. The authors concluded that IORT for head and neck tumors may result in the best outcomes in well selected patients with recurrent disease as an immediate boost as part of a reirradiation regimen together with additional EBRT following salvage surgery with good margins, however additional EBT may still be necessary to reach appropriate dose beyond what is a safe limit for IORT. The review is limited by a lack of well-designed trials that compare outcomes of IORT with the current standard of care such as intensity modulated radiation therapy and volumetric modulated arc therapy.

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In 2019, the American Brachytherapy Society (ABS) published an evidence-based consensus statement on IORT and gave the following recommendations by treatment site (Tom et al., 2019):

- As monotherapy for breast cancer, IORT should not be offered to patients outside of prospective clinical trials. Can be considered as a boost technique in patients that require a tumor bed boost.
- For sarcoma of the extremities, can be considered in cases with close/positive margins, and recurrence with previous EBRT. For sarcoma of the retroperitoneal area, consider in conjunction with EBRT particularly when close/positive margins are expected.
- For pancreatic cancer, IORT can be considered at the time of surgical resection in cases with concern for a close/positive margin.
- For colorectal cancer, IORT can be considered at the time of surgical resection of locally advanced or recurrent malignancies in cases with concern for a positive margin, particularly when pelvic EBRT has already been delivered.

For the following treatment sites, ABS concluded that IORT can be considered for appropriately selected patients at time of surgical resection when there is a concern for positive margins:

- Thorax
- Head and neck

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Code	Description
0766T	Transcutaneous magnetic stimulation by focused low-frequency electromagnetic pulse, peripheral nerve, with identification and mapping of the treatment location, including noninvasive electroneurographic localization (nerve conduction localization), when performed; first nerve
0767T	Transcutaneous magnetic stimulation by focused low-frequency electromagnetic pulse, peripheral nerve, with identification and mapping of the treatment location, including noninvasive electroneurographic localization (nerve conduction localization), when performed; each additional nerve (List separately in addition to code for primary procedure)

Transcutaneous magnetic stimulation (tMS) by focused low-frequency electromagnetic pulse for the treatment of chronic pain is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

On June 11, 2021, the FDA granted 501(k) status to NeuraLace Medical, Inc. for its electromagnetic stimulator for pain relief, with the trade name of Axon Therapy. This device, using brief and focused magnetic pulses, is intended to bring relief of post-traumatic, post-surgical, and chronic intractable pain in adults. For additional information, please refer to the following website: https://www.accessdata.fda.gov/cdrh_docs/pdf21/K210021.pdf. Other electromagnetic stimulator devices have since been approved by the FDA for the treatment of pain. Information on these devices can be found using Product Codes QPL or IPF at the following website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed May 19, 2025)

Clinical Evidence

Transcutaneous magnetic stimulation (tMS), also known as peripheral magnetic stimulation (PMS), is a non-invasive method of delivering a rapidly pulsed, high-intensity magnetic field to the periphery other than the brain.

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In another systematic review and meta-analysis, Dana et al. (2024) evaluated the effects of PMS in the treatment of chronic peripheral neuropathic pain. There were 23 studies (15 RCTs, five case series, two case reports, and one non-randomized trial) that evaluated the use of PMS in adults with chronic neuropathic pain that was present for at least three months duration. The total number of participants in all studies was 1123 adults who had one of 13 different neuropathic pain disorders. PMS regimens varied across studies, ranging from five to 240 minutes per session over one day to one year of treatment and sham device was used in nine studies while the other studies compared a number of different controls, such as physiotherapy, physiotherapy and vitamins, transcutaneous electrical nerve stimulation, laser therapy or standard of care to PMS. The authors reported that results across the studies were mixed with some studies suggesting benefits while other studies showed no significant differences. According to the authors, four of nine placebo-controlled RCTs reported statistically significant findings in favor of PMS use. The authors reported that the meta-analysis showed that PMS significantly reduced pain scores compared to control within zero to one month of use, but not at the one to three months and over three months of PMS use. The authors concluded that there was limited and low-quality evidence to make definitive recommendations on PMS use for the treatment of chronic peripheral neuropathic pain; however, the data was encouraging, especially for short-term applications. Limitations of the study included the heterogenous study designs, neuropathic pain conditions, devices used, sites of applications, duration of intervention, and the overall small sizes of the included studies [The Rao et al. (2023) and Panathoop et al. (2022) studies previously cited in this policy were included in this systematic review and meta-analysis].

Park et al. (2023) evaluated the effect of peripheral magnetic stimulation (PMS) on acute and chronic postoperative pain. A search was conducted using MEDLINE, Cochrane CENTRAL, EMBASE, ProQuest International Dissertations, and ClinicalTrials.gov. A total of seventeen RCTs and one non-randomized clinical trial totaling 958 patients were included for review. PMS was described as pulsed electromagnetic field therapy in all studies and the length of PMS varied from the first 24 hours following surgery to 60 days. The frequency of pulses were identified as either 40 Hz, 75 Hz, or 27.12 MHz and the number of pulses varied amongst the studies. The primary outcome of this review was acute postoperative pain intensity within the first 7 days following the surgical procedure. Secondary outcomes included postop opioid consumption, acute pain intensity one to three months following surgery, chronic pain scores greater than 3 months after surgery and any adverse events. For acute postoperative pain, the authors found seven of ten studies showed a benefit of PMS when compared to sham or no intervention; the other three studies did not provide a benefit of PMS over other interventions. For subacute postoperative pain, two of seven studies found a significant improvement in pain with PMS. For chronic post-surgical pain, the authors found only one study at three months that identified significantly lower pain scores when compared to the sham group. The remaining studies found continued pain or no significant difference between the control and sham groups. The authors concluded that PMS may be a potentially beneficial adjunct service for postoperative pain management, however results are limited by heterogeneity and generally low-quality trials, as well as low or very low quality of evidence according to the GRADE framework. Future high-quality and robust studies are needed to confirm the benefits of PMS devices for postoperative acute and chronic pain along with their safety and efficacy. Limitations included lack of trials on this specific topic, small study bias and a large number of participants that dropped out from several studies with no specific reasons documented. Also, if a study did not see any significant improvements in pain, it was unclear whether it was due the ineffectiveness of the PMS, or patient noncompliance.

Hayes (2023; updated 2024) published an Evolving Evidence Review for Axon Therapy (NeuraLace Medical Inc.) for Chronic Nerve Pain. The report indicated that a review of the evidence suggests that the quantity of published, peer-reviewed clinical data is insufficient to evaluate this technology for the treatment of chronic nerve pain in adults. The report concluded no relevant systematic reviews addressing the use of Axon Therapy (NeuraLace Medical Inc.) for the treatment of chronic neuropathic pain were identified. Additionally, no professional organization recommendations were found for this treatment strategy. In the 2024 update, Hayes reported that there was one relevant, newly published study that may meet the inclusion criteria; however, their level of support remained no/unclear.

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Code	Description
0870T	Implantation of subcutaneous peritoneal ascites pump system, percutaneous, including pump-pocket creation, insertion of tunneled indwelling bladder and peritoneal catheters with pump connections, including all imaging and initial programming, when performed
0871T	Replacement of a subcutaneous peritoneal ascites pump, including reconnection between pump and indwelling bladder and peritoneal catheters, including initial programming and imaging, when performed
0872T	Replacement of indwelling bladder and peritoneal catheters, including tunneling of catheter(s) and connection with previously implanted peritoneal ascites pump, including imaging and programming, when performed
0873T	Revision of a subcutaneously implanted peritoneal ascites pump system, any component (ascites pump, associated peritoneal catheter, associated bladder catheter), including imaging and programming, when performed
0874T	Removal of a peritoneal ascites pump system, including implanted peritoneal ascites pump and indwelling bladder and peritoneal catheters
0875T	Programming of subcutaneously implanted peritoneal ascites pump system by physician or other qualified health care professional

The use of a subcutaneous peritoneal ascites pump system is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

A subcutaneous peritoneal ascites pump system (e.g., the alfapump® System) is an implantable, battery-powered device that moves ascitic fluid from the peritoneal cavity into the bladder. The ascitic fluid is then eliminated through urination. The alfapump System is intended for adult patients with refractory or recurrent ascites due to liver cirrhosis (Sequana Medical NV, 2025).

The alfapump System received U.S. Food and Drug Administration (FDA) premarket approval on December 20, 2024 (Product Code: SDQ). Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm. (Accessed March 14, 2025)

Wong et al., (2025) assessed the safety and efficacy of the alfapump for ascites control and quality of life (QOL) in a prospective, multicenter, single arm study. The study included 40 participants with cirrhosis and refractory ascites (RA). The primary efficacy endpoint was reduction in paracentesis requirement. The primary safety endpoint was device-related adverse events resulting in intervention, explant, or death. The study results revealed therapeutic paracentesis decreased from 3.2 ±1.5 sessions per month pre-alfapump to 0.2 ±0.6 sessions per month at 6 months post-alfapump implant ($p < 0.001$). Seventy-seven percent of participants had a ≥ 50% reduction in paracentesis. Six pumps (15%) were explanted within 6 months due to device-related adverse events. Ten device deficiencies occurred in nine participants over the 6-month postimplant period. There were 79 serious adverse events (SAEs) reported for 24 participants post-implant. Forty-three of the SAEs were determined to be related to either the alfapump, the implant procedure, or to alfapump therapy. Sixteen SAEs for 12 participants were classified as major adverse events, defined as acute kidney injury (AKI) > stage 2, hepatic encephalopathy (HE) > grade 2, and spontaneous bacterial peritonitis or recurrent or refractory infection related to paracentesis, or the alfapump system, procedure, or therapy. There were five deaths within 6 months postimplant, but these were determined as not directly related to the alfapump or alfapump therapy. Ascites-related symptom scores, assessed with a validated participant questionnaire, improved from 51.0 ±19.3 pre-alfapump to 32.2 ±21.9 at 6 months post-alfapump implant ($p < 0.001$). Physical component scores, using a QOL participant questionnaire improved from a mean baseline value of 36.6 ±9.3 to 42.8 ±8.5 at 6 months postimplant ($p < 0.001$). However, mental component scores did not improve. The authors concluded that the alfapump effectively controlled ascites, which improved QOL. The alfapump may be considered as an alternative to repeat therapeutic paracentesis in select patients with RA. The complication rates were determined to be similar to those expected in patients with RA. Limitations of the study include the single arm design, small sample size, and short follow-up period.

Hayes concluded in an emerging technology report that the published clinical evidence for the alfapump showed it significantly reduced the frequency of large-volume paracentesis (LVP) and improved QOL for individuals with RA. However, the alfapump was also associated with a high rate of infections, AKI, and explantation due to skin issues and device-related problems. Design modifications to the alfapump appear to have resolved some device-related issues. The administration of albumin in some cases may have also addressed AKI. The best available published evidence for the current alfapump design includes a prospective study of 30 individuals and a European postmarketing study of 106

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individuals. The results of a randomized controlled trial (RCT) comparing the alfapump with repeated LVP are also published, but the study evaluated earlier versions of the device. Larger studies with a longer-term follow-up are needed to determine if the design modifications to the alfapump improved safety (Hayes 2022; updated 2024).

Stirnimann et al. (2022) investigated the safety and efficacy of the alfapump in a real-world, multicenter, observational, cohort study. A total of 106 individuals with cirrhotic RA and contraindications for transjugular intrahepatic shunt (TIPS) were followed for up to 24 months. Complications, device deficiencies, frequency of paracentesis, clinical status and survival were recorded prospectively. The study results revealed approximately half of the individuals enrolled died on-study. About a quarter of individuals were withdrawn because of an SAE leading to explant. A sixth were withdrawn because of liver transplant or recovery. The most frequent causes of on-study death and complication-related explant were progression of liver disease and infection. The alfapump was found to have reduced the requirement for LVP significantly. More than half of individuals did not require post-implant. Survival benefits were not observed, as 34 individuals (31.5%) died within 6 months (29 individuals on-study and five individuals after an SAE-related explant). Device-related surgical reinterventions were determined to be predominantly caused by device deficiencies. The authors concluded the alfapump reduced paracentesis frequency in a real-world setting. However, complications occurred frequently. This partly reflected the underlying advanced liver disease of the study population and partly the technical problems associated with the device. Technical complications were successfully decreased by optimization of management and device modification. A post-hoc comparison of the first 50 individuals enrolled versus the last 50 individuals enrolled revealed a decreased reintervention rate in the latter, mainly related to peritoneal catheter modifications. Limitations of the study include no standardized protocol. Individuals were selected and managed according to local practices. Selection bias could not be excluded. Additionally, the absence of randomization makes a direct comparison with other treatments impossible. Only nine individuals completed the study at 24 months. Premature discontinuations (91.5% of individuals) were mainly because of SAEs and death, but also because of liver transplantation and resolution of RA (This study is included in the emerging technology report by Hayes 2022; updated 2025).

Will et al. (2022) conducted a systematic review and meta-analysis to assess the efficacy, mortality and complications associated with LVP, TIPS, the alfapump, peritoneovenous shunt (PVS), and permanent indwelling peritoneal catheter (PIPC) for individuals with liver cirrhosis and RA. A total of 77 studies were selected for the systematic review, including six studies for the alfapump. The results revealed mortality for LVP was 45% around 12 months. For individuals with TIPS, the one-year mortality was 33%, with lower mortality in newer studies (26% versus 44%). Mortality at 12 months was 44% for PVS and 45% for LVP. The overall mortality for individuals with PIPC was 66%. At 6 months, the mortality for individuals with an alfapump was 24%. (The meta-analysis was performed at 6 months for the alfapump due to data availability.) The overall AKI rate for individuals with an alfapump was 36%. A 31% AKI rate was observed using a time-averaged analysis around six months. Using data from all studies, the infection rate for individuals with an alfapump was 41%. If the analysis was limited to studies reporting the infection rate at 6 months, the frequency was 44%. The most common infections reported for individuals with an alfapump were urinary tract infection (UTI), bacterial peritonitis, wound site infection, and sepsis. The frequency reported for spontaneous bacterial peritonitis or device-related peritonitis ranged from 30% to 52%, for UTI 7.5% to 50%, for wound site infection 10% to 20%, and 10% to 17.5% for sepsis, respectively. The authors concluded the study results suggest that TIPS, particularly in more recent studies, revealed lower mortality and lower HE, as compared to other treatment modalities. PIPC seemed to be a good option for the palliative care setting. AKI and infections were frequent for individuals with an alfapump. Limitations of the systematic review include the estimation of frequencies rather than a direct comparison in all treatment options due to the observational nature of the studies. It was also not possible to estimate time-dependent variables such as hazard-ratio. Additionally, there was considerable heterogeneity in almost all analyses, e.g., differences in baseline characteristics such as liver function, follow-up medical care, and discrepancies in the assessment of complications.

The American Association for the Study of Liver Diseases (AASLD) published practice guidance for the diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome. In a discussion of alternatives to TIPS, AASLD stated that the insertion of an alfapump has been reported to reduce paracentesis, improve QOL, and nutritional status. However, the AASLD published no guidance statements regarding the alfapump (Biggins et al., 2021).

The British Society of Gastroenterology (BSG), in collaboration with the British Association for the Study of the Liver (BASL), published guidelines on the management of ascites in cirrhosis. BSG/BASL recommended that an automated low-flow ascites pump should only be considered in special circumstances with robust arrangements of clinical governance, audit, or research (Quality of evidence: low; Recommendation: weak) (Aithal et al., 2021).

Will et al. (2020) retrospectively evaluated the characteristics and outcomes of consecutive individuals treated with TIPS or the alfapump for RA at a single center. All individuals diagnosed with RA were considered for either TIPS, alfapump, or repetitive LVP. The treating physician determined the allocation of treatment. Nineteen individuals who were treated with

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TIPS and 40 individuals treated with the alfapump were included in the study analysis. Individuals with TIPS had better liver function and less HE at baseline when compared to individuals with the alfapump. In a sensitivity analysis comparing individuals with similar liver function, hospitalizations and reinterventions were less frequent in individuals with TIPS. Though, individuals receiving an alfapump with a newer catheter design required less reinterventions (26% versus 57% with older catheter designs). Hepatorenal syndrome and prerenal impairment were significantly more frequent in individuals with the alfapump. HE occurred equally frequent in both treatment groups. There was a trend towards a higher infection rate in individuals with the alfapump. Cumulative transplant-free survival after 12 months was 65% in the TIPS group versus 23% in the alfapump group. The authors concluded that both TIPS and the alfapump were effective treatments for RA in cirrhosis. Individuals treated with TIPS had a better one-year transplant-free survival, but also less negative prognostic factors at baseline. Selecting individuals without HE prior to implantation of an alfapump might improve transplant-free survival. Limitations of this study include the small sample size, retrospective design, the different degree of liver failure of individuals treated with TIPS versus those with the alfapump, and indication bias. During follow-up, three individuals in the TIPS group had an alfapump implanted and two individuals in the alfapump group received TIPS. The strength of the evidence is also lessened due to the lack of a direct comparison of the two treatments.

Bendel et al. (2020) evaluated the feasibility, procedural outcomes, and safety of alfapump implantation using interventional radiology (IR) methods. The multicenter, open-label prospective MOSAIC study included 30 individuals with cirrhotic RA who received an alfapump system implanted by IR or open surgical approach. Participating centers were free to select the implantation method according to local standards. Twenty-nine individuals underwent implantation by IR and one individual underwent implantation by open surgical approach. The mean age was 60 years and 56.7% of individuals were male. Technical implant success, defined as an implanted alfapump system that was actively pumping or pumping when activated or programmed to do so, was achieved in all 30 procedures. Of the 30 individuals enrolled, 27 completed the 3-month follow-up period (90%). There were 40 SAEs reported for 18 individuals (60%). Nine individuals experienced greater than one SAE (range, 2 – 7). Two SAEs were determined to be procedure related and one SAE was determined to be possibly procedure related. The two procedure-related SAEs included postoperative bleeding and abdominal pain with fluid leakage at the implant site and fluid collecting in the pump pocket 18 days after the procedure in the same individual. Bacterial peritonitis occurred in another individual 26 days after implantation and was determined to be possibly related to the procedure. There were four surgical revisions and two explants. The total adverse event rate was 31%, which was considered to be in the range of expectations. The authors concluded placement of the alfapump using IR methods was both feasible and technically successful. Limitations of this study included restricted outcome data, short follow-up interval, and a limited demonstration of safety due to the small sample size. There were also no comparisons or controls, limiting the conclusions. Implantation of the alfapump by IR in larger cohorts is warranted (This study is included in the emerging technology report by Hayes 2022; updated 2025).

Wong et al. (2020) also used data from the MOSAIC study to assess the alfapump's effect on safety, efficacy, and QOL for individuals with cirrhosis and RA ineligible for TIPS. The multicenter, open-label prospective study included 30 individuals with cirrhotic RA who received an alfapump system implanted by IR or open surgical approach. Twenty-nine individuals underwent implantation by IR and one individual underwent implantation by open surgical approach. The mean age was 60 years and 56.7% of individuals were male. Following alfapump implantation, individuals were monitored for ascites control, laboratory abnormalities, adverse events, and survival at 12 months. QOL was also evaluated using the Chronic Liver Disease Questionnaire (CLDQ) and Ascites Questionnaire (Ascites Q). By 12 months, 79 SAEs were reported. Twenty-seven SAEs (34.2%) were considered related to the device in 13 (43.3%) individuals. Bacterial infections (15 events in 13 individuals), electrolyte abnormalities (11 events in six individuals), and renal complications (11 events in nine individuals) were the most common SAEs. The alfapump removed ascites volume, reducing the mean LVP frequency from 2.4 ±1.4/patient/month before pump implantation to 0.2 ±0.4/patient/month after pump implantation. Significant improvements in QOL were observed as early as one month after alfapump implantation. Improvements in QOL were maintained at 3 months in both the CLDQ and Ascites Q and at 12 months with the Ascites Q. The authors concluded that the alfapump may be a definitive treatment for RA in cirrhosis, especially in individuals who are not TIPS candidates. Limitations of this study include the lack of a control group, small sample size, and short follow-up interval. (This study is included in the emerging technology report by Hayes 2022; updated 2025).

Lepida et al. (2019) conducted a systematic review and meta-analysis to synthesize the available evidence on the efficacy and safety of automated low-flow ascites pump therapy in individuals with cirrhosis and RA. A total of nine studies involving the alfapump were included in the systematic review. Eight studies were case series, and one study was an RCT. The systematic review revealed pooled estimate rates of 0.62 [95% confidence interval (CI) = 0.49-0.74] for the absence of requirement of LVP after pump insertion, 0.30 (95% CI = 0.17-0.47) for AKI, 0.27 (95% CI = 0.13-0.49) for bacterial peritonitis, and 0.20 (95% CI = 0.09-0.37) for UTI. Results of sensitivity analyses were found to be similar to those of overall analyses. The authors concluded that most individuals treated with an automated low-flow ascites pump no longer require LVP (62%). However, after pump insertion, AKI occurs in 30% of individuals and creatinine levels increase by a mean of 23 μmol/L. Additionally, 27% of individuals experience bacterial peritonitis and 20% of individuals

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experience UTI. Limitations of the systematic review include moderate to high heterogeneity for several analyses, the absence of publication bias could not be affirmed, the limited quality of the included studies, and the available data did not allow for an assessment of prognosis, nutritional status, or QOL. The study by Bureau et al. (2017) is included in this systematic review and meta-analysis.

The National Institute for Health and Care Excellence (NICE) published interventional procedures guidance for subcutaneous automated low-flow pump implantation for RA caused by cirrhosis. NICE determined that the current evidence showed there are serious, but well-recognized safety concerns, including device failure and AKI associated with this procedure. Additionally, the evidence supporting efficacy is limited in quantity. Subcutaneous automated low-flow pump implantation for RA caused by cirrhosis should only be used with special arrangements for clinical governance, consent, and audit or research (NICE, 2018).

The European Association for the Study of the Liver (EASL) published clinical practice guidelines for the management of patients with decompensated cirrhosis. EASL stated that implantation of the alfapump for individuals with RA not amenable to TIPS is suggested in experienced centers. However, close monitoring is warranted because of the high risk of adverse events including renal dysfunction and technical difficulties (Weaker recommendation based on RCTs) (EASL, 2018).

Bureau at al. (2017) assessed the safety and efficacy of the alfapump compared with LVP standard of care (SOC). This prospective, multicenter, open-label, RCT of individuals with RA due to cirrhosis was performed at seven centers from five countries. The primary endpoint was time to first LVP. Secondary outcomes included LVP requirement, safety, health-related QOL, and survival. A total of 60 individuals were randomized, but 58 individuals received the designated treatment and constituted the safety population. There were 27 individuals in the alfapump group and 31 individuals in the LVP SOC group. Baseline characteristics and patient demographics were described as well balanced and with no significant differences between the two treatment groups. The mean age of individuals in the alfapump group was 61.1 ±8.5 years versus 62.6 ±8.4 years in the LVP SOC group. Approximately 80% of individuals were male in both groups. The study results revealed the time to first LVP was significantly longer in the alfapump group compared to the SOC LVP group. The alfapump successfully eliminated the need for LVP in more than 50% of individuals over six months. However, the alfapump group reported more adverse events and SAEs (96.3% and 85.2%) than the SOC LVP group (77.4 and 45.2%). There were significantly more AKI events reported in the alfapump group (29) than in the LVP SOC group (11). The nature and frequency of individuals with SAEs due to infection were similar in both groups. Twelve individuals experienced at least one alfapump device deficiency. Seven individuals required reintervention because of device deficiency, six individuals (22%) required system component replacement or repositioning and three individuals required device explant (11%). There was no significant difference noted in overall survival between the alfapump group and the LVP SOC group. The CLDQ was used to measure QOL. The alfapump group showed significantly improved CLDQ scores compared with LVP SOC group. The authors concluded the alfapump was effective for reducing the need for LVP and improving QOL in cirrhotic patients with RA. While the frequency of SAEs (and by inference hospitalizations) was significantly higher in the alfapump group, these occurrences were generally limited and did not impact survival. Limitations of the study include the small sample size and short follow-up period (This study is included in the emerging technology report by Hayes 2022; updated 2025, and in the systematic review by Will et al., 2022).

Clinical trials to assess the safety and efficacy of the alfapump are ongoing. Refer to the following website for more information: https://clinicaltrials.gov/. (Accessed April 30, 2024).

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Code	Description
17999	Unlisted procedure, skin, mucous membrane and subcutaneous tissue [when used to report ablative laser treatment for wounds]

Ablative laser treatment (full field, and fractional ablation) for wound healing is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Ablative lasers are a group of lasers that vaporize tissue by targeting water. The most commonly used types are the CO2 laser and the erbium-doped yttrium aluminum garnet (Er:YAG) laser. They are most commonly used for burn wound debridement, treatment of unstable burn scars and slow-to-heal wounds, and treatment of existing scars, including hypertrophic scarring and contractures. While ablative laser treatment for open wounds has been investigated, the evidence is insufficient in quantity and quality to support its routine use in clinical practice.

In a retrospective single center cohort study, Tang et al (2023) evaluated the therapeutic effect of diode laser (810 nm) irradiation on chronic wounds. Their study included 89 participants who had all undergone debridement prior to the study. The participants were divided into a control group (n = 41) who received traditional dressing change therapy, or a treatment group (n = 48) who received additional treatment with diode laser (810 nm) irradiation for 10 minutes at each dressing change. The wound areas of the control group and the diode laser treatment group at the first dressing change were 12.01 ±28.02 and 7.67 ±7.45 cm2 , respectively, without a statistically significant difference between the two groups. In the control group, 48.78% of the wounds were surrounded by scar tissue, and in the diode laser treatment group, 70.83% of the wounds were surrounded by scar tissue. The difference was statistically significant. When the dressing change was performed for the first time, the wound pain scores of the control and diode laser treatment groups were 2.66 ±0.73 and 2.75 ±0.81, respectively; the difference was not statistically significant. In addition, in terms of underlying diseases, the proportion of patients with underlying diseases (such as diabetes, hypertension and epilepsy) in the control group and the diode laser treatment group was 24.39% and 16.67%, respectively, with no statistical significance. The authors stated that these measures indicate that the wound condition of the two groups had good homogeneity at the first dressing change as a baseline. The authors stated that the wound healing time of the diode laser treatment group was significantly shorter than the control group (22.71 ±8.99 days vs. 37.44 ±23.42 days) and that the pain relief index of the diode laser treatment group was significantly increased compared with that of the control group (0.081 ±0.055 vs 0.057 ±0.033). Limitations of the study include selection bias as the clinic that the records were retrieved from typically used diode laser therapy for refractory wounds which accounted for the larger proportion of wounds with scar tissue. Other limitations include the heterogeneity between the groups, and the retrospective design. The authors concluded that the diode laser irradiation has the potential to promote healing in chronic wounds and to relieve wound pain.

Liu et al.(2022) conducted a systematic review and meta-analysis to compare the efficacy and safety of topical interventions used for recurrent aphthous stomatitis. Their study included 72 clinical trials with 5272 individuals who participated in clinical trials for 29 different topical interventions. The authors reported that honey, insulin liposome gel, laser, amlexanox, glycyrrhiza and triamcinolone had better efficacy performance while probiotics and chlorhexidine helped to prolong ulcer intervals and reduce recurrence. There were 14 RCTs with laser interventions included in their study (including the Suter study below) with five studies that used diode lasers, six used carbon dioxide (CO_2) lasers, one used Er, Cr: YSGG lasers, one used Nd: YAG lasers, and one used low-level laser therapy (LLLT). The authors noted that the modality used, the wavelength of the laser and the power output were different and that they could not determine whether the different types of laser interventions and the differences in the course and frequency have an impact on the efficacy as studies evaluating these parameters are lacking. The authors grouped different kinds of laser modalities together as laser

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in the study due to this scarcity of studies on individual kinds of lasers and the lack of treatment criteria. The authors determined that lasers were considered superior in terms of healing effect, size reduction effect and symptom reduction effect during the full course of treatment based on the evaluation done by the authors. They stated that the laser demonstrated unparalleled short-term explosive power in daily evaluations and that laser is unquestionable in terms of safety considerations. In conclusion, the authors stated that most of the other local interventions did not show significant differences in the efficacy and safety evaluations. Limitations of the study, as noted above, include the heterogeneity of the studies included in their meta-analysis with regard to types of laser and treatment criteria.

In a single-center, randomized, double-blinded controlled trial, Tinker et al. (2022) sought to define the safety and efficacy of carbon dioxide ablative fractionated laser (CO_2AFL) in management of patients with acute, lower extremity wounds following Mohs micrographic surgery. The study consisted of 48 participants. One group received sham laser (n = 24) and the other group received CO_2AFL (n = 24) on their lower extremity, post-surgical wound following Mohs micrographic surgery. CO_2AFL efficacy was evaluated at weeks 4, 8 and 12 and assessed mean time to complete wound healing, the quantity of wounds completely healed, wound surface area, and the wound temperature. In assessing CO_2AFL safety, data on the occurrence of posttreatment infection, self-reported pain and quality of life was collected. Results of the study concluded there was no notable difference in efficacy between CO_2AFL and the control in terms of wound healing, percent change in surface area, the quality of life, or adverse events at interval evaluation weeks. Regarding safety, CO_2AFL is considered a safe modality but is not an effective treatment in healing acute, lower-level wounds. There are limitations in the study which include the study design and monthly follow-up protocols. In addition, earlier timing points of CO_2AFL implementation post-surgery and longer pulse width applications warrant further studies to evaluate its efficacy.

In a 2021 publication Lu et al. describes the results of their randomized control trial (RCT) to investigate the effectiveness of high-intensity laser therapy (HILT) on chronic refractory wounds. Sixty participants were enrolled in the study and were randomized into control and treatment groups. The control group received conventional wound dressing, whereas the treatment group received irradiation with HILT in addition to standard wound care. Participant scores were evaluated before and after 1, 2 and 3 weeks of treatment utilizing the Bates-Jensen Wound Assessment Tool (BWAT) and Pressure Ulcer Scale for Healing (PUSH). A total of 59 participants completed the trial as one was excluded from the control group. At the end of week 3 treatment, the BWAT scores showed a significant reduction in the treatment group compared with the control group (difference = −3.6; 95% CI −6.3 to–0.8; $p < 0.01$). Similarly, participants in the treatment group showed significantly decreased PUSH scores compared with the control group (difference = −5.3; 95% CI −8.1 to –2.6; $p < 0.01$). The authors concluded that in treatment of chronic refractory wounds HILT is effective and should be considered for use with other therapeutic modalities. Limitations in the study were identified due to various wounds with different etiologies, pathologies, and locations, which leads to confusion as to the best HILT application, small number of participants, and lack of differentiation in healing effects with HILT treatment. Therefore, further investigation and additional studies are warranted.

In a systematic review, Suter et al. (2017) examined a potential benefit of laser use in the treatment of recurrent aphthous stomatitis (RAS). The primary outcome variables were pain relief, duration of wound healing and reduction in episode frequency. A PICO approach was used as a search strategy in Medline, Embase and Cochrane databases. After scanning and excluding titles, abstracts and full texts, a total of 11 studies (10 RCTs and 1 non-RCT) were included. Study selection and data extraction were carried out by 2 observers. Laser treatment included Nd: YAG laser ablation, CO_2 laser applied through a transparent gel (non-ablative) and diode laser in a low-level laser treatment (LLLT) mode. Control groups had placebo, no therapy or topical corticosteroid treatment. Significant pain relief immediately after treatment was found in 5 out of 6 studies. Pain relief in the days following treatment was recorded in 7 studies. The duration of RAS wound healing was also reduced in 5 studies. However, criteria of evaluation differed between the studies. The episode frequency was not evaluated as only 1 study addressed this outcome parameter, but did not discriminate between the study (LLLT) and control (corticosteroid) groups. Jadad scores (ranging from 0 to 5) for quality assessment of the included studies ranged between 0 and 2 (mean = 1.0) for studies analyzing pain relief and between 0 and 3 (mean = 1.1) for studies evaluating wound healing. The use of lasers (CO_2 laser, Nd: YAG laser and diode laser) to relieve symptoms and promote healing of RAS was a therapeutic option. The authors concluded that more studies for laser applications are needed to demonstrate superiority over topical pharmaceutical treatment and to recommend a specific laser type, wavelength, power output and applied energy (ablative versus photo-biomodulation).

Krakowski et al. (2016) stated that ablative fractional resurfacing (AFR) is an emerging therapy for chronic wounds. In a small case-series study, these researchers reported the successful use of AFR to facilitate the healing of chronic wounds in 2 pediatric patients. These patients had chronic wounds within scars that were treated with a micro-fractionated CO_2 laser in a single pass at a pulse energy of 50 mJ and a treatment density of 5%; 1 patient had 1 treatment and the other had 2 treatments 1 month apart. Ablative fractional laser resurfacing led to rapid healing of chronic wounds in both patients. The wounds remained epithelialized after 9 months in 1 patient and 4 months in the other. There were no complications. The authors concluded that the combination of tolerability and efficacy observed in these cases introduced

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AFR as a potential promising adjunct to existing treatments for chronic, non-healing wounds in the pediatric population. The study is, however, limited by lack of comparison group.

Phillips et al. (2015) stated that treating post-traumatic lower extremity wounds can be challenging, especially in elderly patients. Recently, the use of fractional carbon dioxide (CO_2) laser has been shown to improve wound healing in scar-related wounds. These researchers used this treatment modality in post-traumatic wounds that were slow to heal in 3 elderly patients. Each wound underwent 1 fractional CO_2 laser treatment. The wound base was treated at 30 mJ and 5% density. The entire wound edge and 1 to 2 cm into the normal surrounding skin were treated at 50 mJ and 5% density. One pass was completed at 150 Hz per treatment. Treatments were well-tolerated with only mild discomfort. Each wound healed by 60% or greater within 3 weeks. No adverse events were reported aside from mild and transient erythema at site of treatment. The authors concluded that fractional CO_2 laser treatment appeared to accelerate healing in each of these post-traumatic wounds; it may be a helpful adjunct in non-healing post-traumatic wounds. They also concluded that controlled studies are needed to further validate this modality as a second-line treatment for difficult-to-heal lower-extremity wounds.

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Code	Description
33289	Transcatheter implantation of wireless pulmonary artery pressure sensor for long-term hemodynamic monitoring, including deployment and calibration of the sensor, right heart catheterization, selective pulmonary catheterization, radiological supervision and interpretation, and pulmonary artery angiography, when performed
93264	Remote monitoring of a wireless pulmonary artery pressure sensor for up to 30 days, including at least weekly downloads of pulmonary artery pressure recordings, interpretation(s), trend analysis, and report(s) by a physician or other qualified health care professional
C2624	Implantable wireless pulmonary artery pressure sensor with delivery catheter, including all system components
G0555	Provision of replacement patient electronics system (e.g., system pillow, handheld reader) for home pulmonary artery pressure monitoring

Implantable wireless pulmonary artery pressure (PAP) sensor for long-term hemodynamic monitoring (e.g., CardioMEMS™ or Cordella®) is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Notes:
- Monitoring – For members with an existing implanted device, monitoring is a covered service.
- Removal – Removal of an implantable wireless PAP sensor is a covered service in the rare instance when it might be required.

Wireless PAP monitoring sensors implanted into the left or right pulmonary artery during a minimally invasive right heart catheterization. The system is designed to remotely measure and communicate PAP to guide heart failure (HF) management with the goal of reducing hospitalizations.

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The CardioMEMS HF System (Abbott) received U.S. Food & Drug Administration (FDA) premarket approval (P100045) on May 28, 2014. The device was originally indicated for wirelessly measuring and monitoring PAP and heart rate in individuals with New York Heart Association (NYHA) class III HF individuals who have been hospitalized for HF in the previous year. On February 21, 2022, the FDA approved an expanded indication to include individuals with NYHA class II HF who have been hospitalized for HF in the previous year and/or have elevated natriuretic peptides.

The Cordella Pulmonary Artery Sensor System (Edwards/Endotronix) received FDA premarket approval (P230040) on June 20, 2024. The device is intended to measure, record and transmit PAP data from individuals with NYHA Class III HF who are at home on diuretics and guideline-directed medical therapy (GDMT) as well as have been stable for 30 days on GDMT.

Clinical Evidence

Lindenfeld et al. (2024) performed a pooled meta-analysis (n = 1350) of three trials to determine whether management with implantable hemodynamic monitors reduced mortality in patients with HF and reduced ejection fraction (HFrEF) and to confirm the effect of monitoring on HF hospitalization rates reported in previous studies. Two of the trials (CHAMPION and GUIDE-HF) evaluated the CardioMEMS system; the third trial (LAPTOP-HF) evaluated a device that is not commercially available. All trials enrolled patients with HF with a prior HF-related hospitalization or elevated natriuretic peptides and used an implantable hemodynamic monitor for HF management. The meta-analysis was performed utilizing follow-up through 24 months for CHAMPION and LAPTOP-HF and follow-up before COVID-19 for GUIDE-HF. The overall pooled meta-analysis showed a 25% reduction in mortality after two years and a 36% reduction in HF hospitalizations at one year. GUIDE-HF had a notably shorter follow-up compared with the other two studies, but the authors included for completeness despite affecting the pooled mortality analysis. The selected trials utilized different hemodynamic measures, and GUIDE-HF and CHAMPION were single-blinded while LAPTOP-HF was unblinded. Early termination of LAPTOP-HF, and the impact of COVID-19 on GUIDE-HF are also limitations. Furthermore, the meta-analysis was not performed based on findings of a systematic review and could therefore be subject to bias.

An ECRI report on the Cordella system concluded that available studies are too limited in quantity and quality to enable conclusions about whether Cordella improves HF rehospitalization rates, mortality, functional status, and quality of life outcomes compared with clinical decisions guided by usual or alternative PAP monitoring. Additional validation is needed from larger comparison studies (ECRI, 2024).

Additional studies evaluating the Cordella system include a small, multicenter case series (Dauw et al., 2022) and the nonrandomized SIRONA first-in-human study (Mullens et al., 2020). These studies are included in the ECRI (2024) report cited in this policy.

Studies using an implantable wireless PAP sensor to manage individuals with a left ventricular assist device (LVAD) are limited to small observational studies and case series (Thohan et al., 2023; Morris et al., 2022; Veenis et al., 2021; Tschöpe et al., 2018; Feldman et al., 2018). Preliminary results are promising, but further investigation in larger, prospective studies is needed.

Cowie et al. (2022) conducted a prospective, open-label, unblinded, single-arm, post-market study to evaluate the safety, efficacy, and feasibility of hemodynamic-guided HF management using an implanted sensor in the pulmonary artery of patients with NYHA Class III HF. The primary clinical endpoint compared annualized HF hospitalization rates after one year of hemodynamic-guided management vs. the year prior to sensor implantation and a previous HF hospitalization. Freedom from device/system-related complications and pressure sensor failure after two years were the primary safety endpoints. At baseline, all participants (n = 100) were in NYHA Class III HF, 70% were male, mean age was 69 ±12 years, and 39% had an etiology of ischemic cardiomyopathy. The annualized HF hospitalization rate after 12 months was 82% lower than the previous 12 months (0.27 vs. 1.52 events/patient-year, respectively, $p < 0.0001$). Freedom from device/system-related complications and pressure sensor failure at two years was 100% and 99%, respectively. The authors concluded that remote hemodynamic guided HF management that uses frequent assessment of PAP was safe and significantly reduced hospitalization in high-risk patients. Limitations include lack of a contemporary control group, small study size, and manufacturer funding.

An ECRI report concluded that evidence shows that CardioMEMS monitoring is safe and reduces hospitalizations in patients with moderate HF. However, reports of electric and fire hazard related to CardioMEMS interrogation devices raise safety concerns. Until these are addressed, physicians and patients should exercise caution. The current evidence is too limited in quality and quantity to determine how CardioMEMS affects mortality, physical function, and quality of life (QOL). The data is also insufficient to determine whether CardioMEMS benefits patients with mild HF and how CardioMEMS compares with other HF monitoring systems (ECRI, 2022).

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A Hayes technology assessment concluded that low-quality evidence suggests the use of CardioMEMS implantable hemodynamic monitor as an adjunct to standard care for managing adult patients with symptomatic NYHA class III HF improves health outcomes by leading to a consistent reduction of hospitalization risk and mean PAP values with some improvements in cardiac function. However, data on the effects of the device on mortality and health related QOL were inconclusive due to inconsistent findings, short duration of follow-up and variability in reported outcome measures. This uncertainty remains. The device appears to be safe and poses no major risks. Additional large well-designed comparative studies that conduct long-term assessments extending beyond 1-year post implantation are needed (Hayes, 2022; updated 2024).

Thakker et al. (2022) performed a systematic review and meta-analysis evaluating the role of remote PAP monitoring devices in patients with NYHA class III or greater HF. Both randomized and non-randomized studies were included. Five trials identifying baseline characteristics were included in the systematic review and two trials evaluating hospitalization rates were included in the meta-analysis. Baseline characteristics included an average age of 64.6 years, male predominance, mean BMI of 29.6, predominance of HFrEF, hypertension the most prevalent comorbidity and a mean PAP of 27.2 mm Hg. In the meta-analysis, there were 401 hospital admissions, with 168 in the treatment group and 233 in the control group. The follow-up periods ranged from 90 days to 12 months. There was a total of 64 adverse events, mostly non-serious. Patients who underwent remote pulmonary artery monitoring were less likely to be hospitalized compared with patients who did not (Odds Ratio: 0.52; 95% Confidence Interval 0.39, 0.69). Study limitations include varied study periods across trials and lack of randomization in some trials as well as lack of analysis of possible biases in the reviewed studies. (The CHAMPION study noted below is included in the review).

Joint clinical practice guidelines from the American Heart Association, American College of Cardiology and the Heart Failure Society of America on the management of HF make the following recommendations regarding remote monitoring, and note that further study of these devices is needed before they can be recommended for routine clinical care (Heidenreich et al., 2022):

- In selected adult patients with NYHA class III HF and history of a HF hospitalization in the past year or elevated natriuretic peptide levels, on maximally tolerated stable doses of guideline-directed medical therapy (GDMT) with optimal device therapy, the usefulness of wireless monitoring of PAP by an implanted hemodynamic monitor to reduce the risk of subsequent HF hospitalizations is uncertain.
- In patients with NYHA class III HF with a HF hospitalization within the previous year, wireless monitoring of the PAP by an implanted hemodynamic monitor provides uncertain value.

A National Institute for Health and Care Excellence (NICE) report concluded that evidence on the safety and efficacy of percutaneous implantation of PAP sensors for monitoring treatment of chronic HF is adequate to support using this procedure provided that standard arrangements are in place for clinical governance, consent and audit (NICE, 2021).

European Society of Cardiology guidelines found little evidence that device monitoring reduces admissions for HF or mortality. While non-invasive home telemonitoring may be considered for patients with HF in order to reduce the risk of recurrent HF hospitalizations and death, further evidence on management guided by implanted systems is awaited. Recommendations state that monitoring of PAP using a wireless hemodynamic monitoring system may be considered in symptomatic patients with HF in order to improve clinical outcomes (Class IIb; Level of evidence B) (McDonagh et al., 2022). A 2023 Focused Update did not address implanted monitoring systems (McDonagh et al., 2023). A 2025 consensus-based statement noted that implanted PAP-guided management with CardioMEMS may be appropriate in patients with NYHA class II or III HF, who have had one or more HF-related events in the previous year and/or elevated natriuretic peptides. Standardization of the procedure is key to deliver remote PAP-guided management safely and effectively in the real world. Additional studies are needed to further explore the usefulness of this strategy, refine its management, and test novel devices for hemodynamic monitoring (Bayes-Genis et al., 2025).

PROACTIVE-HF

PROACTIVE-HF, originally approved as a prospective, randomized, controlled, single-blind, multicenter trial, evaluated the safety and effectiveness of the Cordella PAP system in individuals with NYHA class III HF with prior HF hospitalization and/or elevated natriuretic peptides. After 160 patients had been randomized 1:1 to the treatment arm (n = 88) or the control arm (n = 72), the design was changed to a single-arm, open-label trial with blinded endpoint assessment and prespecified safety and effectiveness endpoints defined from previous hemodynamic monitoring trials (Guichard et al., 2023). The primary effectiveness endpoint was the 6-month incidence of HF hospitalization or all-cause mortality compared with a performance goal in the modified intention-to-treat population which included all patients in the former treatment arm (n = 88) and single arm (n = 368) who received an implant. The primary safety endpoints were 6-month freedom from device or system-related complications and 6-month freedom from pressure sensor failure in the modified intention-to-treat population. Results showed reductions in PAP as well as improved quality of life and functional status. Overall, the 6-month incidence of HF hospitalization and mortality was low compared to the performance goal across all

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subgroups with PAP-guided HF management. Freedom from device- or system-related complications was 99.2% and freedom from sensor failure was 99.8% through 6 months. Follow-up will continue for five years. The authors concluded that remote management of seated PAP is safe and results in a low rate of HF hospitalizations and mortality. Limitations include the open-label, single-arm design, lack of a concurrent control group, and short-term follow-up (Guichard et al., 2024). Clinicaltrials.gov. NCT04089059.

SIRONA 2

Clinicaltrials.gov. NCT04012944.

Sharif et al. (2022) reported 90-day primary endpoint results from the prospective, multicenter, open-label, single-arm SIRONA 2 trial (n = 70) evaluating the safety and efficacy of the Cordella PAP sensor in patients with NYHA class III HF. The primary efficacy endpoint was the accuracy of PAP measurements compared with the gold standard Swan-Ganz catheter. The primary safety endpoint was freedom from adverse events through 30 days post-implant. The investigators reported that PAP measurements were accurate and equivalent to the gold standard. They also found the device was safe with a low rate of device and system-related complications and no pressure sensor failures.

At 12-months, Sharif et al. (2024) reported additional results from the SIRONA 2 trial that included prespecified secondary endpoints of safety and accuracy of the Cordella PAP sensor, along with HF-related hospitalizations and mortality, HF symptoms, functional capacity, quality of life, and patient compliance. The safety profile was maintained, with no sensor failures and no additional device and system-related complications. PAP measurements were accurate, with good agreement with the gold standard. Secondary endpoints showed significant improvements in patient quality of life, NYHA classification, HF-related hospitalization or death event rates, and high patient compliance. The findings are limited by lack of comparison group.

MONITOR-HF

The MONITOR-HF study (Brugts et al., 2023), a prospective, multicenter, open-label, randomized controlled trial, investigated the effectiveness of remote hemodynamic monitoring on QOL and HF hospitalizations compared to contemporary standard of care in the Netherlands. This was the first randomized controlled trial to investigate the benefits of using a PAP sensor (CardioMEMS) in a European healthcare system. A total of 348 patients were randomly assigned (1:1) to HF management with guideline-directed medical therapy (GDMT) and diuretics (control group; n = 172) or to HF management with GDMT and diuretics with the addition of hemodynamic monitoring using a PAP sensor (CardioMEMS-HF group; n = 176). Eligible patients had chronic HF, any ejection fraction, NYHA class III symptoms and a previous HF hospitalization or urgent visit requiring intravenous diuretics in the past 12 months. All patients were scheduled to be seen by their clinician at three months and six months, and every six months thereafter. All patients were followed for at least 12 months. The average duration of follow-up was 18 months, and the maximum was 48 months. The primary endpoint was the change in QOL measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 12 months. The secondary endpoint was the number of HF hospitalizations and/or urgent visits requiring intravenous diuretics during follow-up. The primary safety endpoints were device-related or system-related complications and sensor failures. All analyses were by intention-to-treat. The mean change in KCCQ overall summary scores between baseline and 12 months among patients in the CardioMEMS-HF group was +7.05 (95% CI 2.77 to 11.33; p = 0.0014), compared with –0.08 points among those in the standard care group (–3.76 to 3.60; p = 0.97). During a mean follow-up of 1.8 years there were 117 HF hospitalizations or urgent visits in the monitoring group and 212 in the control group. The freedom of device-related or system-related complications and sensor failure were 97.7% and 98.8%, respectively. This study is limited by its open-label design.

GUIDE-HF

The GUIDE-HF trial (Lindenfeld et al., 2021) evaluated whether hemodynamic-guided management using remote PAP monitoring could reduce HF events and mortality in patients with HF across the spectrum of symptom severity, including patients with elevated natriuretic peptides but without a recent HF hospitalization. The randomized arm of 1000 patients was a multicenter, single-blind study at 118 centers in the U.S. and Canada. Following successful implantation of a PAP monitor, patients with all ejection fractions, NYHA class II–IV HF, and either a recent HF-related hospitalization or elevated natriuretic peptides were randomly assigned (1:1) to either hemodynamic-guided HF management based on PAP (n = 497) or standard of care (n = 503). The primary endpoint was a composite of all-cause mortality and total HF events (HF-related hospitalizations and urgent HF-related hospital visits) at 12 months assessed in all randomly assigned patients. Safety was assessed in all patients. There were 253 primary endpoint events (0·563 per patient-year) in the treatment group and 289 (0·640 per patient-year) in the control group [hazard ratio (HR) 0·88, 95% CI 0·74–1·05; p = 0·16]. The overall study analysis did not show a benefit of hemodynamic-guided management of HF on the primary outcome of mortality and HF events compared with the control group. However, a pre-COVID-19 impact analysis showed a possible benefit for the primary endpoint, driven by a reduction in HF hospitalizations. The authors reported no apparent

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benefit on all-cause mortality at 12 months. Study limitations include single blinding which has the potential to introduce investigator bias during communication with patients, the 12-month duration of follow-up and the effects of the COVID-19 pandemic in limiting data collection. The trial also includes an ongoing, single-arm, observational study (n = 2600). Clinicaltrials.gov. NCT03387813.

CHAMPION

The multicenter, pivotal CHAMPION trial evaluated patients with NYHA class III HF and a previous hospital admission for HF. Patients were randomly assigned to management with a CardioMEMS system (treatment group) or to a control group. In the treatment group, clinicians used daily measurement of PAP in addition to standard of care versus standard of care alone in the control group. The primary efficacy endpoint was the rate of HF-related hospitalizations at six months. The safety endpoints assessed at six months were freedom from device-related or system-related complications and freedom from pressure-sensor failures. All analyses were by intention to treat. At six months, 83 HF-related hospitalizations were reported in the treatment group (n = 270) compared with 120 in the control group [n = 280; rate 0.31 versus 0.44, hazard ratio (HR) 0.70, 95% CI 0.60-0.84, p < 0·0001]. At the end of six months, clinicians continued to receive PAP information for an additional 13 months. During the entire follow-up [mean 15 months (SD 7)], the treatment group had a 39% reduction in HF-related hospitalization compared with the control group (153 versus 253, HR 0.64, 95% CI 0.55-0.75; p < 0·0001). Eight participants had device-related complications and overall freedom from device-related complications was 98.6% (97.3-99.4) compared with a prespecified performance criterion of 80% (p < 0·0001); and overall freedom from pressure-sensor failures was 100% (99.3-100.0). The study design was not powered beyond the primary 6-month outcomes. Additional limitations include lack of analysis on cardiac-specific mortality and single blinding which has the potential to introduce investigator bias during communication with patients. Participants in the control group were allowed to crossover to the treatment group and receive CardioMEMS at 18 months. In this group, the authors reported sustained efficacy of hemodynamic-guided management of HF to reduce hospital admissions, both during a randomized clinical trial setting, as well as in a follow-up setting more typical of clinical practice (Abraham et al., 2011; Abraham et al., 2016). Clinicaltrials.gov. NCT00531661.

PASSPORT-HF

PASSPORT-HF is an ongoing prospective, randomized, multicenter trial evaluating the effects of a hemodynamic-guided, HF nurse-led care approach using the CardioMEMS HF-System. Clinicaltrials.gov. NCT04398654.

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Code	Description
53451	Periurethral transperineal adjustable balloon continence device; bilateral insertion, including cystourethroscopy and imaging guidance
53452	Periurethral transperineal adjustable balloon continence device; unilateral insertion, including cystourethroscopy and imaging guidance
53453	Periurethral transperineal adjustable balloon continence device; removal, each balloon
53454	Periurethral transperineal adjustable balloon continence device; percutaneous adjustment of balloon(s) fluid volume

Transperineal periurethral balloon continence devices (e.g., ProAct™) are unproven and not medically necessary for the treatment of urinary incontinence due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

ProACT (Uromedica, Inc.) is a minimally invasive, adjustable continence therapy. ProACT received U.S. Food & Drug Administration (FDA) premarket approval on November 24, 2015 (P130018). ProACT is indicated for the treatment of adult men who have stress urinary incontinence (SUI) arising from intrinsic sphincter deficiency (ISD) of at least 12 months duration following radical prostatectomy (RP) or transurethral resection of the prostate (TURP) and who have failed to respond adequately to conservative therapy (Uromedica, Inc., 2025).

ACT® (Uromedica, Inc.) is another minimally invasive, adjustable continence therapy. ACT received FDA Investigational Device Exemption and may only be used as part of a clinical research study for the collection of safety and effectiveness data. ACT is under study for the treatment of female patients who have SUI resulting from ISD (Uromedica, Inc., 2025).

Paillusson et al. (2025) described ProACT implantation using flexible cystoscopic guidance and reported on long-term outcomes. The retrospective study included 196 patients who underwent ProACT implantation for SUI after RP at a single center. The median patient age was 68 (64-72) years. Thirty-six (18%) patients previously underwent radiotherapy and 46 (24%) patients previously underwent SUI surgery. The primary endpoint was efficacy at the last follow-up visit. Efficacy was assessed at 6 months, 1 year, 2 years, and 5 years. Efficacy was defined using a composite criterion combining

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subjective patient impression of improvement (PII) and objective results (daily pad number). Success was defined as ≤ 1 daily pad associated with a numeral rating scale (NRS) ≥ 80%. Improvement was defined as a decrease of ≥ 50% in the number of daily pads associated with an NRS ≥ 50%. All other cases were considered failures. The median interquartile range (IQR) follow-up time was 63 (25-109) months. The study results revealed 125 (64%) patients still had their balloon in place at the last follow-up visit. Eighty-seven (44%) patients still had their initial balloon in place. Success and improvement rates were 62% and 17%, respectively. The median PII was 80/100, with a median of one pad per day. In the overall population, success and improvement rates at the last follow-up visit were 41% and 13%, respectively. The median PII was 70/100, with a median of one pad per day, versus two pads per day (PPD) before ProACT implantation. The perioperative complication rate was 5%, primarily bladder injury and acute urinary retention. During follow-up, 82 (42%) patients experienced at least one complication, most commonly device deflation (28%), followed by migration (10%), and infection (5%). Twenty-eight percent of patients underwent at least one balloon replacement. Definitive explantation was performed in 71 patients (36%), 23 (12%) because of complications and 48 (25%) because of failure. Of these patients, 68 (35%) underwent secondary implantation of an artificial urinary sphincter (AUS). The authors concluded ProACT implantation using flexible cystoscopic guidance appeared to be an effective and safe long-term procedure for men with SUI after RP. Limitations of the study include the single-center, single-arm retrospective design and the absence of data from 23 (18.4%) patients lost to follow-up at 2 years and 53 (42.4%) patients lost to follow-up 5 years.

European Association of Urology (EAU) guidelines for non-neurogenic male lower urinary tract symptoms (LUTS) (2025a) state: “The non-circumferential compression device (ProACT®) is effective for treatment of PPI [post-prostatectomy incontinence] SUI; however, it is associated with a high failure and complication rate leading to frequent explantation and particularly after pelvic radiation therapy.” EAU recommends:

- “Implantation of AUS or ProACT© for men should only be offered in expert centres.” (Weak recommendation)
- “Warn men receiving AUS or ProACT© that, although cure can be achieved there is a high risk of complications, mechanical failure, and the need for explantation.” (Strong recommendation)
- “Do not offer non-circumferential compression device (ProACT©) to men who have had pelvic radiotherapy.” (Weak recommendation)

EAU guidelines for the management of non-neurogenic female LUTS (2025b) state: “Implantation of the adjustable compression therapy (ACT®) device may improve uncomplicated SUI.” However: “Complications, mechanical failure and device explantation often occur with both the artificial sphincter and the ACT®.” EAU recommends:

- “Do not offer mechanical devices to women with mild-to-moderate stress urinary incontinence unless it is part of a well-regulated and closely monitored research study.” (Strong recommendation)
- “Inform women receiving artificial urinary sphincter or adjustable compression device (ACT®) that, although cure is possible, even in expert centres there is a high risk of complications, mechanical failure, or a need for explantation.” (Strong recommendation)

American Urological Association/Society of Genitourinary Reconstructive Surgeons/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction guidelines for incontinence after prostate treatment state:

- “Clinicians may offer adjustable balloon devices to non-radiated patients with mild to severe stress urinary incontinence after prostate treatment. (Conditional Recommendation; Evidence Level: Grade C)”
- “In patients with stress urinary incontinence after primary, adjuvant, or salvage radiotherapy who are seeking surgical management, clinicians should offer AUS over male slings or adjustable balloons. (Moderate Recommendation; Evidence Level: Grade C)” (Breyer et al., 2024)

International Continence Society (ICS) guidelines for PPI state: “Periurethral balloons are a feasible minimally invasive option for treatment of bothersome PPI. However, high complication rates have been reported [Level of evidence (LE) 3-4; grade of recommendation (GR) C]. Heterogeneous data suggest that periurethral balloons were less effective than an adjustable TO [transobturator] sling (LE 3, GR C).” Additionally, “Due to the paucity of data, no definitive recommendation can be made on ProACT for SUI after surgical treatment of benign prostatic obstruction” (ICS, 2023).

Hayes completed a health technology assessment of ProACT for the treatment of post-prostate surgery induced urinary incontinence in adult men unresponsive after 6 to 12 months of more conservative treatment. Overall, the body of evidence was considered to be low quality, lacking controls, and primarily consisting of single-arm observational studies. These studies show moderately consistent evidence that treatment with ProACT resulted in clinical success. However, other outcomes were imprecise and inconsistent across studies. Evidence from a single comparative study was insufficient to determine whether ProACT was better, worse, or the same as current treatment alternatives. The available evidence regarding potential harms suggested that ProACT may be associated with a moderate risk of complications, including revision and explanation. However, there was insufficient evidence to determine the relative safety of ProACT compared with other available treatments (Hayes, 2022; annual review, 2023).

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Guérin et al. (2023) conducted a systematic review of studies reporting on ACT outcomes in female patients with SUI due to ISD. Thirteen retrospective or prospective case series were included in the review. No randomized clinical trials (RCTs) were available for review. The number of individuals in each study ranged from 18 to 277. Age ranged from 62 to 83 years. The study results revealed individuals were discharged the day after ACT implantation in 86.5% of cases. However, the rate of intraoperative complications ranged from 3.5% to 25%. The rate of postoperative complications ranged from 11% to 56%. ACT explantation was required in 6% to 42% of cases. Reimplantation occurred in 13.8% to 63% of cases. The continence rate ranged from 13.5% to 68%. (The mean follow-up period ranged from 10.5 to 72 months.) Between 16% and 83% of individuals declared themselves improved. The procedure was considered a failure for 8% to 42.3% of individuals. The mean PPD varied from 0.41 to 2.2. Between 39.1% and 52% of individuals had less than 2 grams on provocative pad weight testing. Patient Global Impression of Improvement (PGII) scores, when available, showed that 12% to 64% of individuals declared themselves to be very much improved. Full continence was reported in 13.5% of individuals. An improvement of more than 80% in 25% of individuals was also noted. At the last follow-up available, the failure rate was 42.3%. The authors concluded ACT can be considered as an option to treat SUI due to ISD in females. ACT resulted in symptomatic improvement for two-thirds of individuals. However, the complication rate was high. Only studies with a poor level of evidence were available to support the use of ACT. Well-designed, prospective studies, and long-term follow-up data are needed. Other limitations of this systematic review include heterogeneous definitions of continence and small number of individuals, and lack of comparison groups in the included studies.

de Guerry et al. (2023) published a multicenter, retrospective study assessing the effectiveness, safety and risk factors of failure and complications associated with ACT as a treatment for female SUI. The study included 281 women implanted with ACT at five centers. The primary endpoint was effectiveness (“success,” “improvement,” or “failure”) 1 year after ACT implantation. Effectiveness was defined using a composite of objective PPD count and a subjective PII using an NRS. Secondary endpoints included safety and risk factors for failure and postoperative surgical complication. One year after implantation, 37.0% of patients reported “success,” 33.5% “improvement,” and 29.5% “failure.” The median PPD use was 1.0 and the median NRS was rated at 7/10. During the follow-up period, 26.7% of patients underwent uni- or bilateral explantation secondary to lack of efficacy (2.7%) or postoperative surgical complication (97.3%). Thirty-five patients underwent uni- or bilateral reimplantation. Of these, 42.1% reported “success” and 26.3% reported “improvement.” Intraoperative surgical complications occurred in 4.6% of patients. Early (< 90 days) and late (≥ 90 days) postoperative surgical complications were reported in 12.5% and 26.7% of patients, respectively. Intraoperative surgical complications were all classified as Grade 0 or Grade 1 according to EAU Intraoperative Adverse Incident Classification. Most early surgical complications were classified as minor according to Dindo-Clavien classification. Of patients that presented with late postoperative surgical complications, 22.8% underwent explantation without associated sequalae. The authors concluded that despite the frequent, but easily manageable and sequelae-free complications, the minimal invasiveness and short-term effectiveness of ACT suggested its use as a treatment for female SUI. Limitations of the study include lack of comparison group, the retrospective design, short follow-up duration, and use of a composite endpoint that included a subjective NRS of undefined validity.

American Urological Association/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction guidelines for the surgical treatment of female SUI do not address adjustable continence therapy (Kobashi et al., 2023).

Tricard et al. (2023) performed a systematic review and meta-analysis to assess the efficacy and safety of ProACT in treating male individuals with post-RP SUI. The systematic review included 18 mostly uncontrolled studies involving 1,570 individuals. Outcomes of interest included pads or pad weight per day, quality of life (QOL), and safety outcomes. The mean follow-up was 34.7 months (median 38.5; range: 1-128). An average of 60.7% and 40.4% of individuals experienced mild-to-moderate and severe incontinence, respectively. The overall dryness rate was 55.1% using a definition of 0-1 PPD. The mean dryness rate was 53%. The mean overall complication rate was 31.2%, including an explantation rate of 26.5% and a reoperation rate of 22.7%. The authors concluded that implantation of ProACT provided medium outcomes (53%) and an important complication rate (31.2%). Additionally, irradiation is a negative predictive factor for incontinence. A limitation of the systematic review was the heterogeneous methodological quality across the included studies and lack of comparative analyses with other approaches to incontinence.

ECRI performed a clinical evidence assessment that focused on the safety and effectiveness of ProACT and how it compared with AUSs or other adjustable continence balloons (ACBs) for male SUI. One systematic review with meta-analysis that included 19 uncontrolled studies and 1,264 individuals was assessed. Evidence from the uncontrolled studies synthesized in the meta-analysis supported limited conclusions on the safety and effectiveness of ProACT. The meta-analysis was determined to have sufficient consistency, statistical precision, and magnitude to show that ProACT partially or completely relieved SUI in about 82% of individuals. QOL also improved by two-thirds from baseline. However, complications leading to revision or explantation occurred in about 22% of individuals. ECRI noted that the studies included in the meta-analysis were rated as low to good quality. There was significant heterogeneity in demographics and

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outcome measures. Multicenter controlled trials that directly compare ProACT with other ACBs, AUSs, and other treatment options for SUI are needed to bridge evidence gaps (ECRI, 2018; updated 2021).

Angulo et al. (2019) completed a systematic review and meta-analysis to assess the efficacy and safety of the Adjustable Transobturator Male Sling (ATOMS) compared to the ProACT for male SUI. The review included 41 nonrandomized studies of 3,059 individuals. Twenty-one studies reported on the ProACT, and 20 studies reported on the ATOMS. No study reported on comparisons between the ATOMS, ProACT, or any other device. The main etiology of incontinence was RP, but other causes were also included. The results showed higher dryness (68% versus 55%) and improvement rate (91% versus 80%) for ATOMS versus ProACT. Mean pad-count (-4 versus -2.5 PPD) and pad-test decrease (-425.7 versus -211.4 cc) were also significantly lower for ATOMS versus ProACT. Satisfaction was also higher for ATOMS (87% versus 56%). The explant rate was higher for ProACT (5% versus 24%). The complication rate for ProACT was also higher, but not determined to be statistically significant (17% versus 26%). The mean follow-up was 25.7 months, lower for ATOMS than ProACT (20.8 months versus 30.6 months). The rate of working devices favored ATOMS at 1-year (92% versus 76%), 2-years (85% versus 61%), and 3-years (81% versus 58%). Significant heterogeneity was evidenced, due to variable incontinence severity baseline, difficulties for a common reporting of complications, different number of adjustments, time of follow-up, and the absence of randomized studies. Despite the limitations that the studies available were exclusively descriptive and the follow-up limited, the authors concluded that literature findings confirm ATOMS is more efficacious, with higher patient satisfaction and better durability than ProACT to treat male SUI. (This study is included in the Hayes health technology assessment and ECRI clinical evidence assessment.) (The publications by Nash et al., 2019 and Venturino et al., 2015, which were previously cited in this policy, are included in this systematic review.)

Larson et al. (2019) performed a systematic review and meta-analysis to evaluate the efficacy of adjustable balloon devices or adjustable continence therapy (ProACT) for the treatment of male SUI. The review also investigated the safety profile and rates of adverse events associated with the implantation of adjustable balloon devices. Nineteen studies including 1,264 individuals and 4,517 patient-years of follow-up data (mean follow-up time 3.6 years) were reviewed. The results revealed individuals used 4.0 PPD prior to implantation and 1.1 PPD post-implantation. Post-implantation, 60.2% of individuals were considered "dry" and 81.9% of individuals were considered "dry" or improved greater than 50%. (The quantitative measurement for dryness was either no pads or less than one PPD.) QOL was determined to have improved significantly from baseline to post-implantation in all studies. The rate of intraoperative perforation of the bladder or urethra was 5.3%. The rate of infection was 2.2% and the rate of urinary retention was 1.5%. The estimated overall all-cause revision rate was 22.2% during a mean follow-up of 3.6 years. The authors concluded adjustable balloon devices are efficacious and safe for the treatment of male SUI. Additionally, due to the minimal invasiveness of the implant, adjustable balloon devices may be a first-line treatment for nonirradiated individuals with SUI who are not ideal candidates for an AUS. Limitations of the systematic review include that few studies recorded 24 hour pad weight. Daily pad usage was chosen for the analysis, as it was used in the majority of studies. However, the authors noted daily pad usage is not the best objective test to quantify SUI. The mean follow-up was 3.6 years. Only one study had a mean follow-up greater than 5 years. Though, many publications included individuals with longer follow -up, more long-term data is needed to better determine long-term efficacy results. The heterogeneity of the data was also noted as a limitation. The median follow-up ranges, the number of individuals per study, surgical technique, and management of complications were greatly variable across studies. The analysis also lacked detailed baseline characteristics that would have been helpful to determine indicators of device failure. (This study is included in the Hayes health technology assessment and the ECRI clinical evidence assessment).

The National Institute for Health and Care Excellence (NICE) published interventional procedures guidance for extraurethral (non-circumferential) retropubic adjustable compression devices for SUI in women. NICE recommended this procedure only be performed with special arrangements for clinical governance, consent and audit or research. The current evidence on the safety and efficacy of these devices was determined to be inadequate in both quantity and quality (NICE, 2017).

NICE also published clinical guideline for the management of LUTS in men. NICE recommended implanted adjustable compression devices for storage symptoms only as part of an RCT (NICE, 2010; updated 2015).

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Code	Description
55899	Unlisted procedure, male genital system (when used to report UroCuff)

The UroCuff test for diagnosing male lower urinary tract disorders is unproven and not medically necessary due to insufficient quality evidence of safety and/or efficacy.

Clinical Evidence

The UroCuff (SRS Medical, North Billerica, MA) is a diagnostic pressure-flow test for male lower urinary tract disorders (LUTS). Bladder pressure is measured noninvasively with a penile cuff (resembling a blood pressure cuff) instead of a catheter. Optionally, one or two surface EMG electrodes may be applied to the patient to monitor skeletal (sphincter or abdominal) muscle activity during testing. While it is not a replacement for cystometry (which still remains the gold standard), the UroCuff gives information on bladder contraction pressure and it can be used in some cases to confirm the likely diagnosis of obstruction, while avoiding the need for full cystometry. https://www.srsmedical.com/the-urocuff-test-patient-information/.

ECRI (2025) revised the 2023 Clinical Evidence Assessment regarding penile cuff testing (PCT) for diagnosing male bladder outlet obstruction (BOO) with lower urinary tract symptoms (LUTS). Although findings of diagnostic cohort studies reviewed in systematic reviews and synthesized in meta-analyses show that PCT has good diagnostic accuracy using invasive pressure flow study (PFS) as the reference standard. These studies reported that for PCT, which is used as a noninvasive alternative to invasive PFS, sensitivity was 87% relative to PFS, and specificity was 78%. The use of PCT-guided treatment in the current diagnostic pathway leads to equivalent or better outcomes than decisions guided by PFS or other noninvasive urodynamic tests cannot be determined because the evidence is too limited in quantity and bias is high. ECRI continue to conclude that the current evidence is limited and randomized controlled trials with follow-up periods are needed to evaluate the clinical utility.

In an Evidence Analysis Research Brief, Hayes (2024) summarized publications to discern whether there is adequate published peer-reviewed literature to evaluate the evidence related to SRS Medical's UroCuff Test for evaluation of lower urinary tract symptoms (LUTS). The literature search identified 5 abstracts assessing the UroCuff Test for evaluation of LUTS including three studies evaluating clinical validity and two studies evaluating clinical utility. This Brief found no case-

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control studies evaluating the UroCuff Test for the diagnosis of LUTS and no systematic reviews with or without meta-analysis. Additionally, no randomized controlled trials (RCTs) comparing treatment guided by the UroCuff Test compared with treatment guided by standard urodynamic studies found. Hayes' conclusions regarding clinical validity and clinical utility cannot be made within this Brief as drawing conclusions requires full-text review of the evidence. Additionally, a review of full-text clinical practice guidelines and position statements, guidance appears to confer no/unclear support for use of the UroCuff Test for evaluation of LUTS.

The UroCuff (trade name is registered as CT3000Pro), is considered by the FDA to be a Class II device and is 510(k) exempt. Further information can be found here using product code EXQ: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm?id=EXQ. (Accessed May 15, 2025)

In a guideline from the American Urological Association, (AUA 2021; updated 2023), Sandhu et al. reviewed treatment of lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH). Regarding pressure flow studies prior to intervention for these conditions, AUA states: "Pressure flow studies are the most complete means to determine the presence of BOO. Non-invasive tools provide useful information, but only pressure flow studies can document detrusor contractility, or lack thereof." The UroCuff device is not mentioned as a specific device for diagnostic testing. https://www.auanet.org/guidelines-and-quality/guidelines/benign-prostatic-hyperplasia-(bph)-guideline.

Khosla et al. (2022) (included in the ECRI report above), conducted a systematic review and meta-analysis on the use of the penile cuff test (PCT) to diagnose and manage bladder outlet obstruction (BOO). Their study included 17 articles (including the Matulewicz 2015 study previously included in this policy) with 1,335 participants in the qualitative review, with five of these studies with 448 participants included in the meta-analysis. The studies included 11 comparative studies, three prospective cohort studies, two inter-observer comparisons and one comparative and prospective cohort study. The comparison studies used PCT to diagnose BOO and compared it to an invasive pressure flow study (PFS) as the gold standard, while the cohort studies investigated how PCT parameters changed following treatment and the surgical success rates of patients selected for procedures (transurethral resection of the prostate, holmium laser enucleation of the prostate, or both) using PCT. The authors reported that five of the studies that evaluated the penile cuff test procedure reported a 66 to 80% surgical success rate on obstructed patients, although the success rate was defined differently by the studies, so the success rate assessment was not completely homogenous. They also reported that the meta-analysis showed that the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 0.85, 0.78, 0.74, and 0.87, respectively. The authors stated that substantial heterogeneity was noted for sensitivity, specificity, PPV and NPV. The quality of the studies included two low, six moderate and nine high-quality studies based on the authors' application of the GRADE criteria. Limitations included substantial heterogeneity regarding the diagnostic factors, lacking data for detailed demographic information on patient population, the variability in methodological design and criteria used to diagnose BOO across studies, the small sample size available for the meta-analysis, and the small sample sizes in several of the studies included in this review. The authors concluded that the PCT performs sufficiently in diagnosing and managing BOO; however, due to the variability in obstruction criteria assessment, they recommended additional studies to compare diagnostic criteria.

Cheng et al. (2022 included in the ECRI report above), conducted a meta-analysis to determine the diagnostic value of non-invasive methods for diagnosing BOO in men with LUTS by assessing sensitivity (SSY), specificity (SPY), diagnostic odds ratio (DOR), and area under curve (AUC). The authors reviewed 51 non-randomized trials with 7,897 patients from 21 countries that compared invasive pressure flow study (PFS) of urodynamic study as the gold standard diagnostic test to the following non-invasive methods for diagnosing BOO in men with LUTS: the PCT, near-infrared spectrum (NIRS), ultrasonography of post-voided residual (PVR), intravesical prostatic protrusion (IPP), detrusor wall thickness (DWT), bladder wall thickness (BWT), resistive index (RI), prostate volume (PV), and free uroflowmetry. The studies included 22 prospective studies, two retrospective studies, 14 studies blinded studies, 13 non-blinded studies, and the remaining studies did not describe their specific design. The authors selected the most commonly used threshold values for each non-invasive test to perform further analysis and found that DWT (8 studies, n = 1003) had the highest pooled specificity, diagnostic odds ratio and area under curve for diagnosing BOO in men across these index tests reported and that the PCT (10 studies, n = 764) had the second-best diagnostic accuracy. Limitations noted by the authors included the high levels of heterogeneity in the included studies for each type of index test, the lack of any available RCTs, the heterogeneity of the study designs, varying cut-offs and definitions for BOO and the inclusion of English-only written studies.

In a 2020 observational cross-sectional study, Kaplan et al. reviewed the results of UroCuff testing on 50,680 men with lower urinary tract symptoms secondary to benign prostatic hyperplasia (BPH) to evaluate voiding characteristics and quantify changes in urodynamic parameters with age. Data was gathered from 103 urology practices across the country. Inclusion criteria required initial pressure flow study with subsequent tests excluded, voided volume 50 ml or greater, at least 1 cuff inflation and patient over age 20. Pressure, maximum flow rate, flow rate efficiency (maximum flow rate/Pcuff),

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voided volume and post-void residual were plotted by age and stratified by Newcastle Noninvasive Nomogram category. This study showed that symptomatic patients enter urological practices at different urodynamic stages of bladder function and outlet obstruction, that Pcuff, maximum flow rate, voided volume, flow rate efficiency, and post-void residual deteriorate with age, and that UroCuff is a sensitive evaluation of bladder performance. This evidence is limited by population heterogeneity. The authors acknowledge that even if several noninvasive assessments of bladder outlet obstruction have shown promising results, invasive urodynamics remain the gold standard. The main limitation of the study is the lack of data about diagnosis, symptoms and treatment outcomes. Furthermore, the results cannot be extended to a general population considering that study included exclusively men with LUTS enrolled in urological outpatient visits. Further studies comparing UroCuff with validated predictive models as a control tool are needed to better define the clinical efficacy of this new test.

A systematic review by Malde et al. (2017) evaluated the performance of noninvasive tests in diagnosing BOO in men with LUTS. Of 2774 potentially relevant reports, 42 were eligible (n = 4444 patients). The review revealed that according to the literature, a number of noninvasive tests have high sensitivity and specificity in diagnosing BOO in men. Although the quality of evidence was typically moderate across the literature with a low overall risk of bias, the available evidence is limited by heterogeneity. While several tests have shown promising results regarding noninvasive assessment of BOO, invasive urodynamics remain the gold standard. The researchers concluded that noninvasive alternatives to standard urodynamic testing appear to be promising but were not equally accurate. Further research is needed before these tests are routinely used in place of urodynamics.

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SRS Medical. North Billerica, MA. The UroCuff Test, Patient Information.

Code	Description
61715	Magnetic resonance image guided high intensity focused ultrasound (MRgFUS), stereotactic ablation of target, intracranial, including stereotactic navigation and frame placement, when performed

Magnetic resonance image guided high intensity focused ultrasound (MRgFUS) intracranial stereotactic ablation is unproven and not medically necessary for treating movement disorders due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

MRgFUS (ExAblate®; InSightec Ltd.) is a non-invasive treatment that integrates magnetic resonance imaging (MRI) with high-intensity focused ultrasound for the precise planning and control of the localized delivery of high-frequency sound waves to destroy lesions in tissue or bone. On July 11, 2016, the Food and Drug Administration (FDA) approved ExAblate Neuro for individuals with essential tremor (ET) who have not responded to medication. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P150038. (Accessed April 24, 2025)

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In 2022, the FDA approved a label change for indications for the use of the device in idiopathic ET for those with medication refractory tremors. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P150038S022. (Accessed April 24, 2025)

Despite FDA approval, findings from ongoing clinical trials must be completed to determine whether any populations may benefit from this therapy.

Cesarano et al. (2024) conducted a systematic review to evaluate the use of MRgFUS for treating bilateral ET and Parkinson's disease (PD)-related tremor, focusing on its effectiveness and associated risks. The review included nine studies, seven on ET and two on PD. The most common adverse events were dysarthria, ataxia, and gait disturbance. The authors concluded that bilateral MRgFUS could be a promising clinical option for individuals with ET and PD whose tremor is resistant to pharmacological therapy. Studies indicate that bilateral MRgFUS often produces better outcomes than unilateral treatment, particularly in terms of quality-of-life improvements, with additional benefits observed after the second procedure. Reported limitations included the heterogeneity of the studies, which makes robust comparisons and generalizations difficult. The authors noted careful attention to patient selection criteria is essential, ideally identifying those who did not experience adverse events after the first sonification session and who maintained good neuropsychological performance in the following months. High-quality evidence is necessary to achieve higher levels of evidence and to standardize the protocols used.

Essential Tremor

Mortezaei et al. (2024) conducted a systematic review and meta-analysis to assess the feasibility, long-term safety, and efficacy of unilateral MRgFUS for treating ET. The review included 43 studies with a total of 1818 ET individuals who underwent MRgFUS. The most common adverse events were neurological and balance symptoms (26.4%), such as vertigo, ataxia, and dysarthria, followed by sensory symptoms (22.1%) like headache, numbness, and paresthesias. These complications likely result from thermal ablation effects on cerebellar outflow pathways targeted during the procedure. Although generally transient, the authors emphasize the importance of careful patient selection and procedural planning to minimize the risk of persistent deficits. Additionally, long-term paresthesia was a common residual symptom observed five years post-treatment, indicating the need for further investigation into the chronicity of certain adverse events and their correlation with suboptimal lesion targeting or excessive thermal dose. The authors concluded that MRgFUS is effective in reducing tremor severity and improving the quality of life for ET patients, suggesting it could become a first-line treatment option for those with medication-refractory ET. However, they note that current evidence supporting MRgFUS for ET is limited by small sample sizes and heterogeneity in outcome reporting. Future research should aim to refine patient selection criteria and optimize procedural protocols to maximize the benefits of MRgFUS. Long-term follow-up studies are also needed to evaluate the sustainability of tremor relief and monitor for late adverse events. Limitations of the review include potential publication bias and the inherent heterogeneity of included studies, particularly regarding patient populations and treatment protocols, which may influence results. Additionally, the lack of direct comparisons with other interventions was noted as a limitation. Elias et al. (2016) was included in this systematic review.

In 2024, Hayes conducted a Health Technology Assessment on Magnetic Resonance-Guided Focused Ultrasound Unilateral Thalamotomy for ET. The assessment uncovered an overall low-quality body of evidence suggesting that MRgFUS VIM thalamotomy appears safe and has improved symptoms, disability, and quality of life (QoL) over the short term. The assessment concludes that additional studies are needed to confirm the safety and effectiveness of unilateral MRgFUS compared to current competing technologies, compare the efficacy of alternative anatomical targets for ET, and explore the potential for retreatment to address relapse in tremor symptoms (Elias et al., 2016, and Cosgrove et al., 2022 are included in this assessment).

In a report from the Quality Standards Subcommittee of the American Academy of Neurology, the evidence-based guidelines for the treatment of essential tremors were updated. Zesiewicz et al., 2011; reaffirmed 2022 offered conclusions and recommendations for the use of propranolol, primidone (Level A, established as effective); alprazolam, atenolol, gabapentin (monotherapy), sotalol, topiramate (Level B, probably effective); nadolol, nimodipine, clonazepam, botulinum toxin A, deep brain stimulation, thalamotomy (Level C, possibly effective); and gamma knife thalamotomy (Level U, insufficient evidence) which are unchanged from the previous guideline.

Changes to conclusions and recommendations from the previous guideline (2005) include the following:

- Levetiracetam and 3,4-diaminopyridine probably do not reduce limb tremor in ET and should not be considered (Level B).
- Flunarizine possibly has no effect in treating limb tremors in ET and may not be considered (Level C).
- There is insufficient evidence to support or refute the use of pregabalin, zonisamide, or clozapine as a treatment for ET (Level U).

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In 2022, Cosgrove and colleagues evaluated MRgFUS thalamotomy for ET at four- and five-years post treatment and the long-term safety and efficacy in a prospective, controlled, multicenter clinical trial. At four years, 40 individuals completed follow-ups, and 45 completed the follow-ups at five years. Improvements were seen in the Clinical Rating Scale for Tremor (CRST) by 73.3% and 73.1% from baseline at 48 and 60 months after treatment, in that order. Improvements were also seen in the combined hand tremor/motor scores demonstrating 49.5% and 40.4% at 48 and 60 months, respectively. Improvements in functional disability and Quality of Life in Essential Tremor (QUEST) scores. The authors concluded that unilateral MRgFUS thalamotomy demonstrated sustained significant improvement overall at the five-year follow-up. The loss of follow-up and the small sample size are limiting factors in this trial. Investigation of bilateral staged MRgFUS thalamotomy for ET is necessary for future conclusions on this approach's safety, efficacy, and feasibility.

Giordano et al. (2020) performed a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement to compare unilateral MRgFUS thalamotomy to unilateral and bilateral deep brain stimulation (DBS) for treating ET in terms of tremor severity and QoL improvement. Forty-five eligible articles, published between 1990 and 2019, were retrieved. One thousand two hundred and two participants were treated with DBS and 477 were treated with MRgFUS thalamotomy. Postoperative tremor improvement was greater following DBS than MRgFUS thalamotomy ($p < 0.001$). A subgroup analysis was carried out stratifying by treatment laterality: bilateral DBS was significantly superior to both MRgFUS and unilateral DBS ($p < 0.001$), but no significant difference was recorded between MRgFUS and unilateral DBS ($p < 0.198$). Postoperative QoL improvement was significantly greater following MRgFUS thalamotomy than DBS ($p < 0.001$). Complications were differently distributed among the two groups ($p < 0.001$). Persistent complications were significantly more common in the MRgFUS group ($p = 0.042$). While bilateral DBS proves superior to unilateral MRgFUS thalamotomy in the treatment of ET, a subgroup analysis suggests that treatment laterality is the most significant determinant of tremor improvement, thus highlighting the importance of future investigations on bilateral staged MRgFUS thalamotomy.

Halpern et al. (2019) published the three year results of the open-label extension study by Chang et al. (2018). The study assessed the effectiveness, durability, and safety of transcranial magnetic resonance-guided focused ultrasound (tcMRgFUS) thalamotomy for individuals with medication refractory ET. Overall, the three year attrition from the treated cohort was 31%, with a loss of 23 individuals. Scores at 36 months were compared with baseline and at six months after treatment to assess for efficacy and durability. Adverse events were also reported. Measured scores remained improved from baseline to 36 months (all $p < 0.0001$). The range of improvement from baseline was 38%-50% in hand tremor, 43%-56% in disability, 50%-75% in postural tremor, and 27%-42% in QoL. When compared to scores at six months, median scores increased for hand tremor [95% confidence interval (CI) 0-2, $p = 0.0098$] and disability (95% CI 1-4, $p = 0.0001$). During the third follow-up year, all previously noted adverse events remained mild or moderate, none worsened, two resolved, and no new adverse events occurred. The investigators concluded that results at three years after unilateral tcMRgFUS thalamotomy for ET show continued benefit, and no progressive or delayed complications. Individuals may experience mild degradation in some treatment metrics by three years, though improvement from baseline remains significant. Author noted limitations included the high dropout rate and the analysis differed from the cohorts present in the original randomized controlled trial (RCT) and the two-year follow-up. This study provides Class IV evidence that for individuals with severe ET, unilateral tcMRgFUS thalamotomy provides durable benefit after three years.

Altinel et al. (2019) conducted a systematic review and meta-analysis evaluating RCTs of DBS and lesion surgery (LS) in the treatment of tremor. PubMed, Embase, and the Cochrane database were searched to include RCTs with either LS, deep brain stimulation, or controls. The outcomes were the change in tremor score, QoL, cognitive function, and neuropsychiatric function. Fifteen trials, including 1508 participants, met eligibility criteria. No significant difference in change of tremor scale (SMD -0.07, 95% CI: -0.38 to 0.24), QoL (SMD -0.21, 95% CI: -0.69 to 0.27), cognitive function (SMD 0.06, 95% CI: -0.27 to 0.39), or neuropsychiatric function (SMD -0.15, 95% CI: -0.49 to 0.19) were observed between LS and stimulation surgery. Heterogeneity across studies was observed during indirect comparison of QoL. The 70 investigators identified a possible effect modifier: improvement in QoL correlated with duration of disease ($p = 0.035$). The focused-ultrasound LS was associated with a 0.70 SMD increase ($p = 0.014$) in QoL versus DBS in an exploratory subgroup analysis by separating two studies with focused-ultrasound LS from other LS studies. The investigators concluded that although the main analysis showed that LS and DBS were equally effective in treating individuals with tremors, an exploratory subgroup analysis indicated an improvement in QoL with noninvasive focused-ultrasound surgery. The investigators stated that focused ultrasound LS could be considered as a potential choice for tremor control, based on currently available evidence. However, additional evidence from randomized trials comparing stimulation with the focused-ultrasound approach is needed given the lack of direct comparison between the two in the literature and therefore in this meta-analysis. (Elias et al., 2016 is included in this meta-analysis).

The International Parkinson and Movement Disorder Society commissioned a task force on tremor to review clinical studies of treatments for ET. A systematic review of current pharmacological and surgical treatments for ET was conducted, using standardized criteria defined a priori by the International Parkinson and Movement Disorder Society.

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Sixty-four studies of pharmacological and surgical interventions were included in the review. MRI-guided focused ultrasound thalamotomy was, for the first time, assessed and was considered to be possibly useful. This conclusion was based on a single RCT (Elias et al., 2016) with a follow-up limited to 12 months. According to the investigators, there is a need to improve study design in ET and overcome the limitation of small sample sizes, cross-over studies, short-term follow-up studies, and use of non — validated clinical scales (Ferreira et al., 2019).

The American Society of Stereotactic and Functional Neurosurgery (ASSFN), which acts as the joint section representing the field of stereotactic and functional neurosurgery on behalf of the Congress of Neurological Surgeons and the American Association of Neurological Surgeons, provided expert consensus opinion on evidence-based best practices for the use and implementation of MRgFUS for ET. The ASSFN concluded that MRgFUS is an effective and safe treatment option for medically refractory ET. According to the ASSFN, long- term follow-up studies should continue to be pursued in larger cohorts of subjects. Investigations into precise targeting and dosing as well as temperature limits and correlations with outcomes should be evaluated (Pouratian et al., 2019).

A systematic literature review was conducted by Langford et al. (2018) to identify and analyze evidence supporting the use of the emerging MRgFUS compared to alternative stimulatory and ablative interventions (ablative interventions included radiofrequency thalamotomy, unilateral DBS, and stereotactic radiosurgery) for treating medication-refractory ET. Because of the lack of comparative evidence found, a feasibility assessment was performed to determine possible comparisons between interventions. The systematic literature review identified 1,559 records, and screening provided 46 relevant articles. The matching-adjusted indirect comparison and simulated treatment comparison results demonstrated no evidence of a difference in efficacy (measured by CRST Total) and health-related QoL (measured by CRST Part C) outcomes between MRgFUS and unilateral DBS in the short term (≤ 12 months). According to the authors, this study provides preliminary evidence that MRgFUS could elicit similar short-term tremor and health-related QoL -related benefits to DBS, the current standard of care. The authors indicated that the limited high-quality evidence available from the systematic literature review (e.g., lack of large-scale, comparative studies) and the inconsistencies in reporting of CRST maximum achievable scores in the literature meant comparisons were only possible for two interventions (MRgFUS and DBS) and two outcomes (CRST Total and Part C scores). Data availability allowed analyses only at the 1-, 3-, 6-, and 12-month time points, meaning conclusions on efficacy were limited to the short-term effect of these interventions. Further analyses are required to determine the comparative efficacy between these two interventions on a long—term basis with direct comparison. The study is limited by indirect comparison.

Mohammed et al. (2018) conducted a meta-analysis to analyze the overall outcomes and complications of MRgFUS in the treatment of ET. The change in the CRST score after treatment was analyzed. The improvement in disability was assessed with the QUEST Questionnaire score. Nine studies with 160 individuals who had ET were included in the meta-analysis. The ventral intermediate nucleus was the target in eight of the studies. The cerebellothalamic tract was targeted in one study. There was one randomized controlled trial, six studies were retrospective, and two were prospective. On meta-analysis with the random-effects model, the pooled percentage improvements in the CRST Total, CRST Part A, CRST Part C, and QUEST scores were 62.2%, 62.4%, 69.1%, and 46.5%, respectively. Dizziness was the most common in-procedure complication, occurring in 45.5%, followed by nausea and vomiting in 26.85% (pooled percentage). At three months, ataxia was the most common complication, occurring in 32.8%, followed by paresthesia in 25.1% of the participants. At 12 months posttreatment, the ataxia had significantly recovered, and paresthesia became the most common persisting complication, at 15.3%. The authors concluded that MRgFUS therapy for ET significantly improves the CRST scores and improves the QoL for individuals with ET, with an acceptable complication rate. According to the authors, there are several limitations of this meta-analysis. Most of the included studies were retrospective case series; only one RCT (Elias et al., 2016) was included. Thus, the possibility of bias is high. Other limitations include a short follow-up period and a small population. According to the authors, randomized trials comparing DBS (the current standard surgical treatment for medication-refractory ET) to MRgFUS are needed. (Author Elias et al., 2016is included in this meta-analysis).

Chang et al. (2018) reported on the results at a two- year follow-up after MRgFUS thalamotomy for ET. A total of 76 individuals with moderate-to-severe ET, who had not responded to at least two trials of medical therapy, were enrolled in the original randomized study of unilateral thalamotomy (Elias et al., 2016) and evaluated using the CRST. Sixty-seven of the individuals continued in the open-label extension phase of the study with monitoring for two years. Nine individuals were excluded by two years for example because of alternative therapy such as DBS (n = 3) or inadequate thermal lesioning (n = 1). However, all individuals in each follow-up period were analyzed. Mean hand tremor score at baseline improved by 55% at six months. The improvement in tremor score from baseline was durable at one year (53%, 8.9 ±4.8, 70 individuals) and at two years (56%, 8.8 ±5.0, 67participants). Similarly, the disability score at baseline improved by 64% at six months. This improvement was also sustained at one year and at two years. Paresthesia and gait disturbances were the most common adverse effects at one year-each observed in 10 individuals with an additional five individuals experiencing neurological adverse effects. None of the AES worsened over the period of follow up and two of these

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resolved. There were no new delayed complications at two years. The authors stated that tremor suppression after MRgFUS thalamotomy for ET is stably maintained at two years and latent or delayed complications do not develop after treatment. The authors indicated that there are some important limitations of this study. Nine individuals, many of whom had unsuccessful treatment or a suboptimal benefit, crossed over to an alternative treatment, dropped out, or were lost to follow-up. The exclusion of non-responders from the analysis introduces a bias and an overestimate of the benefit in those that remained in the study. According to the authors, additional follow-up will be required to determine the incidence of recurrence and the efficacy of MRgFUS over the long term. The authors also stated that further work is required to optimize participant selection, improve clinical results, and avoid adverse effects.

A Health Quality Ontario (HQO) evidence-based guideline indicated that MRgFUS thalamotomy provides a treatment option for people with ET who are ineligible for invasive neurosurgery and offers a noninvasive option for all people with ET considering neurosurgery. The health technology assessment found no significant differences in tremor severity, disability, or QoL with MRgFUS compared with DBS and no significant difference in tremor severity compared with radiofrequency thalamotomy (very low certainty of the evidence). MRgFUS was found to be significantly more effective than a sham procedure (high certainty of the evidence). Significant improvements in tremor severity, disability, and QoL were noted in non-comparative studies (low certainty of evidence) (HQO, 2018).

The National Institute for Health and Care Excellence (NICE, 2018) evidence-based guideline for unilateral MRgFUS thalamotomy concluded that MRgFUS thalamotomy for treatment-resistant ET raises no major safety concerns, but evidence of efficacy was limited in quantity. NICE recommends that this procedure should not be used unless there are special arrangements for oversight. NICE suggests that future research include the identification of patient selection criteria and long-term follow-up data.

Elias et al. (2016) conducted a double-blind, sham-controlled randomized trial to evaluate the efficacy of MRgFUS thalamotomy for treating ET. Trial selection criteria included individuals with moderate or severe postural or intention tremor of the hand (≥ 2 on the CRST) and refractory to at least two trials of medical therapy, including at least one first-line agent (propranolol or primidone). A total of 74 participants were randomized to unilateral focused ultrasound thalamotomy or sham treatment. Hand-tremor scores improved more after focused ultrasound thalamotomy (from 18.1 points at baseline to 9.6 at 3 months) than after the sham procedure (from 16.0 to 15.8 points); the between group difference in the mean change was 8.3 points (95% CI, 5.9 to 10.7; $p < 0.001$). The improvement in the thalamotomy group was maintained at 12 months (change from baseline, 7.2 points; 95% CI, 6.1 to 8.3). Secondary outcome measures assessing disability and QoL also improved with active treatment (the blinded thalamotomy cohort) as compared with the sham procedure ($p < 0.001$ for both comparisons). Adverse events in the thalamotomy group included gait disturbance in 36% of the participants and paresthesia or numbness in 38%; these adverse events persisted at 12 months in 9% and 14% of individuals, respectively. The investigators concluded that MRI-guided focused ultrasound thalamotomy reduced hand tremor for individuals with ET. Side effects included sensory and gait disturbances. This RCT was included in the systematic reviews above.

In 2011, the American Academy of Neurology (AAN) published a guideline on treating essential tremor syndrome. This guideline does not mention the use of magnetic resonance guided focused ultrasound therapy as a treatment option (Zesiewicz et al., 2011, reaffirmed on July 16, 2022).

Parkinson Disease

The FDA approved an expansion of the indication of ExAblate Neuro to include the treating individuals with tremor-dominant Parkinson's disease (PD) on December 16, 2018.

In 2021, the FDA expanded approval of Insightec's ExAblate Neuro focused ultrasound device to include the treatment of those with advanced PD who suffer from dyskinesia, mobility, and rigidity. Additional information is available at: https://www.fusfoundation.org/posts/fda-approves-focused-ultrasound-treatment-for-parkinsons-disease/. (Accessed April 24,2025).

Balduino de Souza AL et al. (2025) conducted a systematic review and meta-analysis to assess the safety profile of MRgFUS for treating PD. Among the three included RCTs, 115 out of 161 participants underwent unilateral MRgFUS. Despite variations in patient populations and clinical outcomes based on the specific target, dizziness was identified as the most frequently reported procedure-related adverse event (AE), typically occurring immediately after the procedure and being mild in 90% of cases. Other procedure-related events, such as pin-site complications and headaches, were less common and showed no significant differences between groups. Ablation-related AEs, including gait disturbances (e.g., ataxia and postural instability), facial disturbances, and speech disturbances, were also observed. The authors concluded that the promising safety profile of MRgFUS supports its potential as a valuable tool for managing refractory PD. The infrequent occurrence of serious adverse events further supports MRgFUS as a viable alternative to more

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invasive treatments for PD and parkinsonian tremor, particularly for patients who decline or are ineligible for other interventions. Additionally, MRgFUS offers advantages such as non-incisional, MRI-guided precision, and real-time monitoring of temperature and lesion formation, potentially limiting perilesional edema. However, the study has limitations, including the small number of included RCTs, resulting in a limited sample size (n = 161), which may affect the robustness and generalizability of the results. Furthermore, the studies targeted different ablation sites (thalamus, subthalamic nucleus, and globus pallidus internus), which could influence the incidence and nature of adverse events. This variability complicates direct comparisons and introduces clinical heterogeneity, making it challenging to draw uniform conclusions about the safety of MRgFUS across different anatomical targets. Lastly, the follow-up duration varied among the studies, which may have led to under-reporting or missed detection of late-onset adverse events. Future research should focus on standardizing ablation sites and protocols to enhance the comparability of studies and strengthen the evidence base for MRgFUS in PD. [Martínez-Fernández et al. (2020) is included in this systematic review.]

In 2022, the European Academy of Neurology/Movement Disorder Society- European Section guideline on treating PD focused on the invasive therapies for those who suffer from the illness. The society created a clinical consensus statement stating, “No sufficient RCTs available for uni- or bilateral MRgFUS of the thalamus for medically resistant tremor in PD. Despite promising preliminary data, this treatment should only be applied within clinical studies or registries (16 voters, 100%).” The society also said: “Consider using unilateral MRgFUS of the STN in people with distinctly unilateral PD only within clinical studies or registries due to the limited data on this new treatment (16 voters, 100%).” Research and use of MRgFUS are currently rapidly developing, but essential questions are still open (Deuschl et al. 2022).

Ge et al. (2021) performed a meta-analysis of RCTs to evaluate the application of MRgFUS for individuals with PD. The safety and efficacy in the treatment of PD was evaluated for qualified RCTs comparing a focused ultrasound surgery (FUS) group to a sham procedure group utilizing databases of Medline, EMBASE, and Cochrane library. Recovered from the exploration were 777 possible records for inclusion. However, 166 records were duplicates, 552 omitted due to irrelevant content, leaving two RCTs to complete the meta-analysis. With the two studies, the blinded phase lasted four months in one experiment and up to three months in the other. Of the two RCTs included, one review concentrated on individuals with asymmetric motor symptoms in PD and the other on those with tremor-dominant subtypes of PD. Individuals in both reviews had failed symptom control of motor signs with medication or were unable to tolerate side effects of medication dose adjustments. The FUS group exhibited noteworthy improvement in limb tremor on the treated side, and capability to complete activities of daily living (ADLs) compared to the sham group, however no substantial group differences in any other indicators were reported. Adverse events such as dizziness were common in the treatment group, with no group differences in the residual adverse events. The authors suggest useful effects of MRgFUS in individuals with PD however propose larger multicenter studies to select the most fitting target and surgical device setup parameters. Furthermore, the review implies the need for improvement in reducing adverse events such as mild hemiplegia.

Lennon & Hasson (2021) completed a systematic review utilizing data bases PubMed, CINAHL, PsycINFO, and Cochrane Library from January 2016 to January 2020. The authors reviewed clinical trials comprehensively assessing pre- and post-operative neurocognitive functioning for individuals with PD undergoing MRgFUS through Guidelines for Preferred Reporting Items for Systematic Review and Meta-Analysis. Limited literature was discovered for tremor-dominant Parkinson’s disease (TDPD); therefore, the search was expanded to PD with severe dyskinesia. The review resulted in 22 abstracts for inclusion, however, after removal of duplicates, and full text review, only two studies were chosen. The two studies were utilized due to their inclusion of comprehensive neuropsychological evaluations of individuals with PD undergoing MRgFUS thalamotomy or pallidotomy. Results showed minimal cognitive decline following MRgFUS for individuals with PD from baseline at three and six months follow up, with exceptions in verbal fluency and inhibition. Limitations to the review were small sample size and lack of diversity. The authors conclude significant methodological gaps, with few studies to date having administered comprehensive neuropsychological batteries to establish MRgFUS risks of adverse neurocognitive functioning in PD. Additionally, the first systematic review concentrated on non-motor neurocognitive outcomes of MRgFUS in PD which accentuates the limitations in the capability to report on these conclusions. The small number of clinical trials, obtainable articles on these trials, and overall studies do not permit robust conclusions. Furthermore, the authors suggest studies that extend beyond brief screeners when assessing PD populations susceptible to decline would be beneficial. Lastly, a consensus on a comprehensive battery to better serve replicability and the capability to engage in useful meta-analyses is needed.

Lin et al. (2021) compared the efficacy of DBS and MRI-guided focused ultrasound (MRIgFUS) in Parkinsonian tremors. The literature was searched for articles published between January 1990 and October 2020 using three databases: PubMed, Embase and Cochrane Library (The Cochrane Database of Systematic Reviews). A total of 24 studies were included in the analysis, comprising data from 784 participants. The findings revealed similar efficacy of DBS and MRIgFUS in Parkinsonian tremor suppression. Compared with internal globus pallidus (GPi)-MRIgFUS, GPi-DBS -1.84

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(-6.44, 2.86), pedunculopontine nucleus (PPN)_DBS -3.28 (-9.28, 2.78), PPN and caudal zona incerta (cZI)-DBS 0.40 (-6.16, 6.87), subthalamic nucleus (STN)_DBS 0.89 (-3.48, 5.30), STN and cZI-DBS 1.99 (-4.74, 8.65), ventral intermediate nucleus (VIM)_DBS 1.75 (-2.87, 6.48), VIM_FUS 0.72 (-5.27, 6.43), cZI-DBS 0.27 (-4.75, 5.36) there was no significant difference. Compared with VIM-MRIgFUS, GPi-DBS -2.55(-6.94, 2.21), GPi-FUS -0.72 (-6.43, 5.27), PPN_DBS -4.01(-9.97, 2.11), PPN and cZI-DBS -0.32 (-6.73, 6.36), STN_DBS 0.16 (-3.98, 4.6), STN and cZI-DBS 1.31(-5.18,7.87), VIM-DBS 1.00(-3.41, 5.84) and cZI-DBS -0.43 (-5.07, 4.68) there also was no significant difference. With respect to the results for the treatment of motor symptoms, GPi-DBS, GPi-MRIgFUS, STN-DBS and cZI-DBS were significantly more efficacious than baseline (GPi-DBS 15.24 (5.79, 24.82), GPi-MRIgFUS 13.46 (2.46, 25.10), STN-DBS 19.62 (12.19, 27.16), cZI-DBS 14.18 (1.73, 26.89). The results from the surface under the cumulative ranking results showed that STN-DBS ranked first, followed by combined PPN and cZI-DBS, and PPN-DBS ranked last. MRIgFUS, an efficacious intervention for improving parkinsonian tremor, has not demonstrated to be inferior to DBS in parkinsonian tremor suppression. Hence, clinicians should distinguish individual's symptoms to ensure that the appropriate intervention and therapeutic approach are applied.

Xu et al. (2021) conducted a systematic review to investigate the safety and efficacy of MRgFUS for PD by systematically reviewing related literature. Eleven studies containing 80 participants were included. Nine studies were observational studies with no controls. Two publications included a randomized and controlled phase and appear to report on the same sample of individuals. Most studies included tremor-dominant PD. Ten studies reported decline in Unified Parkinson's Disease Rating Scale (UPDRS)-III scores after MRgFUS, and five reported a statistically significant decline. Nine studies evaluated the QoL. Significant improvement of QoL was reported by four studies using the 39-item Parkinson's disease questionnaire. Four studies investigated the impact of MRgFUS on non-motor symptoms. Most tests indicated that MRgFUS had no significant effect on neuropsychological outcomes. Most adverse events were mild and transient. The two publications reporting on RCT mostly failed to show significant difference between the active and sham interventions at three months, possibly due to small sample size, and lacked longer term outcomes in the randomized phase of the study. The investigators concluded that MRgFUS is a potential treatment for PD with satisfying efficacy and safety. However, studies in this field are still limited. According to the investigators, more studies with strict design, comparison groups, larger sample size, and longer follow-up are needed to further investigate its efficacy and safety for PD.

Martínez-Fernández et al. (2020) conducted a randomized trial on focused ultrasound subthalamotomy for PD by randomly assigning individuals in a 2:1 ratio. Individuals with markedly asymmetric PD whose motor signs were uncontrolled by medication or those disqualified for deep-brain stimulation surgery received the focused ultrasound subthalamotomy on the opposite side of main motor sign or received a sham procedure. The characteristics of the participants were similar in the two groups at baseline. Efficacy and principal safety results were measured at four months. Efficacy outcomes in the between-group variances from baseline to four months was assessed with the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) for the affected side in the off-medication state. The trial consisted of 40 individuals, 27 assigned to focused ultrasound subthalamotomy and 13 in the sham procedure. The average MDS-UPDRS III score for the most affected side indicated improvement from 19.9 at baseline to 9.9 at four months in the active-treatment group. The control group resulted in MDS-UPDRS score of 17.1 from 18.7 at four months ensuing a between-group difference of 8.1 points. Adverse events in the non-medicated, active-treatment individuals were recorded with results as follows: Dyskinesia was noted in six individuals; with symptoms persisting at three months follow-up, and dyskinesia found in six individuals who were on medication; with persistent symptoms at one month follow-up. Weakness was recorded in five individuals on the treated side and continued in two individuals at four months follow up. Speech disturbances were documented in 15 individuals and continued in three individuals at four months. Facial weakness was logged in three individuals and persisted in one individual at four months. Gait disturbance was noted in 13 individuals which persisted in two individuals at four months. In the active-treatment group, six individuals were recorded to have the same deficits present at 12 months follow up. Limitations include small sample size. The authors conclude focused ultrasound subthalamotomy in one hemisphere improved motor features of PD in selected individuals with asymmetric signs. However, adverse events included speech and gait disturbances, weakness on the treated side, and dyskinesia. Longer-term and larger trials are needed to determine the role of focused ultrasound subthalamotomy in the management of PD and its effects compared with other available treatments.

In 2018, NICE developed interventional procedures guidance on unilateral MRI-guided focused ultrasound thalamotomy for moderate to severe tremor in Parkinson's disease. NICE's recommendations are as follows:

- Current evidence on the safety and efficacy of unilateral MRI-guided focused ultrasound thalamotomy for moderate to severe tremor in Parkinson's disease is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research.
- Further research, which could include randomized controlled trials, should address patient selection and report on long-term follow-up.

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Code	Description
63268	Laminectomy for excision or evacuation of intraspinal lesion other than neoplasm, extradural; sacral

Surgical treatment (e.g., laminectomy and sacral reconstruction) of a sacral perineural Tarlov cyst is proven and medically necessary for individuals with ALL the following:

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- Pain directly attributable to the Tarlov cyst; or
- Neurologic conditions attributable to the Tarlov cyst (e.g., motor loss, urinary or fecal incontinence, cauda equina syndrome)
- Radiologic evidence of a Tarlov cyst that by its anatomic location, size and compression or displacement or neural elements correlates to the neurologic signs and symptoms found on current evaluation; and
- Failure to improve with non-surgical treatment for at least 12 weeks.

Clinical Evidence

Tarlov cysts are sacs filled with cerebrospinal fluid that most often affect nerve roots in the sacrum, the group of bones at the base of the spine. These cysts (also known as meningeal or perineural cysts) can compress nerve roots, causing lower back pain, sciatica (shock-like or burning pain in the lower back, buttocks, and down one leg to below the knee), urinary incontinence, headaches (due to changes in cerebrospinal fluid pressure), constipation, sexual dysfunction, and some loss of feeling or control of movement in the leg and/or foot. Tarlov cysts are difficult to diagnose because of the limited knowledge about the condition, and because many of the symptoms can mimic other disorders. They are usually diagnosed incidentally, and a specific treatment is not necessary. Tarlov cysts should be operated on, only if they produce or have disabling neurologic symptoms clearly attributable to them and have failed an appropriate course of non-operative treatments (National Organization for Rare Disorders, 2015; updated 2017).

Tarlov cysts may cause pressure to the adjacent nerves, which can cause pain and deterioration of the surrounding bone. If these cysts are left untreated, permanent damage to the nervous system may result from the nerve root compression (NINDS, 2024).

Abdi et al. (2025) conducted a retrospective, systematic review of literature to assess the outcome of surgical treatment (partial sacral laminectomy) for Tarlov cysts. Ninety-six Individuals who were operated on for Tarlov cysts from 1995 to 2020 were identified and included in this study, with the authors evaluating their medical records and radiological images. “Improvement of symptoms after surgery was observed in 76.0% of patients (excellent or good individual-reported outcome) and the complication rate was 17.5%. Sacral or lower back pain as a preoperative symptom was associated with improvement after surgery ($p = .007$), whereas previous lower back surgery was more common in patients who did not benefit from surgery ($p = .034$).” The authors concluded that individuals in a select patient population would be likely to experience symptom improvement. Additionally, they stated that retrospective studies appear to be the main strategy for researching this condition, as large-scale prospective or randomized studies are limited due to the controversial nature, and rarity of Tarlov cysts.

In a patient fact sheet, the American Association of Neurological Surgeons state that “neurosurgical techniques for symptomatic Tarlov cysts include simple decompressive laminectomy, cyst and/or nerve root excision and microsurgical cyst fenestration and imbrication” (AANS, 2024).

Medani et al. (2019) conducted a retrospective chart review and analysis for individuals who underwent surgical intervention for symptomatic Tarlov cyst(s) in the period 2007–2013. Operative reports, preoperative and postoperative clinic visit reports were reviewed. Modified MacNab criteria were used for evaluation of the final clinical outcome. Thirty-six surgical patients were identified. The presenting symptoms were low back pain, sensory radiculopathy, bladder and bowel dysfunction sexual dysfunction and motor dysfunction. The authors concluded that laminectomy with cyst fenestration and nerve root imbrication are both surgical techniques to treat symptomatic Tarlov cyst(s), and both can result in clinical improvement.

“Tarlov cysts may be drained and shunted to relieve pressure and pain, but relief is often only temporary and fluid build-up in the cysts will recur. Corticosteroid injections may also temporarily relieve pain. Other drugs may be prescribed to treat chronic pain and depression. Injecting the cysts with fibrin glue (a combination of naturally occurring substances based on the clotting factor in blood) may provide temporary relief of pain. Some scientists believe the herpes simplex virus, which thrives in an alkaline environment, can cause Tarlov cysts to become symptomatic. Making the body less alkaline, through diet or supplements, may lessen symptoms. Microsurgical removal of the cyst may be an option in selected individuals who do not respond to conservative treatments and who continue to experience pain or progressive neurological damage.” [Society for Neuroscience (SfN]). https://www.sfn.org/sitecore/content/home/brainfacts2/diseases-and-disorders/neurological-disorders-az/diseases-a-to-z-from-ninds/tarlov-cysts.

Guo et al. (2007) investigated the microsurgical results of symptomatic sacral perineurial cysts of 11 individuals and to discuss the treatment options of the past 10 years. Nine of the 11 individuals (82%) experienced complete or substantial relief of their preoperative symptoms. One individual (Patient 4) experienced worsening of bladder dysfunction after surgery and recovered slowly to subnormal function during the subsequent 2 months. The symptoms of Patient 9 did not

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resolve, and magnetic resonance imaging showed that the cyst had reoccurred. The patient underwent reoperation three months later without any improvement. One individual (Patient 11) experienced a cerebrospinal fluid leakage complication. This was an uncontrolled study of extremely small sample size.

Tanaka et al. (2006) investigated the surgical outcomes and indicators for surgical intervention. Twelve consecutive individuals harboring symptomatic sacral perineural cysts were treated between 1995 and 2003. All individuals were assessed for neurological deficits and pain by neurological examination. The researchers performed a release of the valve and imbrication of the sacral cysts with laminectomies in eight cases or recapping laminectomies in four cases. After surgery, symptoms improved in 10 (83%) of 12 individuals, with an average follow-up of 27 months. Ten individuals had sacral perineural cysts with signs of positive filling defect. Two (17%) of 12 individuals experienced no significant improvement. In one of these individuals, the filling defect was negative. In conclusion, a positive filling defect may become an indicator of good treatment outcomes. This was an uncontrolled series of extremely small sample size.

Caspar et al. (2003): There is agreement that symptomatic perineurial sacral cysts should be treated surgically. However, it is still debated whether the preference should be given to the curative option, consisting of excision of the cyst with duraplasty, or to drainage of the cyst to relieve symptoms. In this retrospective study the efficacy of microsurgical cyst resection with duraplasty is evaluated. In 15 individuals presenting with pain and neurologic deficits, myelography and/or MRI detected sacral cysts. The clinical features suggested that the space-occupying lesions caused the disturbances. Microsurgical excision of the cyst along with duraplasty or plication of the cyst wall was performed in all the cases. Postoperative care included bed rest and CSF drainage for several days. In 13 out of 15 individuals the preoperative radicular pain disappeared after surgery. The two individuals with motor deficits and the six individuals with bladder dysfunction recovered completely. In all except one of the 10 individuals complaining of sensory disturbances a significant improvement was achieved. No complications were observed. Microsurgical excision of the cyst combined with duraplasty, or plication of the cyst wall is an effective and safe treatment of symptomatic sacral cysts and, in the view of the authors, the method of choice. This was an uncontrolled retrospective study of extremely small sample size.

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Code	Description
64454	Injection(s), anesthetic agent(s) and/or steroid; genicular nerve branches, including imaging guidance, when performed

Due to insufficient evidence of safety and/or efficacy, genicular nerve block (GNB) is unproven and not medically necessary for treating knee pain, including post-operative knee pain management.

Note: For information on radiofrequency ablation of the genicular nerve, refer to the section above.

Clinical Evidence

In a GNB procedure, an anesthetic agent (e.g., lidocaine, bupivacaine) is injected near the genicular nerves of the knee under ultrasound or fluoroscopic guidance. A corticosteroid may also be injected adjunctively. The procedure specifically targets the superior lateral, superior medial, and inferior medial genicular nerves. GNBs may be performed to relieve pain

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in those who may not be a candidate for knee surgery, before total knee arthroplasty (TKA), for use managing postoperative pain following knee replacement surgery, or other knee surgeries, and as a diagnostic tool prior to genicular neurotomy or genicular nerve ablation (Hayes, 2023; updated 2024; Vilchez-Cavazos et al., 2024).

In a randomized, double-blind, non-inferiority clinical trial, Kertkiatkachorn et al. (2024) evaluated the combination of GNB and continuous adductor canal block (CACB) compared to periarticular infiltration (PAI) and CACB as a postoperative analgesic regimen after knee replacement surgery. One hundred and forty individuals undergoing TKA were randomized into either the GNB group or the PAI group. The primary outcome was assessed at 12 hours postoperatively and was pain at rest and during movement. At 12 hours postoperatively, the PAI and GNB groups had median resting pain scores of zero (zero to two) and zero (zero to two), respectively. The median difference was zero, with the 95% confidence interval (CI) upper limit below the prespecified non-inferiority margin. The median pain score during movement was 1.5 (zero to 2.3) and two (one to 3.1) in the PAI and GNB groups, respectively. The median difference was 0.9, failing to demonstrate non-inferiority. The GNB group had higher intravenous morphine consumption at 12 hours postoperatively and a shorter time to first rescue analgesia. The authors concluded that GNB provided pain relief at rest comparable with PAI at 12 postoperative hours, but did not demonstrate non-inferiority for pain relief during movement. Limitations included that the PAI anesthetic dose was double that of GNB, and failure to produce blockade may occur with the blinded technique but was not evaluated.

Vilchez-Cavazos et al. (2024) conducted a systematic review and meta-analysis to assess GNB compared with placebo and various intraarticular procedures for the treatment of primary knee osteoarthritis (OA). Five randomized controlled trials (RCTs) with a minimum follow-up period of three months that evaluated pain and knee function scores were included in the review. Two hundred and thirty-one individuals grade two to four knee OA were included in the review. The results revealed pain statistically significant scores were demonstrated in one and three months with an overall total effect of 1.43 (95% CI, 0.86, 1.99; p = 0.00001; I^2 = 85%). Similarly, for knee function a total effect of 0.71 (95% CI, 0.35, 1.06; p = 0.00001; I^2 = 69%) at one and three months, was statistically significant. The minimal clinically important difference regarding pain was achieved at one and three months. According to the authors, GNB attained the minimal clinically important differences for knee OA pain and had statistically significant improvements in knee function. However, the authors noted that although GNB is a safe procedure, it is a novel therapy that requires additional evidence supporting routine use. Furthermore, the authors mentioned that while GNB has been utilized as an adjunct in knee surgeries, its potential role as a preoperative strategy for TKR or other knee procedures remains to be explored. Limitations included short-term follow-up and small study sizes. Kim et al., 2019 and Kim et al., 2018, which were previously cited in this policy, are included in this review.

Xue et al. (2024) conducted a systematic review and meta-analysis designed to compare the pain-relieving effectiveness of various nerve block techniques, including femoral nerve block (FNB), adductor canal block (ACB), infiltration between the popliteal artery and the capsule of the posterior knee (iPACK), and genicular nerve block, following TKA. Inclusion criteria included individuals over 18 year of age who had a TKA with any of the following post-operative analgesic procedures (alone or in combination), FNB, ACB, iPACK, GNB, and control/placebo. Studies with minimally invasive knee surgery or incomplete/unavailable data were excluded. Forty-two studies (n = 2857 participants) were included in the study. Pain scores during rest and mobilization at 24 and 48 hours post-surgery were the primary outcomes. The results suggested that ACB + iPACK was the most efficacious option for improving ambulation ability and shortening the length of hospital stay. Furthermore, ACB + iPACK was the best regimen for resting-pain and movement-pain relief (78% and 87%, respectively) and for reducing opioid consumption (90%) at 48 hours. However, FNB + iPACK was the most efficacious option for relief of resting pain (42%) and reducing opioid consumption (68%) at 24 hours; GNB was the most efficacious option for movement pain relief at 24 hours (94%). The authors concluded that ACB combined with iPACK can effectively enhance functional knee improvement and expedite rehabilitation following TKA. Additionally, those treated with ACB and iPACK show better pain scores and reduced morphine consumption at 48 hours. Yet the authors did not recommend this technique for short-term (24-hour) pain control and morphine consumption. Limitations included the varied concentration of volume of local anesthetic between studies, the study did not limit the type of local anesthetic administration (bolus or continuous infusion), and the study did not include local infiltration anesthesia, although it is commonly used. The authors recommended additional robust RCTs are needed to support these results. The study by Rambhia et al., 2021, which was previously cited in this policy, is included in this review.

Cuñat et al. (2023) conducted a randomized non-inferiority trial to evaluate the efficacy of GNB compared to local infiltration analgesia (LIA) in the first 24 hours after TKA. Individuals were randomized to receive either an ultrasound-guided block of five genicular nerves (n = 29) or LIA (n = 30). The primary outcome was rest pain Numeric Rating Scale (NRS) (zero to 10) at 24 hours. Secondary outcomes included pain NRS (rest and movement) and cumulative opioid consumption during the first 24 hours. The median difference (95% CI) in postoperative rest pain at 24 hours (non-inferiority criteria, Δ = 1) was -1.0(-2.0 to 1.0, p < 0.001). Median difference in cumulative opioid consumption was 0.0 mg,(-3.0 - 5.0, p < 0.001) meeting the non-inferiority criteria, Δ = 23 mg. The authors concluded GNB compared to LIA

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during the first 24 hours following surgery provided non-inferior analgesia with a considerable reduction in the local anesthesia dose. The authors note further evidence is needed to establish efficacy and safety to identify the local anesthesia distribution in the knee compartments and clinical implications. Limitations include small sample size, numeric rating scale, which is a subjective score, as a primary outcome, and individuals receiving GNB were not blinded to the intervention.

Eid et al. (2023) conducted a RCT aimed to compare GNB with PAI for postoperative analgesia following TKA. Participants (n = 88) above 50 years of age were randomized into two groups: Group one received intraoperative PAI [0.5 milliliters (mL) adrenaline (4.5 µg/mL), 20 mL bupivacaine 0.5% with 89.5 mL saline] and Group two received immediate postoperative GNB (15 mL bupivacaine 0.25% with 2.5 g/mL adrenaline). The primary outcome was postoperative morphine consumption during the first two postoperative days. Time to rescue analgesia, pain scores, and functional outcomes were the secondary outcomes. The postoperative morphine consumption during the first two postoperative days and pain scores at rest at 12 hours postoperatively were less in Group one than in Group two ($p < 0.001$). Pain scores during movement on the first postoperative day were lower in the periarticular group than the genicular group at six, 12 and 24 hours ($p < 0.001$). At 18 hours, pain scores were higher in the periarticular group than in the genicular group at rest and movement ($p < 0.001$). Quadriceps motor strength scores were comparable between groups ($p > 0.05$). The knee range of motion and time up and go test during both days showed a statistically significant difference in the periarticular group compared to the genicular group ($p < 0.05$). The authors concluded PIA and GNB after TKA could be considered safe, had effective post-op analgesia, and functional outcomes. The PAI group consumed less morphine overall during the first two postoperative days than the GNB group. Limitations include small sample size, lack of control group, and the surgical teams lack of blinding to the pain management methodology with differing local anesthetic doses.

A Hayes technology assessment evaluated the efficacy and safety of GNB when compared to standard treatments of managing osteoarthritis (OA) of the knee in adults. The assessment states the overall body of evidence is very low quality and while GNB given adjunctively with corticosteroids appears to be safe, there were inconsistent findings as to whether GNB resulted in statistically and clinically significant improvement in function and pain scores (Hayes, 2023; updated 2024).

Radwan et al. (2023) conducted a RCT to evaluate the effect of GNB on individuals with juvenile idiopathic arthritis (JIA) and persistent unilateral knee arthritis. One-hundred and four participants were randomized into two groups. Group one was treated with GNB, and group two was treated with intra-articular triamcinolone. Pain, inflammatory parameters, function, and range of motion were assessed at baseline, week two and week twelve. Visual analog scale (VAS) pain, tenderness, swelling, sonography of large joints in rheumatology (SOLAR) grey scale, and power Doppler (PD) scores were significantly reduced after two weeks in both groups ($p < 0.05$). This was greater in the GNB group regarding VAS and tenderness, while SOLAR and swelling were reduced in triamcinolone group. After twelve weeks, all outcome measures showed lower values in the GNB group compared to triamcinolone and was significant regarding VAS pain. Additionally, the Lysholm functional score was significantly increased in both groups at both intervals; and higher values were seen in the triamcinolone group compared to GNB after two weeks. The authors concluded pain, improved function, and inflammation of the knee joint were controlled by GNB in those with JIA and may be considered a promising therapy. The authors noted steroids showed better results after two weeks, but GNB had an equivalent longer-term improvement after 12 weeks. Limitations include small sample size and short-term follow-up. The authors recommended future research to evaluate the effect of different nerve block techniques on inflammatory arthritis.

Shanahan et al. 2023) conducted a 12-week parallel-group, placebo-controlled randomized trial to determine if ultrasound-guided GNB is effective in reducing knee OA pain in individuals with longstanding disease. The active arm group (n = 31) received three injections of 5.7 mg celestone chronodose and 0.5% bupivacaine to the inferomedial, superomedial, and superolateral genicular nerve, while the placebo group (n = 28) received injections of normal saline. The participants recorded their pain and disability on a 100-mm VAS and the Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC), and the Intermittent and Constant Osteoarthritis Pain scale at baseline and at weeks two, four, eight, and 12. The participants in the active group noted improvements in pain scores with a decrease of the effect over time. Visual analog scale scores at baseline and at weeks two, four, eight, and 12 in the active group versus placebo group were 6.2 versus 5.3 ($p = 0.294$), 2.7 versus 4.7 ($p < 0.001$), 3.2 versus 5.1 ($p < 0.001$), 3.9 versus 4.9 ($p < 0.001$),and 4.6 versus 5.1 ($p = 0.055$), respectively. Total WOMAC scores at baseline and at weeks two, four, eight, and 12 in the active group versus the placebo group were 54.5 versus 48.1 ($p = 0.177$), 32.9 versus 44.4 ($p < 0.001$), 33.7 versus 45.8 ($p < 0.001$), 39.2 versus 44.8 ($p = 0.001$), and 42.65 versus 45.1 ($p = 0.012$), respectively. The authors concluded GNB for individuals with OA of the knee was safe and effectively provided pain relief in the short-term. Limitations include small study size and short-term follow-up.

Güler et al. (2022) conducted a prospective randomized study on 102 participants with chronic knee OA comparing the effectiveness of ultrasound guided GNB (n = 51) and physical therapy (PT) (n = 51) along with a standard home exercise

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program. Participants were assessed pre-treatment, and at two weeks and 12 weeks post treatment using scores for pain on a VAS, WOMAC and six minute walking test (6MWT). VAS scores in the ultrasound guided GNB group at zero, two and 12 weeks were 7.01 ±1.36; 3.71 ±2.18; 5.08 ±2.22 ($p < 0.001$) and 6.64 ±1.99; 4.35 ±1.09; 5.25 ±1.33, ($p < 0.001$) in the PT group. While the increase in the 6MWT test in the second week was similar for both groups ($p = 0.073$), the increase in walking distance was greater in the ultrasound guided GNB group at 12 weeks ($p = 0.046$). The authors concluded that pain reduction and functional improvement by PT and ultrasound-guided GNB are comparable, however, ultrasound-guided GNB increased the physical capacity that persisted up to twelve weeks. Limitations included lack of control group, short follow-up period, and exercise compliance was based only on individuals verbal confirmation. The authors state future studies are needed to examine ultrasound guided GNBs long-term effectiveness.

Fonkoue et al. (2021) assigned 55 individuals with chronic knee OA in a double-blinded RCT designed to compare the effectiveness of GNB using classical anatomical targets versus revised targets. The groups received a GNB [using a fluid mixture of two mL of lidocaine 1% and 20 milligrams (mg) triamcinolone] with either classical targets (n = 28) or revised targets (n = 27). Numeric Rating Scale, Oxford Knee Score (OKS), WOMAC, Quantitative Analgesic Questionnaire (QAQ), and Global Perceived Effects Scale (GPES) were assessed at baseline, and at one-hour, 24-hours, one, four, and 12-weeks post-intervention. The revised targets group had a greater reduction in NRS mean score at one-hour post intervention and a higher proportion of participants achieving more than 50% knee pain reduction at each follow up interval. However, the differences were only statistically significant at one-hour post intervention. Both protocols resulted in substantial pain reduction and joint function improvement that lasted up to 12-weeks post intervention. The authors concluded the revised technique resulted in more pain relief and a higher proportion of successful responders at one-hour post intervention. Limitations include the large volume injected for GNB which did not allow to clearly discriminate the effects of the anatomical precision of the targets in both techniques, participant highly subjective reported outcomes, and no sham-controlled trials performed to demonstrate the efficacy of therapeutic GNB.

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Code	Description
64624	Destruction by neurolytic agent, genicular nerve branches including imaging guidance, when performed
64999	Unlisted procedure, nervous system [when used to report cooled radiofrequency ablation]

Due to insufficient evidence of safety and/or efficacy, radiofrequency ablation (RFA), using any RFA method, is unproven and not medically necessary for the treatment of joint pain, including but not limited to hip, knee, or shoulder pain.

This policy does not apply to RFA treatment of facet joint or sacroiliac pain. For information on RFA for spinal indications, refer to the Medical Policy titled Ablative Treatment for Spinal Pain (for Pennsylvania Only).

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Clinical Evidence

RFA uses an electrode-tipped probe to deliver radiofrequency energy to nervous tissue, creating heat lesions that inactivate the nerve pathway that sends pain signals to the brain. Conventional RFA uses heat that is concentrated at the probe tip, while cooled RFA (e.g., Coolief) transmits thermal radiofrequency energy using water-cooled electrodes/probes (Avanos Medical website, ECRI, 2021).

Ciaffi et al. (2024) performed a systematic review and meta-analysis on the efficacy of minimally invasive interventional procedures, including RFA, in patients with osteoarthritis (OA) or inflammatory arthritis. Both randomized controlled trials (RCTs) and nonrandomized studies were included. Anatomical sites included knee, hip, foot and ankle, shoulder, hand and wrist, sacroiliac joints. The main outcome was change in pain intensity using the 0-10 visual analog scale (VAS) from baseline to 1 month. Additional timepoints at 3, 6 and 12 months were assessed. Change in functional status was evaluated. Pooled estimates were calculated as the mean difference (MD) and 95% confidence interval relative to baseline. The meta-analyses of RCTs and nonrandomized studies were conducted separately. A total of 164 studies were included in the systematic review and 111 (38 RCTs and 73 nonrandomized studies) were selected for the meta-analysis. Only one article described individuals with inflammatory arthritis. In the meta-analysis of RCTs, one month after the procedure, MD in VAS was -4.34 (-4.96 to -3.71; k = 2) for hip RFA, -3.83 (-4.52 to -3.15; k = 3) for shoulder RFA and -4.93 (-5.58 to -4.28; k = 14) for sacroiliac joints RFA. Significant decrease in pain intensity was found also at 3, 6 and 12 months. Additionally, functional status improved at all the assessed timepoints. Author noted limitations include a lack of blinding and well-defined treatment protocols in the majority of included studies. Additionally, the included studies differed with respect to disease duration, severity of the underlying condition, baseline characteristics, previous treatments and follow-up time periods. The sample size of the studies was highly variable and the pooled estimates had significant heterogeneity. High quality RCTs with adequate sample size and long-term follow-up are needed to evaluate the risk-to-benefit ratio and to identify the place of these treatments in the therapeutic armamentarium. (Davis et al., 2018, which was previously cited in this policy, is included in this systematic review.)

American College of Rheumatology/Arthritis Foundation guidelines for the management of OA of the hand, hip, and knee state that RFA is conditionally recommended for patients with knee OA. A number of studies have demonstrated potential analgesic benefits with various ablation techniques; however due to the heterogeneity of techniques and controls used and lack of long-term safety data, the recommendation is conditional. The Voting Panel made conditional recommendations when the quality of the evidence proved low or very low and/or the balance of benefits versus harms and burdens was sufficiently close that shared decision-making between the patient and the clinician would be particularly important. No mention was made of RFA for treatment of the hand or hip.

Hip

An ECRI report (2021) evaluated cooled RFA for treating hip pain and found that the evidence is too limited in quantity and quality to permit conclusions. RCTs assessing cooled RFA compared with other treatments for chronic hip pain (e.g., corticosteroid injections) are needed.

The American Society of Pain and Neuroscience (ASPN) advises that hip joint radiofrequency neurotomy (ablation) targeting the obturator and femoral nerve branches may be used for the treatment of hip joint pain following diagnostic blocks. GRADE II-1 B. However, further investigation is needed to determine the optimal patient selection and protocol for improving outcomes. A review of the available literature found variable outcomes with regard to pain reduction ranging from eight days to three years. Anatomical variations of the femoral, obturator, and accessory obturator nerves are factors in the success of neurotomy. RFA modality (cooled versus traditional), number of lesions, and cannula size are also important (Lee et al., 2021).

A Hayes Evolving Evidence report evaluated cooled RFA for treating hip pain. Three pretest-posttest studies were identified in the clinical literature. While the studies appear to show clinical improvements in pain, all three studies are of poor quality and have limited follow-up. No systematic reviews or clinical practice guidelines were identified to support the use of cooled RFA for hip OA (Hayes, 2023; updated 2025).

In a small retrospective case series, Kapural et al. (2018) described technique and evaluated initial outcomes of patients who underwent ablation of the femoral and obturator nerves of the hip using cooled RFA guided by ultrasound and fluoroscopy. Data was collected on 52 ablations of the hip in 23 consecutive patients. Change in pain scores went from the baseline 7.61 ±1.2 to 2.25 ±1.4 after the RFA ($p < 0.01$). There were no reported adverse events, except one case of neuritis that resolved within a week after the procedure. Opioid use did not decrease significantly. Study limitations include retrospective design, small patient numbers, lack of blinding, and no comparison group.

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American Academy of Orthopaedic Surgeons (2023) guidelines on the management of OA of the hip make no mention of RFA for hip OA pain.

Knee

Articular branches of various nerves (common peroneal, femoral, obturator, saphenous, and tibial) innervate the knee joint. These branches around the knee joint are known as genicular nerves.

Almeida et al. (2025) performed a meta-analysis of 25 RCTs and cross-over trials (n = 2049) evaluating the efficacy and safety of minimally invasive interventions targeting the genicular nerves in knee OA. Comparators included sham/placebo (main comparison), intra-articular injections, and usual care. The primary outcomes were pain intensity, physical function, and serious adverse events. Secondary outcomes included quality of life and patient-reported global perceived effect. The certainty of evidence was consistently low to very low across all comparisons. The analysis showed that RFA may provide moderate short-term pain relief compared to sham at 4 weeks and 12 weeks, but there was no benefit at 24 and 48 weeks, and no improvements in function at any time point. No differences in serious adverse events were observed between minimally invasive interventions and sham/placebo. The authors noted that the evidence supporting the use of RFA for the management of knee OA is highly uncertain, with modest, short-term benefits that are not sustained. Given the very low certainty of current data, the authors advise against its routine use until more robust evidence is available.

Two additional systematic reviews and meta-analyses reported similar results, showing short-term benefits. RCTs evaluating the long-term safety and efficacy of RFA for treating knee pain are needed (Soetjahjo et al., 2024 and Wu et al., 2022).

A National Institute for Health and Care Excellence (NICE) guidance document states that radiofrequency denervation for OA knee pain may be used if standard arrangements are in place for clinical governance, consent and audit. While there is good evidence to show that this procedure relieves pain in the short term, long-term evidence is generally limited (NICE, 2023).

Chen et al. (2023) performed a meta-analysis of evaluating the short-term and long-term efficacy of RFA in treating patients with chronic knee OA. Nine RCTs (n = 714) were included in the analysis. The meta-analysis revealed that RFA demonstrated a significant short-term efficacy in reducing pain compared to the control group at 6 months using the VAS and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scores. However, the long-term efficacy of RFA at 12 months remained uncertain for both pain scores. The authors concluded that further research is needed to determine the long-term efficacy of RFA in managing knee OA pain.

A meta-analysis of RCTs to assess the effect of RFA on pain and function in knee OA was conducted by Liu et al. (2022). Fifteen RCTs (n = 1009) were included in the analysis. “The results demonstrated that RF treatment correlated with improvements in pain relief (VAS/NRS score, all $p < 0.001$) and knee function (WOMAC, all $p < 0.001$) at 1–2, 4, 12, and 24 weeks after treatment as well as patients’ degree of satisfaction with treatment effectiveness (GPE scale, 12 weeks, $p < 0.001$). OKSs did not differ significantly between the two groups. Moreover, treatment with RF did not significantly increase adverse effects. Subgroup analysis of knee pain indicated that the efficacy of RF treatment targeting the genicular nerve was significantly better than intra-articular RF at 12 weeks after treatment ($p = 0.03$).” While the authors concluded that RF is efficacious and safe for the treatment of knee pain and function in knee OA, they also acknowledge that limitations of this meta-analysis include differences in study protocols, follow-up periods, lack of blinding, and small sample size. Additionally, they state that further double-blind, multi-center RCTs of RF therapy that have large sample sizes are still needed.

American Academy of Orthopaedic Surgeons (2021) guidelines on the management of OA of the knee only mention one high quality study comparing bipolar intra-articular pulsed RF thermocoagulation over unipolar intra-articular pulsed RF thermocoagulation for pain improvement. The strength of recommendations for denervation therapy has been downgraded to “limited” due to concerns addressed in the evidence to decision framework.

The ASPN advises that genicular nerve radiofrequency neurotomy (RFN) may be used for the treatment of OA related and post-surgical knee joint pain. GRADE II-1 B. The guidelines note that there have been multiple studies, including RCTs, evaluating the efficacy of genicular RFN. These studies have included pain scales and validated measures of function at up to 12 months of follow-up. Further studies will enable the ideal use of this treatment modality. Further research topics should include the examination of demographic factors (e.g., BMI, gender, severity of OA), improve patient selection, the utility of prognostic blocks and repeat RFN. In general, the ideal timing of RFN in the setting of a multimodal management algorithm should also be established. Long-term outcomes, beyond a year, will also be important due to the chronic nature of the conditions typically treated with this modality (Lee et al., 2021).

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Conger et al. (2021) completed a review of the literature including RCTs, appropriate patient selection, and safety relating to genicular RFA. As cadaveric studies demonstrate significant variability in the location of the genicular nerves, it has stimulated debate about the ideal target locations for genicular RFA. Despite this, the authors found that favorable outcomes have been observed in studies targeting only the superior medial genicular nerve, inferior medial genicular nerve, and superior lateral genicular nerve. Several RCTs demonstrate superiority of genicular RFA compared with intra-articular steroid, visco supplementation, and oral analgesics. Genicular RFA of the superior medial genicular nerve, inferior medial genicular nerve, and superior lateral genicular nerve appears to be an effective treatment for painful knee OA but targeting additional sensory nerves may further improve treatment success. Although genicular RFA appears relatively safe on the basis of the available data, the authors concluded that additional large-scale studies are needed to provide greater confidence.

An ECRI report (2020) assessed cooled radiofrequency for treating knee OA and found that evidence is inconclusive for the efficacy and safety of this procedure due to very low-quality comparative data. Study limitations from two low-quality multicenter randomized crossover studies included lack of binding of outcomes assessors, and short follow-up. RCTs with longer follow-up are needed to determine how cooled RFA compares with nonsurgical procedural treatments for knee OA.

Chen et al. (2021) conducted a systematic review comparing genicular nerve thermal (heated or cooled) RFA to other nonsurgical treatments for the treatment of knee OA. Seven studies were included in the review. The authors concluded that RFA of the knee (cooled and conventional) provided better results than intra-articular steroid injections or other comparators. RFA improved pain, function, and composite scores compared with sham, oral analgesics, and intraarticular steroid or hyaluronic acid injections for up to 3 to 6 months. Further studies with longer follow-up are needed to confirm these findings.

The results of one multicenter RCT comparing cooled RFA with intra-articular steroid injections for the management of OA-related knee pain were published in three publications. Davis et al. (2018) randomized 151 patients with chronic (≥ 6 months) knee pain that was unresponsive to conservative therapies to cooled RFA (Coolief) (n = 76) or intra-articular steroid injection (n = 75). Participants were followed-up at one, three, and six months after the intervention. The primary efficacy end point was the proportion of subjects whose knee pain was reduced by 50% or greater from baseline. At six months, cooled RFA reduced index knee pain by at least 50% in 74.1% of treated participants compared with 16.2% in the intra-articular steroid group. The cooled RFA group consistently experienced greater pain relief throughout the study, with a mean Numeric Rating Scale (NRS) reduction of 4.9 compared with 1.3 in the intra-articular steroid group. There were no procedure-related serious AEs. At 12 months, Davis et al. (2019) reported that 65% of the original cooled RFA group had pain reduction 50% or greater, and the mean overall drop was 4.3 points on the NRS. Hunter et al. (2020) conducted an extension study using a subset of patients from the original study. Of the 33 patients enrolled, 25 were evaluated at 18 months after cooled RFA treatment. The mean NRS score was 3.1 ±2.7, with 12 patients reporting ≥ 50% pain relief compared to baseline. At 24 months, 18 patients reported a mean NRS score of 3.6 ±2.8, with 11 demonstrating ≥ 50% pain relief. Functional improvement, measured by the Oxford Knee Score, continued to be present, with an overall mean change from baseline of 26.0 ±9.6 points at 18 months and 29.9 ±10.4 points at 24 months. In this small subset of patients, cooled RFA provided sustained pain relief, improved function, and perceived positive effect through 24 months. Additional RCTs with longer reported outcomes are needed to further evaluate cooled RFA for the treatment of knee pain due to OA.

Kapural et al. (2019) evaluated the clinical effectiveness of cooled RFA in the treatment of chronic knee pain from both OA and post-TKA as part of a retrospective case series. Data was analyzed for 183 patients who received cooled RFA. Results demonstrated 65% of patients receiving cooled RFA reported more than 50% pain relief and the mean duration of > 50% pain relief was 12.5 months. Fourteen percent of patients reported no pain at all after the cooled RFA. A subgroup of 21 patients were treated with cooled RFA for chronic knee pain post TKA and demonstrated no difference in the degree of pain or duration of pain relief. Use of opioids did not change significantly despite reduced pain scores. The study is limited by lack of comparison group.

McCormick et al. (2017) assessed outcomes of cooled RFA of the genicular nerves for the treatment of chronic knee pain due to OA. Thirty-three patients (52 discrete knees) met the inclusion criteria. After 6 months, the study reported that genicular cooled RFA demonstrated a success rate of 35% based on a combination of patient-reported outcome measures. Nineteen percent of patients experienced complete pain relief. Reports of 80% or greater relief from diagnostic blocks and duration of pain of less than five years were predictors of treatment success. Further prospective studies are needed to optimize the patient selection protocol and success rate of this procedure. The findings of this study are limited by the lack of comparison group.

Gupta et al. (2017) conducted a systematic review of studies investigating conventional, pulsed, or cooled RFA for the treatment of chronic knee pain. The seventeen studies included were a mix of small RCTs, retrospective or prospective

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case series and case reports. Four of the included publications (1 RCT, 1 case series, and two case reports) used cooled RFA. Overall, the studies showed promising results for the treatment of severe chronic knee pain by RFA at up to one year with minimal complications. The majority of the studies reported positive patient outcomes, but the inconsistent procedural methodology, inconsistent patient assessment measures, and small study sizes limit the applicability of any specific study to clinical practice. The authors also reported a low level of certainty in supporting the superiority of any specific RFA procedure modality.

Shoulder

Jain et al. (2024) performed a systematic review evaluating RFA as a treatment for chronic shoulder pain. A total of 29 studies were included in the review. In several studies, RFA was compared to conservative options such as physical therapy or corticosteroid injections. While results showed that RFA can serve to reduce pain scores, provide lasting pain relief, increase function, and increase patient satisfaction, the studies were limited by a lack of consistent approach to ablation, the retrospective nature of most studies, and the difference in follow-up duration. Additional large RCTs are needed to analyze the efficacy and safety of RFA in patients with chronic shoulder pain.

Albishi et al. (2023) completed a systematic review of 51 studies where RFA techniques were used for the shoulder joint. The studies showed positive outcomes when the ultrasound-guided technique was compared with the fluoroscopy-guided technique to identify the suprascapular nerve (SSN) and the axillary nerve. However, other studies indicated that there is still a lack of evidence of an analgesic effect despite the potential pain reduction. In addition, the pain reduction appeared to be temporary and deteriorated in 3 to 6 months in some cases.

Vij et al. (2022) conducted a systematic review which found radiofrequency techniques to be promising but showed ongoing concerns with complications. The most common adverse events of RF use are thermal injuries due to high temperature of the fluid and surrounding tissue. The authors concluded further research is warranted.

American Academy of Orthopaedic Surgeons (2020) guidelines on the management of glenohumeral joint osteoarthritis makes no mention of RFA for the treatment of glenohumeral joint OA.

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Code	Description
66683	Implantation of iris prosthesis, including suture fixation and repair or removal of iris, when performed
C1839	Iris prosthesis

Insertion of iris prosthesis is unproven and considered not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Through a multicenter, prospective, unmasked, nonrandomized, interventional clinical trial, Ayres et al. (2022) reported on the results of the United States Food and Drug Administration Clinical Trial of the Custom Flex Artificial Iris to evaluate the safety and efficacy of the device, for treating congenital and acquired iris defects. The trial consisted of participants with photophobia, sensitivity secondary to partial or complete congenital or acquired iris defects, or both. The individuals were evaluated on day 1, week 1, and 1,3, 6, and 12 months after surgery. The outcomes measured were slit-lamp findings, intraocular pressure, implant position, subjective visual symptoms, and complications. At 3, 6, and 12 months, corrected distance visual acuity (CDVA) and endothelial cell density (ECD) were measured as added safety evaluations. The 25-item National Eye Institute Visual Function Questionnaire (NEIVFQ-25) was utilized to assess the health-related quality of life affected by vision. And to evaluate cosmetic results, the Global Aesthetic Improvement Scale was used. The results showed at 12 months postoperatively, a 59.7% reduction in marked to severe daytime light sensitivity ($p < 0.0001$), 41.5% reduced marked to extreme nighttime light sensitivity ($p < 0.0001$), 53.1% marked to severe daytime glare reduction ($p < 0.0001$), and 48.5% severe nighttime glare reduction ($p < 0.0001$) uncovered. The NEIVFQ-25 scores showed a 15.4-point improvement ($p < 0.0001$), with 98.3% of individuals showing an improvement in cosmesis, measured by the Global Aesthetic Improvement Scale at 12 months following the surgery. No loss of CDVA of > 2 lines related to the device was found, and a median ECD loss was 5.3% at six months post-operative and 7.2% at 12 months post-surgery. The authors concluded that the artificial iris (AI) surpassed all critical safety endpoints for an adverse device, intraocular lens (IOL), or implant surgery-related adverse events. The AI also met all the essential efficacy endpoints, including decreased light and

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glare sensitivity, improved health-related quality of life, and satisfaction with cosmesis appearances created by congenital or acquired iris defects. The findings are limited by the lack of comparison group.

Romano et al. (2022) conducted a systematic review to evaluate the literature on the use of AI implants in congenital aniridia, focusing on the different surgical implantation techniques, the clinical outcomes achieved, complications, and the risk of bias of the studies included. All the studies were retrospective, with a relatively small sample size, and without a control group. Even if the low incidence of aniridia makes clinical studies with adequate sample size complex, strong scientific evidence is needed, and thus conclusions drawn from the literature may be considered less dependable. The major drawback of small studies is that they are vulnerable to overestimating the size of an association, which is a limitation of this review. All reviewed papers were single-surgeon studies, and due to the rarity of individuals with aniridia, there were no strict inclusion criteria, resulting in selection bias [Figueiredo and Synder (2020), and Ayres et al. (2022) are included in this systematic review].

In a 2022 Hayes evolving evidence review, the CustomFlex Artificial iris (HumanOptics AG, Clinical Research Consultants Inc.) for aniridia, clinical evidence from poor or very poor-quality studies without control groups suggested that the implantation of an AI is technically possible. The AI was associated with improved glare, photosensitivity, aesthetics, and quality of life. Complications and adverse events were commonly reported and may be related to the additional ophthalmic comorbidities and the invasiveness and complexity of the procedures. Without control groups, it was unclear which complications can be attributed to AI implantation. A guideline against using AI insertion for congenital aniridia outside research settings was identified. No ongoing clinical studies were identified. A review of full-text clinical studies suggests minimal support for using CustomFlex Artificial Iris (HumanOptics AG) to treat aniridia. A review of full-text systematic reviews offers no/unclear support for using CustomFlex Artificial Iris (HumanOptics AG) for treating aniridia, as no relevant systematic reviews were identified. Based on a review of full-text clinical practice guidelines and position statements, the guidance offers strong support against using CustomFlex Artificial Iris (HumanOptics AG) to treat aniridia. The updated evidence review in 2024 found two newly published clinical studies and two systematic reviews both with minimal and no/unclear support for using CustomFlex Artificial Iris (HumanOptics AG) for treating aniridia. Furthermore, the review of clinical practice guideline abstracts showed a strong support against the use of CustomFlex Artificial Iris (HumanOptics AG) for treating aniridia. A review of abstracts in 2025 revealed 2 newly published clinical studies and 2 systematic reviews that may meet the inclusion criteria set out in the initial report published in 2022. The review of the clinical studies showed minimal support for the use of CustomFlex Artificial Iris. The systematic reviews reporting on the use of the technology showed no/unclear support, which is an upgrade in the current level of support. There is a strong support against the technology from the uncovered clinical practice guidelines reporting the utilization of the technology. Additionally, a review of U.S. Food and Drug Administration (FDA) regulatory information and the Hayes Knowledge Center indicates that no new applications of the technology have been identified since publication of the 2022 Evolving Evidence Review. [Figueiredo and Synder (2020), Rickman et al. (2016), and Spitzer et al. (2016) are included in the 2022 evolving evidence review. Ayres at al. (2022) and Romano et al. (2023) are included in the 2025 evolving evidence review update].

In a 2021 ECRI Clinical Evidence Assessment on CustomFlex Artificial Iris Prosthesis (HumanOptics AG) for Repairing Iris Defects, the evidence found was inconclusive and exceptionally low quality. CustomFlex improves light and glare sensitivity and eye aesthetics for individuals with aniridia based on very low-quality evidence from one large and four small case series. However, available studies are at too high a risk of bias to permit conclusions. CustomFlex's safety still needs to be clarified because some of the small case series report frequent adverse events (AEs). Large, prospective, multicenter studies are required in order to confirm findings and validate CustomFlex for individuals with congenital and acquired aniridia, but none are ongoing [Figueiredo and Snyder (2020) is included in this clinical evidence assessment].

Figueiredo and Snyder (2020) evaluated the effectiveness and safety of the CustomFlex device when used to treat photic symptoms in individuals with congenital aniridia. The retrospective single-surgeon case series involving 50 individuals and 96 eyes included those with more than six months follow-up (mean follow-up 44 months, 36 ±36 months). Pre- and post-operative data were collected regarding CDVA, subjective photophobia and glare, keratopathy, glaucoma, intraocular pressure (IOP), glaucoma drops, and other comorbid pathologies. Additional post-operative data were collected regarding post-operative complications, prosthesis decentration, and further surgeries. In all cases, additional procedures were performed during implantation, including phacoemulsification, IOL implantation repositioning or replacement, limbal relaxing incision, keratectomy (superficial and lamellar), or vitrectomy. Intraoperative complications were reported in 14 eyes (14.6%). Regarding photophobia, 95.7% (89/93) reported a reduction in symptoms, 3.2% (3/93) reported no change in symptoms, and 1.1% (1/93) reported a worsening of symptoms. The results were similar for the subjective reporting of glare; 95.2% (79/83) reported a reduction in symptoms, 3.6% (3/83) reported no change in symptoms, and 1.2% (1/83) reported a worsening of symptoms. When preoperative visual acuity (VA) was compared to the last measured post-operative VA, 58.3% (56) of the eyes improved to two or more lines, 32.3% (31) of the eyes stayed within two lines of preoperative measurements, and 9.4% (9) of the eyes dropped two or more lines. Compared to the best-measured post-

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operative VA, there were declines during the post-operative follow-up period. These declines were attributed to underlying comorbidities, including worsening of the ocular surface, aniridia fibrosis syndrome (AFS), retinal detachment, and posterior capsule opacification. Aniridic keratopathy, which was present in 84.4% (81) of the eyes preoperatively, was present in 85.4% (82) at the last visit. A total of 28.4% (23) of the eyes with preoperative keratopathy had progression of the disease. At the earlier visit, aniridic glaucoma was present in 33.3% (32) of the eyes preoperatively and in 51.0% (49). A total of 53.1% (17) of the eyes with preoperative glaucoma had progression of the disease. Added complications included AFS [3.1%; 95% confidence interval (CI): 0.6 to 8.9%], prosthesis decentration (9.4%), choroidal folds/effusion secondary to ocular hypotony (2.1%), retinal detachment (1.0%), cystoid macular edema (1.0%) and vitreous hemorrhage (1.0%). During the follow-up period, 33.3% (32) of eyes required added surgical intervention, with a mean of 2.97 ±1.87 surgeries performed/eye. While the study was limited to individuals with congenital aniridia, the group had significant heterogeneity related to aniridic pathology. The findings are further limited by the lack of contemporary comparison group.

In 2020a, interventional procedures guidance produced by NICE on AI insertion for congenital aniridia states:

- Evidence on the safety and efficacy of AI implant insertion for congenital aniridia needs to be improved in quantity and quality. Therefore, this procedure should only be used in the context of research.
- Research could include the use of observational data from cohort studies or high-quality case series. Studies should report details of patient selection, and the type of implant used. Outcomes should include quality of life and other patient-reported results.

The 2020b interventional procedures guidance produced by NICE on AI insertion for acquired aniridia states:

- Evidence on the safety and efficacy of AI implant insertion for acquired aniridia is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research.
- Research could include using observational data from cohort studies or high-quality case series. Studies should report details of patient selection, and the type of implant used. Outcomes should consist of quality of life and other patient-reported results.

In 2019, Mayer and colleagues, through an interventional case series in a single center study, described previously unrecognized late complications associated with AI implantation by evaluating the effect of an AI implant on the remnant iris. Individuals with remnant iris tissue who underwent AI implantation between June 2011 and December 2016 (n = 42) were evaluated to decide the influence of the prosthesis on the residual iris. A retraction of the residual iris was detected in 7 individuals. In all cases, the syndrome was seen via photographic comparisons rather than by the treating ophthalmologists or the treated individual. A total of 4 of the 7 affected individuals showed severe complications, including highly raised IOP, pigment dispersion associated with glaucoma, and recurrent bleeding into the anterior chamber. Several individuals needed additional invasive procedures, including glaucoma shunt surgery and an implant explanation. This study underscores the need for long-term data to predict better risks associated with specific techniques or comorbidities and to monitor for unanticipated complications.

The U.S. Food and Drug Administration on May 30, 2018, approved the first stand-alone prosthetic iris in the United States, CustomFlex Artificial Iris is a surgically implanted device to treat adults and children whose iris (the colored part of the eye around the pupil) is completely missing or damaged due to a congenital condition called aniridia or other damage to the eye. Additional information is available:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P170039. (Accessed May 29,2025)

Spitzer et al. (2016) retrospectively evaluated the functional, cosmetic, and complication outcomes in 34 individuals who received the AI implant. Individuals with a history of a severe globe injury with total or subtotal iris loss in one eye who received an AI were included. Distance visual acuity, IOP, and the rate of complications (long-term inflammation and corneal decompensation leading to corneal transplantation) were evaluated. The median follow-up period was 24 months. Postoperatively, 14 individuals had a VA improvement between 0.2 and 2.1 logMAR units, 11 had a VA change of less than 0.2 logMAR units, and nine individuals (26%) reduced VA (between 0.2 and 1.4 logMAR units). The median group VA was unchanged following AI implantation. Complications were noted. Post-operative hypotony was reported in ten individuals, 7 of whom had low pressure before AI implantation. In 2 of these individuals, the low IOP led to phthisis and blindness, and, ultimately, enucleation. Hypertony was seen in 6 individuals, 3 of whom had pre-existing glaucoma. Other complications, including persistent intraocular inflammation (9%) and macular edema (12%), were noted. A total of 12 individuals required corneal transplantation following AI implantation, with 6 of these cases showing endothelial decompensation post-AI implantation. Suspected post-operative endophthalmitis was recorded in one case. In many instances, other procedures, such as keratoplasty, repositioning of the AI, or strabismus surgery, were required. The authors noted that several factors could have contributed to the variability in responses to the AI, including pathophysiology related to the original trauma, complications or surgeries post-AI implantation, which were independent of the AI, and complications resulting from the AI implantation itself. While 34 individuals were included in the case series,

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only 20 of these participants were available to report subjective symptoms such as discomfort and glare. The findings are further limited by the lack of contemporary comparison group undergoing a different treatment approach.

In a retrospective interventional case series, Rickmann et al. (2016) evaluated the long-term clinical outcome (2 years or greater) and complication spectrum after AI implantation in 34 individuals with congenital, traumatic, or iatrogenic aniridia. Cases included individuals with complete and partial aniridia. Before implantation, five eyes were hypotonic, ten eyes had glaucoma, six had pre-existing keratopathy, and in 4 eyes, there was silicone oil in the anterior chamber. Complications included glaucoma (3), keratopathy (2), silicone oil in the anterior chamber (3), hemorrhage of the remnant iris (1), and retinal detachment (2). Consecutive surgery was needed in 5 eyes. When the VA at baseline was compared to the final examination, 16 eyes gained two or more VA lines, 15 remained stable, and three lost two or more VA lines. There was no significant difference in the mean IOP when the baseline was compared to the final examination. With the study being single-center and single-surgeon, additional studies are needed to improve the generalizability of the results. Furthermore, no comparison group was present and selection of only participants with two-year follow-up could have introduced biases in the findings.

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Code	Description
80145	Adalimumab
80230	Infliximab
80280	Vedolizumab

Note: The above codes are used to describe therapeutic drug assays for these medications and does not apply to the use of the drugs which are reported with a different CPT code.

Laboratory measurement of antidrug antibodies and serum levels of biologic agents and biosimilars (e.g., infliximab, adalimumab, vedolizumab, ustekinumab, certolizumab pegol, golimumab) for assessing treatment response for the following conditions are unproven and not medically necessary due to insufficient evidence of safety and/or efficacy:

- Inflammatory bowel disease (including ulcerative colitis and Crohn's disease)
- Juvenile Rheumatoid Arthritis/Rheumatoid Arthritis
- Hidradenitis Suppurativa
- Plaque Psoriasis
- Psoriatic Arthritis
- Ankylosing Spondyloarthritis

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Clinical Evidence

Therapeutic drug monitoring (TDM) involves measurement of drug or active metabolite levels and anti-drug antibodies (ADA), and is based on the premise that there is a relationship between drug exposure and outcomes, and that considerable inter-individual variability exists in how patients metabolize the drug (pharmacokinetics) and the magnitude and duration of response to therapy (pharmacodynamics) (Vande Casteele et al., 2017). TDM is also used to assess compliance and to guide dose adjustments or switch off therapy (e.g., where patients are relapsing despite therapeutic levels, or have developed high titer anti-drug antibodies with low levels). (Lamb, 2019). Proactive TDM involves the measurement of serum drug levels and anti-drug antibodies regardless of disease activity. The drug dose can then be adjusted if needed to achieve a target serum level within a therapeutic range. Reactive TDM is the measurement of drug concentrations and anti-drug antibodies triggered by a clinical event such as a disease flare. The goals of both proactive and reactive TDM are to optimize individual patient dosage regimens to improve disease management outcomes (Kawano-Dourado, 2024).

Manceñido Marcos et al. (2024) conducted a systematic review and meta-analysis to assess efficacy and safety of proactive TDM versus conventional management during maintenance treatment with anti-TNFα in patients with IBD. Nine studies (1 systematic review, 6 RCTs, and 2 cohort studies) were analyzed in this review. No superior efficacy was observed for proactive TDM. Data suggested that proactive TDM could improve anti-TNFα treatment durability, prevent acute infusion reactions, lower adverse events, and reduce the probability of surgery, at lower economical expenditure. The authors concluded proactive TDM does not appear to be superior to conventional management of anti-TNFα therapy for maintaining clinical remission in patients with IBD. Proactive TDM should not be recommended for the management of patients with IBD receiving anti-TNFα therapy. Limitations in the study included small samples sizes, small number of high-quality studies, identification of disease type (UC or Crohn's) or phenotype variations in proactive TDM, and implementation of proactive TDM in real clinical practice. (Authors Vande Casteele 2015, D'Haens 2022, Assa 2019, Strik 2021, and Syversen 2021, which were previously cited in this policy, are included in this systematic review.)

Nguyen et al. (2022) conducted a systematic review and meta-analysis of RCTs comparing proactive TDM with conventional management in patients with IBD, primarily based on clinical response and inflammatory markers. This study included nine RCT and meta-analyses that assessed 1405 patients with IBD treated with TNFα antagonists. No statistically significant differences between proactive TDM and conventional management were identified in trials of maintenance therapy or in the single trial of induction therapy [relative risk (RR), 0.96; 95% confidence interval (CI), 0.81–1.13]. No differences were observed in risk of developing antidrug antibodies or serious adverse events. Participants in the proactive TDM arm were more likely to undergo dose escalation. The authors concluded there was no benefit observed for proactive TDM compared with conventional management in achieving and/or maintaining clinical remission in patients with IBD. Limitations in the study include participant population (proportion of patients on concomitant immunomodulators, and those who underwent prior optimization of therapy), interventions with variability in thresholds, comparators, and outcome definitions. Future studies focusing on TDM during induction therapy, or in a subset of patients with active disease and unfavorable pharmacokinetics who may be at high risk of immunogenicity, are warranted. (Publications by Vande Casteele 2015, D'Haens 2022, Assa 2019, Strik 2021, Bossuyt 2022, and Syversen 2021, which were previously cited in this policy, are included in this systematic review.)

In 2021, Tikhonova et al. conducted a health technology assessment systematic review on behalf of the National Institute for Health Research (NIHR) to provide NICE with the most up-to-date evidence on the clinical and cost effectiveness of alternative testing and monitoring approaches for assessing TNF-α inhibitor levels and antibodies to TNF-α inhibitor levels in people with RA undergoing treatment with adalimumab (ADL), ETN, infliximab (IFX), cimzia (CTZ) or golimumab (GLM). The results regarding the clinical effectiveness of this testing included two studies, both conducted in Spain and included participants with RA as < 70% of the study population. Both studies were of poor quality with significant limitations. A non-randomized trial in which less than 40% of the participants had RA, and contained input from other studies, as well as expert advice, showed there was an insignificant reduction in the risk of disease flare in the treatment group when compared to the control, and the observational study concluded that TDM was associated with an insignificant reduction in the mean Disease Activity Score in 28 joints which indicates lower disease activity at seven year follow up. The authors concluded that there is limited evidence and much uncertainty in relation to the clinical effectiveness of enzyme-linked immunosorbent assay test-based TDM in rheumatoid arthritis. Additional high quality research is needed to assess the clinical impact of using enzyme-linked immunosorbent assay tests for monitoring TNF-α in rheumatoid arthritis patients who have achieved remission or low disease activity.

Vermeire et al. (2018) conducted a systematic review of articles published January 2009 to August 2015 reporting immunogenicity to adalimumab (ADM), certolizumab pegol (CZP), golimumab, infliximab (IFX), ustekinumab, and vedolizumab in IBD. Eligible articles were reviewed, and quality assessed by independent reviewers. Overall, 122 publications reporting 114 studies were assessed. ADAs were reported for all agents, but the percentage of patients developing ADAs was extremely variable, with the highest (65.3%) being for IFX administration to patients with IBD. ADA

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presence was frequently associated with a reduction in primary efficacy and a loss of response, and, for IFX, an increase in adverse events (AEs). Lower serum levels of ADM, CZP and IFX were seen in ADAs-positive rather than ADAs-negative patients; pharmacokinetic data were unavailable for other therapies. The authors found little information regarding the timing of ADA development; studies reported their detection from as early as 10-14 days up to months after treatment initiation. The authors concluded that biologic therapies carry an intrinsic risk of immunogenicity, although reported rates of ADAs vary considerably. The clinical implications of immunogenicity are a concern for effective treatment; further research, particularly into the more recently approved biologics, is required. The publication did not address whether antibody measurements improve patients' outcomes. (Publications by Karmiris 2009, Paul 2013, Baert 2014, and Vande Casteele 2013, which were previously cited in this policy, are included in this systematic review.)

Adalimumab (Humira®)

A 2024 Hayes Evidence Analysis Research Brief was performed to summarize the volume of publications and to determine whether there was adequate published, peer-reviewed literature to evaluate the evidence related to the clinical utility of therapeutic drug monitoring (TDM) of adalimumab (Humira; AbbVie Biotechnology Ltd.) for the management of patients with inflammatory bowel disease (IBD). Two randomized controlled trials (RCTs), 5 comparative studies, and 4 systematic reviews/meta-analyses were identified. The authors concluded that there is adequate published peer-reviewed literature to evaluate the evidence related to the clinical utility of TDM of adalimumab for the management of patients with IBD. Conclusions about clinical validity or clinical utility cannot be made within this report because drawing conclusions requires a full-text review of the evidence.

Li et al. (2024) conducted a systematic review if the evidence with regard to the benefits of TDM for optimizing treatment in patients being treated with adalimumab (ADM) therapy. Three key issues were assessed; if proactive TDM improves outcomes, if TDM can assist in guiding treatment strategies in patients who had failed response, and can TDM inform dose reduction or discontinuation in patients with low disease activity or remission. Nine studies were included in this systematic review and narrative analysis. The results of 3 RCTs and one observational study showed that proactive TDM showed no significant superiority to reactive TDM or standard management. With regard to TDM guiding treatment in patients with treatment failure, the results of two retrospective studies showed conflicting results, with one showing that in patients that had relapse and negative antibody tests, had a higher clinical remission rate, while the other did not demonstrate a clear predictive value. One non-randomized trial compared dose intensification with changing drug in patients receiving ADM who experienced loss of response with ADM drug levels > 4.9 µg/mL These results showed a longer median time without discontinuation in the group that switched drugs compared to those that had current drug dose intensified. The authors concluded that TDM may assist in the understanding of treatment failure and subsequent treatment decisions. Two studies evaluated the value of TDM in guiding dose reduction or discontinuation of treatment. These results showed that ADM dose halving is feasible for patients who have achieved remission and adequate drug levels. One study evaluated whether or not ADM and ADA status is predictive of disease flares following ADM discontinuation in patients that received it for more than one year and achieved remission for 6 months. These results showed that no ADM concentration level clearly predicted disease flares in this population. These findings are limited by a lack of overall studies. Additional high quality studies are needed.

In 2022, D'Haens et al. reported the results of the SERENE CD phase 3, randomized, double-blind, multicenter trial that performed across 93 sites in 19 countries to evaluate higher vs standard adalimumab induction dosing as well as clinically adjusted (CA) vs TDM maintenance in patients with moderate to severe CD. Participants were first randomized to the higher induction regimen or standard induction regimen followed by 40 mg every other week from week 4 onward. Primary end points included clinical remission at week 4 and endoscopic response at week 12. At week 12, patients were re-randomized to maintenance therapy optimized by the Crohn's Disease Activity Index and C-reactive protein or serum adalimumab concentrations and/or clinical criteria. A 44-week double blind maintenance study was added with all participants. Exploratory end points were then evaluated at week 56. The results showed similar proportions of patients receiving higher induction regimen and standard induction regimen achieved clinical remission at week 4 and endoscopic response at week 12. Week 56 efficacy was similar between CA and TDM. The authors concluded that a higher induction regimen was not superior to standard induction regimen, and CA and TDM maintenance strategies were similarly efficacious. Maintenance dose adjustment primarily by serum adalimumab levels was not more efficacious than clinically adjusted dosing. The SERENE CD trial confirms the appropriateness of the approved adalimumab Induction dose regimen. Although exploratory, no clinical advantage for TDM over clinical adjustment during maintenance therapy was observed (This study is included in Hayes 2024 report).

In a 2018 ECRI evidence analysis on the Anser ADA Assay (Prometheus Laboratories, Inc.) to monitor serum adalimumab (Humira) and antiadalimumab antibodies for guiding treatment with this immunotherapy, it was concluded that the available studies provide low-quality data on the clinical validity and none for clinical utility. Large, multicenter cohort studies are needed to validate Anser ADA's diagnostic accuracy and to compare clinical outcomes of patients treated empirically or with Anser ADA monitoring. Studies are also needed to compare Anser ADA and other assays.

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Assa et al. (2019, included in Li, 2024 above) performed a nonblinded, randomized controlled trial of 78 children to investigate whether proactive drug monitoring is associated with higher rates of clinical remission in pediatric patients with CD. Participants were randomly assigned to groups that received proactive monitoring (trough concentrations measured at weeks 4 and 8 and then every 8 weeks until week 72, n = 38) or reactive monitoring (physicians were informed of trough concentrations after loss of response, n = 40). In both groups, doses and intervals of adalimumab were adjusted to achieve trough concentrations of 5 μg/mL. The primary endpoint was sustained corticosteroid-free clinical remission at all visits (week 8 through week 72). The primary endpoint was achieved by 31 children (82%) in the proactive group and 19 children (48%) in the reactive group (p = .002). Sixteen patients in the proactive monitoring group (42%) achieved a composite outcome of sustained corticosteroid-free remission, C-reactive protein ≤ 0.5 mg/dL, and level of fecal calprotectin ≤ 150 μg/g compared with 5 patients in the reactive monitoring group (12%) (p = .003). By week 72 of treatment, 33 patients in the proactive monitoring group had received adalimumab intensification (87%) compared with 24 patients in the reactive monitoring group (60%) (p = .001). The authors concluded that proactive monitoring of adalimumab trough concentrations and adjustment of doses and intervals resulted in significantly higher rates corticosteroid-free clinical remission than reactive monitoring (measuring trough concentration after loss of response). Independent confirmation with larger sample sizes, longer follow-up, and a broader age range are necessary before these findings can be translated into routine clinical practice (This study is included in Hayes 2024 report).

In a multicenter retrospective cohort study, Papamichael et al. (2019, included in Li, 2024 above) compared the long-term outcome of patients with IBD who received at least one proactive TDM of adalimumab (ADA) with standard of care, defined as empiric dose escalation and/or reactive TDM. Patients (n = 382) received either at least one proactive TDM (n = 53) or standard of care (empiric dose escalation, n = 279; reactive TDM, n = 50). Treatment failure was defined as drug discontinuation for secondary loss of response or serious adverse event or need for IBD-related surgery. Serum adalimumab concentrations and antibodies to adalimumab were measured using the Prometheus homogeneous mobility shift assay. Patients were followed for a median of 3.1 years (interquartile range, 1.4-4.8 years). Multiple Cox regression analyses showed that at least one proactive TDM was independently associated with a reduced risk for treatment failure [hazard ratio (HR): 0.4; 95%CI: 0.2-0.9; p = 0.022]. In the authors' opinion, this study provides the first evidence that proactive TDM of adalimumab may be associated with a lower risk of treatment failure compared to standard of care in patients with IBD. Long-term randomized controlled trials are needed to further validate these findings (This study is included in Hayes 2024 report).

Baert et al. (2016, included in ECRI evidence analysis) evaluated 536 prospectively collected serum samples of patients with IBD for analysis of ADA concentration and antibodies-to-adalimumab (ATA) using homogeneous mobility shift assay. A mixed model repeated measure analysis was performed to assess the independent effects of serum ADA concentration and ATA on C-reactive protein (CRP) and response. ATA were detected in 20% of patients after a median of 34 (12.4-60.5) weeks. ATA-positive samples correlated with lower serum ADA concentration (p < 0.001). The model revealed that both lower serum ADA concentration and ATA were independently associated with future CRP (p = 0.0213 and p = 0.0013 respectively). ATA positivity was associated with discontinuation of ADA because of loss of response (OR = 3.04; 95% CI 1.039 to 9.093; p = 0.034). Further studies are needed to evaluate the impact of ATA on drug management.

Golimumab (Simponi®)

A Hayes (2022a) Evidence Analysis Research Brief on TDM of Golimumab (Simponi) found that there currently is not enough published peer-reviewed literature to evaluate the evidence related to TDM of golimumab for IBD in a full assessment.

Infliximab (Remicade®)

Brun et al. (2024) conducted an open label study to analyze data from two randomized controlled NOR-DRUM trials. NOR-DRUM A, a 38-week trial, and NORDRUM B, a 52-week trial, assessed the effect of proactive therapeutic drug monitoring compared with no therapeutic drug monitoring (standard therapy) in patients initiating infliximab (NOR-DRUM A) and in patients on infliximab maintenance therapy (NOR-DRUM B). From the 616 patients included in the trials, 615 patients (181 with spondyloarthritis, 120 with rheumatoid arthritis, 72 with psoriatic arthritis, 114 with ulcerative colitis, 83 with Crohn's disease, and 45 with psoriasis) had at least one serum infliximab and antidrug antibody assessment. Antidrug antibodies were detected in 147 patients. Remission at week 30 occurred in 25 of 72 patients with antidrug antibodies and 180 of 335 without antidrug antibodies. In comparison in patients with antidrug antibodies versus patients without antidrug antibodies, higher rates were found for: disease worsening over 52 weeks, infusion reactions, and infliximab discontinuation. These associations were more pronounced in patients with high concentrations of antidrug antibodies than in those with low concentrations of antidrug antibodies. Independent of antibody status, therapeutic drug monitoring was associated with a lower risk of disease worsening or an infusion reaction and was associated with an increase in the rate of infliximab discontinuation. The authors concluded that in patients where antidrug antibodies were detected, remission was less likely to be reached and sustained, and infusion reaction or discontinuation of infliximab was

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more likely. Timely detection of antidrug antibodies by proactive TDM facilitated treatment decisions that reduced the negative outcomes, both regarding infliximab effectiveness and safety. The role of proactive TDM in infliximab therapy is emphasized for patients at risk for developing antidrug antibodies. Limitations were identified and included the study was open label and exploratory. Second, the possibility for sparse-data bias for some of the hazard ratio (HR) estimates. Third, the lack of establishing a causal effect of antidrug antibodies on the outcomes, both due to possible unmeasured confounding and due to selection bias of HRs. Finally, association outcomes in patients who are antidrug antibody-negative initially, but later detected with antidrug antibodies might differ in patients who are antidrug antibody-negative and never develop antidrug antibodies.

Bossuyt et al. (2022) conducted a pragmatic trial to compare outcomes of an ultra-proactive TDM algorithm of infliximab based on point of care testing, with reactive TDM in patients with IBD on maintenance infliximab for at least 14 weeks. The trial was conducted in two large non-academic IBD centers, one focused on ultra-proactive TDM in 115 patients and the other focused on reactive TDM in 72 patients. The primary endpoint was failure of IFX therapy after 1 year, defined as infliximab discontinuation, IBD-related surgery or hospitalization, add-on treatment, and allergic reaction to infliximab. One secondary endpoint included sustained clinical remission based on physician global assessment which included the number of trough level (TL) measurements per patient per year, the percentage of interval changes, the percentage of patients with infliximab discontinuation, and percentage of patients with sustained clinical remission. Another secondary endpoint included mucosal remission based on endoscopy and/or fecal calprotectin between 6 and 12 months. The results showed a significant difference in the use of TL measurements between the two groups, with the patients in the ultra-proactive TDM cohort having a mean number of 8.8 TL measurements per year compared with only one TL measurement per year in the reactive group. The higher number of TL measurements led to a significant difference in dose flexibility in the ultra-proactive TDM group. Half of the patients in the ultra-proactive cohort had an interval shortening compared with only 15% in the reactive group. Additionally, more interval prolongations and bidirectional changes were applied in the ultra-proactive group. However, no differences were seen in infliximab failure rates after 2 years of follow-up: 19% of patients in the ultra-proactive cohort versus 10% in the reactive cohort. For the secondary clinical outcomes, no difference was seen in infliximab discontinuation rate nor in the sustained clinical remission rate. There was a significant difference in the proportion of patients with mucosal remission, with 79% in the reactive TDM cohort compared with 52% in the ultra-proactive TDM cohort, however these results need to be interpreted with caution as the assessment based on endoscopy or fecal calprotectin was part of standard of care and was only taken into account between 6 and 12 months and data were only available in 71 patients. The authors concluded that these results show that ultra-proactive TDM has no superior impact on clinical outcomes over reactive TDM which remains the strategy of choice during maintenance infliximab treatment. It is acknowledged that this pragmatic trial only addresses patients on maintenance treatment and further studies are needed for TDM during induction treatment. The findings are limited by lack of randomization (This study is included in Hayes report).

Hayes (2022b, updated in 2024) completed a health technology assessment on the use of anti-infliximab antibody levels to monitor Infliximab treatment in patients with Crohn's Disease. Based on the results of 3 randomized controlled trials (RCTs), 3 prospective cohort studies, 4 retrospective cohort studies, 1 prospective trial with historical controls, and 1 retrospective registry analysis it was concluded that there has not been enough high-quality evidence to demonstrate sufficient diagnostic or prognostic accuracy or capacity to improve management or health outcomes, and additional well-designed studies are needed.

In a 2021 randomized clinical trial (NOR-DRUM), Syversen et al. assessed whether proactive TDM during maintenance therapy with infliximab improves treatment efficacy by preventing disease worsening compared with standard infliximab therapy without TDM. The trial included 458 adult patients with immune-mediated inflammatory diseases and included rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease, or psoriasis who had been undergoing maintenance therapy with infliximab for a minimum of 30 weeks and a maximum of 3 years. Patients were randomized 1:1 to receive either TDM in the TDM group, in which infliximab dosing was adjusted according to an algorithm designed to maintain infliximab levels within the therapeutic range of 3 to 8 mg, or standard therapy in which administration was based on clinical judgement. The primary outcome was sustained disease control without worsening during the study period of 52 weeks. The results showed this outcome was achieved for 74% of patients in the TDM group and 56% in the standard therapy group. Secondary outcomes reflected disease activity, remission rate and patient reported outcomes at week 52 and there were no significant differences between the two groups. Adverse events were reported in 60% and 63% patients in the TDM and standard therapy groups, respectively. The number of infections was higher in the TDM group. Three patients in the standard therapy group and none in the TDM group experienced an infusion reaction. The authors concluded that proactive TDM was more effective than treatment without TDM in sustaining disease control during maintenance therapy without disease worsening, and further research is needed to compare proactive TDM with reactive TDM to validate these findings.

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Strik et al. (2021) conducted a randomized control, multicenter study to investigate the efficacy of dashboard driven Infliximab (IFX) dosing compared to standard dosing in a prospective trial for individuals. Eighty individuals were randomly assigned to receive either dashboard driven IFX dosing (precision dosing group, PG) or continued IFX maintenance treatment without adjustments of the dose and/or treatment interval (conventional dosing group, CG). IFX is administered through intravenous infusions using weight-base (5 mg/kg) with an induction schedule at week 0, 2, 6 and followed by 8-weekly maintenance treatments with a goal to achieve and maintain remission in individuals with IBD. During maintenance treatment, an association was reported between IFX trough levels (TL) of 3 mcg/ml to correlate with improved clinical outcomes. After one year, 28/32 (88%) of individuals in the PG were in sustained clinical remission versus 25/39 (64%) of the CG individuals. The authors concluded that a higher percentage of individuals receiving dashboard guided IFX dosing maintained clinical remission during one year of follow-up compared to patients who did not receive proactive dose adjustments. In the majority of patients with TLs > 3 mcg/ml dose reduction did not lead to clinical Loss of Response (LOR). However, a small proportion of patients may need higher target TLs depending on the specific treatment goal. Future trials should be performed to investigate dashboard guided dosing of IFX in individuals with IBD during induction treatment. Limitations of the study included lack of endoscopies performed due to the use of FCP as a reliable measurement of disease activity, use of drug-sensitive assay to detect glow ADA levels, but presence was clinically insignificant and a lower IFX target concentration which might not have been an optimal target (This study is included in Hayes report).

In a systematic review and meta-analysis, Ricciuto et al. (2018) examined the effectiveness of TDM used to improve clinical outcomes in patients with IBD treated with anti- anti-TNF drugs. The search identified nine studies (three RCTs, six observational), which focused on IFX maintenance therapy in adults. The results of the review showed that neither proactive nor reactive TDM was associated with superior clinical remission rates compared to empiric dose optimization. However, evidence of a cost benefit, particularly for reactive TDM vs empiric care, was identified. In several studies, TDM, particularly proactive TDM, was associated with favorable outcomes related to durability of anti-TNF response, such as lower drug discontinuation rates compared to empiric care and reactive TDM, and lower relapse rates compared to empiric care. No consistent benefit was found for endoscopic or surgical outcomes. The authors recommend additional, longer-term studies, particularly to further investigate proactive TDM, and to generate data on other anti-TNF agents, the induction period and pediatric populations (This study is included in Hayes report).

In a systematic review and meta-analysis, Moore et al. (2016) evaluated studies that reported serum IFX levels according to outcomes in IBD. The primary outcome was clinical remission, and secondary outcomes included endoscopic remission, and CRP levels. A total of 22 studies met the inclusion criteria, including 3483 patients; 12 studies reported IFX levels in a manner suitable for determining effect estimates. During maintenance therapy, patients in clinical remission had significantly higher mean trough IFX levels than patients not in remission: 3.1 µg/ml versus 0.9 µg/ml. The standardized mean difference in serum IFX levels between groups was 0.6 µg/ml [95% confidence interval (CI) 0.4-0.9, p = 0.0002]. Patients with an IFX level > 2 µg/ml were more likely to be in clinical remission [risk ratio (RR) 2.9, 95% CI 1.8-4.7, p < 0.001], or achieve endoscopic remission (RR 3, 95% CI 1.4-6.5, p = 0.004) than patients with levels < 2 µg/ml. The authors concluded that there is a significant difference between serum IFX levels in patients with IBD in remission, compared with those who relapse, and a trough threshold during maintenance > 2 µg/ml is associated with a greater probability of clinical remission and mucosal healing.

Baert et al. (2014) studied 128 consecutive patients (105 patients with CD, 23 patients with UC) who restarted IFX after a median 15-month discontinuation (range, 6-125 months) to investigate correlations among response to treatment, infusion reactions, treatment modalities, trough levels, and antibodies to IFX. The absence of antibodies to infliximab at T+1 [hazard ratio (HR), 0.14; 95% confidence interval (CI), 0.026-0.74; p = .021] and re – initiation with concomitant immunomodulator therapy were associated with short-term responses (HR, 6.0; 95% CI, 1.3-27; p = .019). Based on the results, the authors concluded that reinitiating IFX therapy can be safe and effective for patients with CD or UC after a median 15-month discontinuation period. Additional studies are needed to validate these findings (This study is included in Hayes report).

In a pilot retrospective observational study, Vaughn (2014, included in Hayes report) examined the use of proactive therapeutic concentration monitoring (TCM) and titration of IFX to a target concentration for patients with IBD (n = 48) in clinical remission at a tertiary care center. The primary aim was to describe the clinical course of patients who had proactive TCM. A secondary analysis was done to assess if this strategy was superior to the standard of care. Fifteen percent of patients had an initial undetectable trough concentration. Twenty-five percent (12 of 48) of patients escalated IFX after the first proactive TCM while 15% (7 of 48) of patients de-escalated IFX therapy over the study period. A control group of 78 patients was identified. Patients who had proactive TCM had a greater probability of remaining on IFX than controls (hazard ratio, 0.3; 95% confidence interval, 0.1-0.6; log rank test; p = 0.0006). The probability of remaining on IFX was greatest for patients who achieved a trough concentration > 5 µg/mL (hazard ratio, 0.03; 95% confidence interval, 0.01-0.1; p < 0.0001 versus trough < 5 µg/mL). Fewer patients in the proactive TCM group stopped IFX (10% versus 31%,

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p = 0.009). Although the authors concluded that proactive TCM of IFX frequently identified patients with low or undetectable trough concentrations and resulted in a greater probability of remaining on IFX, additional studies are needed to determine clinically meaningful thresholds.

Vedolizumab (Entyvio®)

In a 2024 phase 4 randomized controlled trial (ENTERPRET), Jairath et al. assessed the efficacy of dose optimization in patients with UC who have early nonresponse (ENR) to vedolizumab and high drug clearance. The trial included 278 participants with moderate to severe UC who had high drug clearance at 5 weeks (serum concentration < 50 mg/mL) and non-response to standard vedolizumab treatment at week 6. The primary end point was the proportion of patients achieving endoscopic improvement, (defined as a Mayo endoscopic sub score of 1 or less) at week 30. The study was comprised of a 28-day screening period, a 6-week lead-in period, and a 24-week randomized treatment period. Participants that had a clinical response in the lead in period were not randomized and received standard care. There were 108 patients who were nonresponders at week 6 who also had a serum vedolizumab concentration less than 50 mg/mL at week 5 and were randomized 1:1 to receive treatment with the standard vedolizumab dosing regimen or with dose optimized vedolizumab. The results showed that at week 30 there were no statistically significant differences between the groups with ten patients in the standard dosing group and eight in the dose optimized group showing endoscopic improvement, and five participants in each treatment group achieving clinical remission. Antivedolizum antibody (AVA) development was similar in both groups with 11.3% in the standard dosing group having at least one positive result for AVAs and 7.5% for neutralizing AVAs. In the dose-optimized group, 9.1% had at least 1 positive result for AVAs and 7.3% had a positive result for neutralizing AVAs. Adverse events (lead -in group were included) were mild to moderate. There were eight serious AEs that led to discontinuation of the drug. These results showed that 47.5% of participants in this trial had a clinical response to vedolizumab at week 6 of treatment. For those who did not respond, and had high drug clearance, results were similar for those that then received dose optimized treatment. For the primary end point, approximately 16% of patients who did not respond to treatment at week 6 had endoscopic improvement at week 30, irrespective of the dosing regimen they received. The authors concluded that some patients with ENR may gain a response between weeks 6 and 30 with extended treatment, suggesting that the duration of treatment may be a more important factor in gaining a response than serum drug level.

Yarur et al. (2019) conducted a prospective cohort study to assess the relationship of serum vedolizumab concentrations (SVC) during induction and endoscopic remission in 55 patients with IBD after 52 weeks of therapy with vedolizumab (VDZ). The authors also sought to assess the incidence of antibody to vedolizumab (ATV) formation, the effect of ATV on drug pharmacokinetics and efficacy, and identify variables associated with SVC through the first 30 weeks of treatment. Collected variables included demographics, clinical disease activity, biomarkers, pre-infusion SVC, and ATV measured at weeks 2, 6, 14, 22, and 30. The primary outcome was steroid-free endoscopic remission at week 52. Patients that achieved steroid-free endoscopic remission by week 52 had higher SVC at weeks 2, 6, 14, 22, and 30, but only achieved statistical significance at weeks 2 and 6. Only 3 out of the 55 study subjects (5.5%) had detectable ATV through the follow-up. Overall, there were a positive correlation between SVC and serum albumin and a negative correlation with C-reactive protein, fecal calprotectin, and body mass. Vedolizumab concentrations ≥ 23.2 mcg/ml at week 2 were associated with endoscopic remission at week 52 [OR 8.8 (95% CI 2.6-29.7), p < 0.001]. VDZ concentrations during induction were associated with endoscopic remission at week 52. The authors concluded that interventional studies looking into improved efficacy with higher drug exposure are warranted.

Pouillon et al. (2019) evaluated the association between VDZ trough levels through TDM, and histological healing in UC in a single-center retrospective cohort study. Thirty-five histological samples from patients with UC on VDZ maintenance therapy were included. Per-event analysis was performed. Histological healing was defined as a Nancy histological index ≤ 1. The results showed that histological healing was associated with higher VDZ trough levels during maintenance therapy in UC. Based on this analysis, the authors found that a VDZ trough level threshold of 25 μg/mL proved most optimal to predict histological healing according to the Nancy histological index. Confirmation of these data in larger, independent cohorts is needed.

In a 2018 ECRI evidence analysis on the Anser VDZ Assay (Prometheus Laboratories, Inc.) to monitor serum vedolizumab (Entyvio) and antiadalimumab antibodies for guiding treatment with this immunotherapy, it was concluded that no available studies provide data to assess Anser VDZ's clinical validity or utility in patients with IBD. Diagnostic cohort studies are needed to validate Anser VDZ's diagnostic accuracy, and controlled trials that compare outcomes of vedolizumab therapy with and without Anser VDZ monitoring are needed to assess the test's clinical utility.

In a retrospective cohort study, Dreesen et al. (2018) investigated the correlation between VDZ exposure and response to identify patient factors that affect exposure and response. Serum concentrations of VDZ were drawn on 179 consecutive patients (66 with UC and 113 with CD) before all infusions and up to week 30. Effectiveness endpoints included endoscopic healing (UC, Mayo endoscopic sub-score ≤ 1; CD, absence of ulcers), clinical response (physicians' global

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assessment), and biologic response or remission (based on level of CRP) and were assessed at week 14 (for patients with UC) and week 22 (for patients with CD). VDZ trough concentrations > 30.0 μg/mL at week 2, > 24.0 μg/mL at week 6, and > 14.0 μg/mL during maintenance therapy associated with a higher probability of attaining the effectiveness endpoints for patients with UC or CD ($p < .05$). Higher body mass and more severe disease (based on high level of CRP and low level of albumin and/or hemoglobin) at the start of VDZ therapy associated with lower trough concentrations of VDZ over the 30-week period and a lower probability of achieving mucosal healing ($p < .05$). Mucosal healing was achieved in significantly more patients with UC than patients with CD, even though a diagnosis of UC was not an independent predictor of higher VDZ trough concentrations. Prospective studies are needed to evaluate the impact of TDM on clinical management (This study is included in Hayes 2022a and 2022b report).

Ustekinumab (Stelara®)

Vasudevan et al. (2024) conducted a systematic review and meta-analysis to determine if trough concentrations during maintenance therapy are associated with treatment response in patients with IBD. Included were 14 observational studies that included 919 patients in clinical remission (63% with Crohn's disease) and 290 patients with endoscopic remission (all with Crohn's disease). The primary outcome was the difference in serum ustekinumab trough concentrations between responders and nonresponders. Five studies compared median trough concentrations for patients in clinical remission with CD and compared the results to those that did not achieve remission. Those results showed a higher mean trough concentration in those with clinical remission with a mean difference of 1.61 ug/mL. Two studies showed that the mean trough concentration was also higher in patients in endoscopic remission (mean difference of 1.22 ug/mL). Two studies reported the rates of clinical remission based on trough levels (one in CD, one in UC) of ustekinumab and the results showed higher concentrations were associated with higher clinical remission. Endoscopic remission was also associated with higher levels of ustekinumab, but this was not clinically significant. Also included were studies that reported rates of clinical and endoscopic remission based on designated cut off values for trough concentration. These results showed no significant differences between 2 ug/mL with those that ranged from 4 to 5 ug/mL. Immunogenicity results from seven RCTs showed antidrug antibodies ranging from 4.2% to 5.6%. The data from 13 observational studies showed a rate of 1.2% of patients. The authors concluded that for patients being treated with ustekinumab for IBD, there is an association between higher drug trough levels and improved clinical and endoscopic outcomes, with stronger evidence for clinical outcomes. Limitations of these findings include a lack of randomized trials available for analysis, as well as a lack of standardized assays used. Further high quality research is needed to assess the clinical utility of these tests.

In a 2018 ECRI evidence analysis regarding the Anser UST Assay (Prometheus Laboratories, Inc.) for monitoring serum and anti-ustekinumab antibody levels in patients receiving this immunotherapy to guide treatment, it was concluded that there is very limited data on the clinical validity and none on clinical utility. Multicenter diagnostic cohort studies enrolling at least 100 patients each are needed to validate Anser UST's diagnostic accuracy. Controlled studies are needed to assess clinical utility in terms of how therapeutic drug monitoring using Anser UST affects treatment decisions and patient-oriented outcomes compared with empirical therapy escalation or other therapeutic drug monitoring methods.

Clinical Practice Guidelines

In 2024, an international panel (including patient partners, clinicians, and methodologists) convened to make recommendations on proactive therapeutic drug monitoring of biologic drugs, and assess whether or not it improves outcomes compared to standard care in adult patients with inflammatory bowel disease, inflammatory arthritis, or psoriasis. These recommendations were based on a systematic review and meta-analysis, and included ten trials comprised of 2383 participants and include the following recommendations (Kawano-Dourado et al.,2024):

- For adult patients with inflammatory bowel disease, inflammatory arthritis, or psoriasis receiving treatment (maintenance) with intravenous infliximab proactive TDM rather than reactive TDM or no TDM is suggested.
- For adult patients with inflammatory bowel disease, inflammatory arthritis, or psoriasis receiving treatment (maintenance) with adalimumab or other biologic drugs not using proactive TDM is suggested.
- For adult patients with inflammatory bowel disease, inflammatory arthritis, or psoriasis starting treatment with intravenous infliximab, adalimumab, and other biologic drugs not using proactive TDM is suggested.

National Institute for Health and Care Excellence (NICE)

In a 2019 diagnostic guidance document on therapeutic monitoring of TNF-alpha inhibitors using enzyme-linked immunosorbent assay's (ELISA) in rheumatoid arthritis, NICE states that this testing shows promise but there is currently insufficient evidence to recommend their routine adoption in rheumatoid arthritis.

American College of Gastroenterology (ACG)

In a 2018 clinical guideline on the management of CD in adults, the ACG states that therapeutic drug monitoring has become very common in the management of CD especially among patients who initially responded to biologic therapy but

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then developed loss of clinical response. While a detailed critical examination of the role of therapeutic drug monitoring was beyond the scope of this guideline, if active CD is documented, the assessment of biologic drug levels and antidrug antibodies (therapeutic drug monitoring) should be considered.

In a 2019 clinical guideline on the management of ulcerative colitis in adults, the ACG states the following:
Induction of remission in moderately to severely active ulcerative colitis:

- The patient with nonresponse or loss of response to therapy should be assessed with therapeutic drug monitoring to identify the reason for lack of response and whether to optimize the existing therapy or to select an alternate therapy.
- Maintenance of remission in patients with previously moderately to severely active ulcerative colitis.
- There is insufficient evidence supporting a benefit for proactive therapeutic drug monitoring in all unselected patients with UC in remission.

American Gastroenterological Association (AGA)

The 2017 American Gastroenterological Association (AGA) Institute's technical review of the role of TDM in the management of IBD states that it "is a promising strategy" that can be used to optimize inflammatory bowel disease therapeutics. It is based on the premise that there is a relationship between drug exposure and outcomes, and that considerable interindividual variability exists in how patients metabolize the drug (pharmacokinetics) and the magnitude and duration of response to therapy (pharmacodynamics).

The Institute identified knowledge gaps and future directions for TDM:

- Observational and comparative evidence is needed to define minimal effective exposure thresholds that are associated with clinically meaningful outcomes after induction and maintenance therapy.
- The maximum threshold concentration beyond which a ceiling effect is observed (i.e., above which further attempts at increased trough concentrations is highly unlikely to be effective) needs to be identified.
- Acknowledgment that such thresholds may be different for different outcomes of interest (e.g., clinical remission, endoscopic remission, fistula healing, management of CD after surgically induced remission, and left-sided UC vs pan-UC).
- Once thresholds are identified, randomized trials comparing the efficacy and safety of early optimized therapy based on TDM to target trough concentration(s) vs standard induction dosing should be evaluated.

The 2017 AGA clinical guideline for TDM in IBD includes the following:

- In adults with active IBD treated with anti-TNF agents, the AGA suggests reactive TDM to guide treatment changes. (Conditional recommendation, very low quality of evidence).
- In adult patients with quiescent IBD treated with anti-TNF agents, the AGA makes no recommendation regarding the use of routine proactive therapeutic drug monitoring due to a knowledge gap.
- There are several knowledge gaps in TDM that have been identified for which prospective observational and RCTs are warranted, which have been highlighted in the Technical Review above that accompanies this guideline.
- It is unclear whether TDM should be performed during induction therapy in patients with suboptimal response (as opposed to empiric dose escalation) and, if it is performed, what the target trough concentrations should be.
- Similarly, target trough concentrations when performed in the reactive setting in patients on maintenance therapy with different agents is unclear, and whether it should be different based on disease phenotype, disease state, and treatment target (clinical remission vs mucosal healing).
- Further studies are also needed to better define clinically meaningful vs insignificant anti-drug antibodies, based on titers and/or persistence on repeated testing, and at which titers can anti-drug antibodies be suppressed before needing to change drug therapies.
- Additionally, well-designed RCTs are needed that compare routine proactive TDM vs reactive TDM, and empiric dosing changes on patient relevant outcomes, and also the frequency and timing of proactive TDM.
- Finally, as newer biologic agents are approved, the use of TDM to optimize these drugs will need to be evaluated.

British Society for Rheumatology

In the 2022 guideline for the treatment of psoriatic arthritis (PsA) with biologic and targeted synthetic disease-modifying anti-rheumatic drug (DMARDs), the British Society for Rheumatology states that for patients with PsA that have an inadequate response to a biologic or targeted synthetic disease-modifying anti-rheumatic drug (b/tsDMARD), clinicians should consider potential factors that could be addressed including confirming correct diagnosis, adherence, pain due to other causes, drug levels and immunogenicity. It is further stated that a treat-to-target strategy, in which disease activity is proactively measured and treatment escalated accordingly should be offered to all patients with PsA (Tucker et al. 2022)

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Code	Description
81490	Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score

The use of a multi-biomarker disease activity (MBDA) test is unproven and not medically necessary for managing individuals with rheumatoid arthritis (RA) due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

The Vectra test (also referred to as the Vectra DA Disease Activity Test) (Laboratory Corporation of America Holdings) is a multi-biomarker blood test that measures levels of 12 molecular markers. A weighted algorithm based on the levels of these markers, along with age, gender, and adiposity, is used to calculate the adjusted multi-biomarker disease activity (aMBDA) score, resulting in a single number ranging from 0 to 100 to rank disease activity. The Vectra test is intended to measure disease activity in adult individuals who have rheumatoid arthritis (RA), with the goal of informing treatment decisions in conjunction with standard clinical assessment. Two testing options are available: Vectra, (which includes Vectra score, and risk for radiographic progression), and Vectra with CV Risk, (which includes a third component of risk of cardiovascular events). Hayes concluded that there was overall a very low-quality body of evidence, which was insufficient to evaluate the efficacy of the aMBDA score to measure rheumatoid arthritis activity or predict risk of disease progression, or to predict a risk of a cardiovascular event. The Vectra test is regulated under the Food and Drug Administration's (FDA) Clinical Laboratory Improvement Amendments (CLIA). Premarket approval from the FDA is not required for this test (Hayes, September 2024).

A prospective, observation study, sponsored by Sequenon (a molecular technology developer), in collaboration with LabCorp, is currently recruiting individuals to study the clinical benefit of using Vectra to guide treatment decisions in individuals with rheumatoid arthritis. This study expects to include 1,500 participants, with an expected completion date of September, 2025. ClinicalTrials.gov ID NCT03631225.

Another prospective, observational study, again sponsored by Sequenon (a molecular technology developer), in collaboration with LabCorp, looked at whether treatment decisions guided by MBDA scores would result in reduced disease activity relative to usual care in 444 individuals with rheumatoid arthritis. Study completion date was October 2022, with no study results posted. ClinicalTrials.gov ID NCT03810144.

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In a small interventional trial, Giles et al. (2024) looked at multi-biomarker panels (MBDAs) for RA disease, and if they would be associated with changes in arterial inflammation. Individuals with RA, with active disease despite treatment with methotrexate, were randomly assigned to additionally receive a TNF inhibitor or sulfasalazine+hydroxychloroquine (triple therapy). Fluorodeoxyglucose–PET/CT scans were done at baseline and at 24 week follow-up to assess for change in arterial inflammation "measured as the maximal arterial target-to-blood background ratio of FDG uptake in the most diseased segment of the carotid arteries or aorta [MDS (most diseased segment)-TBR_{max} (maximal target-to-background ratio)]. The MBDA test, measured at baseline and weeks six, 18 and 24, was assessed for its association with the change in MDS-TBR_{max}." At week 24, scans and MBDA score for 112 participants were reviewed. "The MBDA score at week 24 was significantly correlated with the change in MDS-TBR_{max} (Spearman's rho¼0.239; p¼0.011) and remained significantly associated after adjustment for relevant confounders. Those with low MBDA at week 24 had a statistically significant adjusted reduction in arterial inflammation of 0.35 units *vs* no significant reduction in those who did not achieve low MBDA. Neither DAS28-CRP nor CRP predicted change in arterial inflammation. The MBDA component with the strongest association with change in arterial inflammation was serum amyloid A. "The authors concluded that "low disease activity by the MBDA at 24 weeks was associated with a clinically meaningful reduction in arterial inflammation, like high- intensity statins, in a way not predicted using other RA disease activity measures, suggesting that treatment-associated improvements in arterial inflammation may be indicated by specific biomarkers that overlap those used to track articular disease activity." However, the authors stated that it is unknown whether arterial inflammation detected on FDG-PET/CT correlates with CVD events in individuals with RA.

Abdelhafiz et al. (2022) directed a systematic review on the biomarkers for the diagnosis and treatment of RA. The study systematically explored through four different databases identifying the role of biomarkers for the diagnosis and treatment of RA. The biomarkers studied were C-reactive protein (CRP), rheumatoid factor (RF) anti-cyclic citrullinated protein (anti-CCP), 14-3-3n protein and the MBDA score. Initial MBDA scores correlated with the future responses in disease activity after 6 and 12 weeks of treatment. The MBDA was a robust predictor of radiographic development of RA, foretold remission over a one year period, and was able to distinguish among small variances in disease activity. The authors determined the biomarkers examined are supportive tools in diagnosis, monitoring of treatment and foreseeing prognosis in patients with RA. Though, additional investigation is required to explore novel biomarkers for the pretreatment selection of potentially responsive patients before initiating therapy for a precision medicine regarding RA.

Fleischmann et al. (2021) compared the utility of the multi-biomarker disease activity (MBDA) score in assessing rheumatoid arthritis (RA) disease activity with that of the Disease Activity Score 28-erythrocyte sedimentation rate (DAS28-ESR) and the Clinical Disease Activity Index (CDAI) in a multicenter, randomized, placebo-controlled trial of repository corticotropin injection (RCI) in patients with persistently active RA. Patients received 80 U of RCI twice weekly during a 12-week open-label period; those who achieved low disease activity at week 12 were randomly assigned to receive either 80 U of RCI or placebo twice weekly during a 12-week double-blind period. Changes in disease activity (measured by DAS28-ESR, CDAI, and MBDA) and correlations between MBDA scores and both DAS28-ESR and CDAI scores were assessed. Changes from baseline in DAS28-ESR and CDAI scores suggested that RCI therapy led to clinically meaningful improvements in disease activity, but improvements from baseline in MBDA scores were below the minimally important difference threshold. For the DAS28-ESR and CDAI, correlations with total MBDA and individual component scores were generally low ($r \leq 0.3$), occasionally moderate ($r > 0.3$ but < 0.5). The investigators concluded that their results suggest overall MBDA scores are not sufficiently responsive for assessing RA disease activity after RCI therapy. These findings are consistent with those seen with other RA drugs and, although they are from a clinical trial, suggest the MBDA should not be a preferred disease activity measure in clinical practice.

Curtis et al. (2021) assessed the adjusted MBDA score and performed a combined analysis of it as a prognostic test for radiographic progression in RA. A newer version of the MBDA score, adjusted for age, sex, and adiposity, has been validated in two cohorts (OPERA and BRASS) for predicting risk for radiographic progression. The investigators extend these findings with additional cohorts to further validate the adjusted MBDA score as a predictor of radiographic progression risk and compare its performance with that of other risk factors. Four cohorts were analyzed: the BRASS and Leiden registries and the OPERA and SWEFOT studies (total n = 953). Treatments included conventional DMARDs and anti-TNFs. Associations of radiographic progression (ΔTSS) per year with the adjusted MBDA score, seropositivity, and clinical measures were evaluated using linear and logistic regression. The adjusted MBDA score was (1) validated in Leiden and SWEFOT, (2) compared with other measures in all four cohorts, and (3) used to generate curves for predicting risk of radiographic progression. Univariable and bivariable analyses validated the adjusted MBDA score and found it to be the strongest, independent predicator of radiographic progression (ΔTSS > 5) compared with seropositivity (rheumatoid factor and/or anti-CCP), baseline TSS, DAS28-CRP, CRP SJC, or CDAI. Neither DAS28-CRP, CDAI, SJC, nor CRP added significant information to the adjusted MBDA score as a predictor, and the frequency of radiographic progression agreed with the adjusted MBDA score when it was discordant with these measures. The rate of progression (ΔTSS > 5) increased from < 2% in the low (1-29) adjusted MBDA category to 16% in the high (45-100) category. A modeled risk curve indicated that risk increased continuously, exceeding 40% for the highest adjusted MBDA scores.

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According to the investigators, the adjusted MBDA score was validated as an RA disease activity measure that is prognostic for radiographic progression. The adjusted MBDA score was a stronger predictor of radiographic progression than conventional risk factors, including seropositivity, and its prognostic ability was not significantly improved by the addition of DAS28-CRP, CRP, SJC, or CDAI. The investigators indicated that the limitations of the present study are that radiographs were assessed by different readers in each cohort, patient global assessments were unavailable for the Leiden cohort, and, except for one patient, TNF inhibitors were the only biologic drugs included in the four cohorts. Data on smoking were not evaluated here [46], but a prior analysis of the SWEFOT cohort found that the original MBDA score was a strong independent predictor of progression (TSS > 5) after adjusting for current smoking status. This study was supported by Myriad Genetics, Inc.

Baker et al. (2020) assessed the impact of adjustment of the multi-biomarker disease activity score (MBDA) for age, sex, and leptin, over the range of age and adiposity, and assessed relationships with clinical disease activity. Individuals with RA, ages 18-75 years, were recruited from clinical practices and completed whole-body DXA to quantify fat mass indices (FMI, kg/m2). FMI Z-scores were calculated based on distributions in a reference population. Descriptive statistics described relationships between age, FMI Z-score, and the original MBDA and adjusted MBDA (aMBDA). Swollen joint counts (SJC) and the clinical disease activity index (CDAI) were assessed over MBDA categories. There were 104 participants (50% female) with mean (SD) age of 56.1 (12.5) and body mass index (BMI) of 28.8 (6.9). Older age was associated with higher MBDA scores in men. The aMBDA was not associated with age. The original MBDA score was associated with FMI Z-score among women (Rho = 0.42, p = 0.002) but not men. The aMBDA was not associated with FMI Z-score in either women or men. The aMBDA score was lower than the original MBDA in the highest quartile of FMI in women and was higher in the lowest FMI quartiles in women and men. CDAI, SJC, and radiographic scores were similar across activity categories for the original MBDA score and aMBDA. The investigators concluded that the aMBDA demonstrated reduced associations with adiposity, particularly among women. The investigators also indicated that the aMBDA may be less likely to overestimate disease activity in women with greater adiposity and to underestimate disease activity in men and women with lesser adiposity.

Ma et al. (2020) used the multi-biomarker disease activity (MBDA) test to explore the role of biomarkers in predicting point remission and sustained remission. Individuals with RA on > 6 months stable therapy in stable low disease activity (DAS28-ESR ≤ 3.2) were assessed every 3 months for 1 year. Baseline, intermittent (IR) and sustained (SR) remission were defined by DAS28-ESR, DAS28-CRP, simple disease activity index (SDAI), clinical disease activity index (CDAI) and ACR/EULAR Boolean criteria. Individuals not fulfilling any remission criteria at baseline were classified as 'low disease activity state' (LDAS). Individuals not fulfilling any remission criteria over 1 year were classified as 'persistent disease activity' (PDA). MBDA score was measured at baseline/3/6 months. The baseline MBDA score, the 6-month time-integrated MBDA score and MBDA biomarkers were used for analyses. The area under the receiver operating characteristic curve (AUROC) assessed the ability of the MBDA score to discriminate between remission and non-remission. Biomarkers were analyzed at baseline using the Mann-Whitney test and over time using the Jonckheere-Terpstra trend test. Of 148 participants, 27% were in the LDAS, 65% DAS28-ESR remission, 51% DAS28-CRP remission, 40% SDAI remission, 43% CDAI remission and 25% ACR/EULAR Boolean remission at baseline. Over one year, 9% of participants were classified as PDA. IR and SR were achieved in 42%/47% by DAS28-ESR, 46%/29% by DAS28-CRP, 45%/20% by SDAI, 44%/21% by CDAI and 35%/9% by ACR/EULAR Boolean criteria, respectively. By all remission criteria, baseline MBDA score discriminated baseline remission (AUROCs 0.68-0.75) and IR/SR (AUROCs 0.65-0.74). The 6-month time-integrated MBDA score discriminated IR/SR (AUROCs 0.65-0.79). Baseline MBDA score and concentrations of IL-6, leptin, SAA and CRP were significantly lower in all baseline remission criteria groups vs LDAS. They and the 6-month time-integrated values were lower among individuals who achieved IR/SR vs PDA over one year. According to the investigators, this study demonstrated that the MBDA score, and its biomarkers IL-6, leptin, SAA, and CRP differentiated between small differences in disease activity (i.e., between low disease activity and remission states). They were also predictors of remission over one year. The investigators indicated that the limitations of the study included the relatively small number of individuals in sustained remission, particularly in the group meeting the ACR/EULAR Boolean definition and in the group with no remission at any time point, i.e., the PDA group. Secondly, because the different remission groups contained overlapping populations, it was not possible to formally compare them to each other. Thirdly, Anti-citrullinated protein antibodies (ACPA) status was not analyzed as a predictor of remission in REMIRA because the focus of this study was the MBDA score and its biomarkers and because ACPA data were incomplete. Lastly, BMI data was not collected in this study and the MBDA scores were not adjusted for adiposity.

The 2016 update of the European Alliance of Associations for Rheumatology recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs indicated that although MBDA testing has been reported to improve patient monitoring during RA treatment with biological agents, this test may give falsely elevated results in patients who have an infection (Smolen et al., 2017). The 2019 EULAR updated recommendations (Smolen et al., 2020), and updated recommendations (Smolen et al., 2022) no longer mention the Vectra DA (MBDA) test.

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The American College of Rheumatology (ACR) updated their Recommended Rheumatoid Arthritis Disease Activity Measures and included the original Vectra DA test as meeting a minimum standard for regular use in most clinical settings. The content validity and structural validity of the Vectra DA test were identified as strong (consistent findings in multiple studies of good methodological quality –OR- in one study of excellent methodological quality). The reliability of the Vectra DA test was indicated as unknown (studies only of poor methodological quality). Using a feasibility score of zero to four, the authors identified five "preferred" RA activity measures for regular clinical use (those with the most support for performance and feasibility). MBDA (with a feasibility score of one), was one of seven other RA activity measures that were determined as meeting a "minimum standard" for regular use (those with adequate performance and feasibility). However, the guideline committee could not achieve consensus on the use of MBDA, and it was thus deemed as inconclusive for preferred use. (England et al., 2019).

Curtis et al. (2019c) developed and evaluated an adjusted score for the MBDA test to account for the effects of age, sex, and adiposity in individuals with RA. Two models were developed to adjust MBDA score for age, sex, and adiposity, using either serum leptin concentration or BMI as proxies for adiposity. Two cohorts were studied. A cohort of 325 781 individuals with RA who had undergone commercial MBDA testing and had data for age, sex and serum leptin concentration was used for both models. A cohort of 1411 individuals from five studies/registries with BMI data was used only for the BMI-adjusted MBDA score. Univariate and multivariate linear regression analyses evaluated the adjusted MBDA scores and conventional clinical measures as predictors of radiographic progression, assessed in terms of modified total Sharp score (ΔmTSS). Two models were developed, based on findings that MBDA score was higher in females than males and increased with age, leptin concentration and BMI. In pairwise regression analyses, the leptin-adjusted ($p = 0.00066$) and BMI-adjusted ($p = 0.0027$) MBDA scores were significant independent predictors of ΔmTSS after adjusting for DAS28-CRP, whereas DAS28-CRP was not, after adjusting for leptin-adjusted ($p = 0.74$) or BMI-adjusted ($p = 0.87$) MBDA score. Moreover, the leptin-adjusted MBDA score was a significant predictor of ΔmTSS after adjusting for the BMI-adjusted MBDA score ($p = 0.025$) or the original MBDA score (0.027), whereas the opposite was not true. According to the investigators, Leptin-adjusted MBDA score significantly adds information to DAS28-CRP and the original MBDA score in predicting radiographic progression. The investigators indicated that it may offer improved clinical utility for personalized management of RA. This study was supported by Crescendo Bioscience Inc.

Curtis et al. (2019a) compared the multi-biomarker disease activity (MBDA) score with the DAS28-CRP and CRP for predicting risk of radiographic progression in patients with rheumatoid arthritis. Published studies of the MBDA score and radiographic progression with ≥ 100 patients per cohort were evaluated. Patient-level data from studies having all three measures was pooled to: (1) determine a combined RR for radiographic progression in the high vs. not-high categories for each measure; and (2) compare the predictive ability of MBDA score vs. DAS28-CRP by comparing the rates of radiographic progression observed in subgroups created by cross-classifying the high and not-high categories of each measure. Five cohorts were identified for inclusion (total n = 929). In each, radiographic progression was more frequent with increasing MBDA scores. Among the three cohorts with requisite data, PPVs were generally similar using categories of MBDA score, DAS28-CRP, or CRP but NPVs were greater for MBDA score (93-97%) than DAS28-CRP or CRP (77-87%). RRs for radiographic progression were greater when based on categories of MBDA score than DAS28-CRP or CRP and the combined RR was greater for MBDA score than DAS28-CRP or CRP. For patients cross-classified by MBDA score and DAS28-CRP, high vs. not-high MBDA score significantly predicted radiographic progression independently of DAS28-CRP. The authors concluded that high and not-high MBDA scores were associated with increased and low risk, respectively, for radiographic progression over one year. MBDA score was a better predictor of radiographic progression than DAS28-CRP or CRP. This study did not validate MBDA findings with improved treatment outcomes.

Curtis et al. (2019b) evaluated the clinical utility of the multi - biomarker disease activity (MBDA) test for rheumatoid arthritis (RA) management in routine care. Using 2011-2015 Medicare data, each individual with RA was linked to their MBDA test result. Initiation of a biologic or Janus kinase (JAK) inhibitor in the six months following MBDA testing was described. Multivariable adjustment evaluated the likelihood of adding or switching biologic/JAK inhibitor, controlling for potential confounders. For individuals with high MBDA scores who added a new RA therapy and were subsequently retested, lack of improvement in the MBDA score was evaluated as a predictor of future RA medication failure, defined by the necessity to change RA medications again. Among 60,596 individuals with RA with MBDA testing, the proportion adding or switching biologics/JAK inhibitor among those not already taking a biologic/JAK inhibitor was 9.0% (low MBDA), 11.8% (moderate MBDA), and 19.7% (high MBDA). Similarly, among those already taking biologics/JAK inhibitor, the proportions were 5.2%, 8.3%, and 13.5%. After multivariable adjustment, referent to those with low disease MBDA scores, the likelihood of switching was 1.51-fold greater for individuals with moderate MBDA scores, and 2.62 for individuals with high MBDA scores. Among those with high MBDA scores who subsequently added a biologic/JAK inhibitor and were retested, lack of improvement in the MBDA score category was associated with likelihood of future RA treatment failure. The authors concluded that the MBDA score was associated with both biologic and JAK inhibitor medication

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addition/switching and subsequent treatment outcomes. This study did not compare the MBDA test with other methods of disease activity assessment to determine whether they would have had similar influences on RA patient management.

Johnson et al. (2018) performed a systematic review of the multi-biomarker disease activity (MBDA) and meta-analysis of the correlation between the MBDA and other rheumatoid arthritis (RA) disease activity measures. Twenty-two studies were identified in the systematic review, of which eight (n = 3,242 assays) reported correlations of the MBDA with RA disease activity measures. Pooling results from these eight studies in the meta-analysis, the MBDA demonstrated modest correlations with DAS28-CRP and DAS28-ESR with weaker correlations observed with SDAI, CDAI, and RAPID3. Correlations between change in MBDA and change in disease activity measures ranged from r = 0.53 (DAS28-ESR) to r = 0.26 (CDAI). The authors concluded that MBDA demonstrates moderate convergent validity with DAS28-CRP and DAS28-ESR, but weaker correlations with SDAI, CDAI, and RAPID3. While it appears to complement existing RA disease activity measures, further assessment of the MBDA's performance characteristics is warranted.

Hambardzumyan et al. (2017) analyzed data from 157 individuals who had an inadequate response to methotrexate monotherapy (MTX-IRs) from the Swedish Pharmacotherapy (SWEFOT) trial who were randomized to receive triple therapy (MTX plus sulfasalazine plus hydroxychloroquine) versus MTX plus infliximab. Among the 157 participants, 12% had a low MBDA score, 32% moderate, and 56% high. Of those with a low MBDA score, 88% responded to subsequent triple therapy, and 18% responded to MTX plus infliximab; for those with a high MBDA score, the response rates were 35% and 58%, respectively. Clinical and inflammatory markers had poorer predictive capacity for response to triple therapy or MTX plus infliximab. The authors concluded that in individuals with RA who had an inadequate response to MTX, the MBDA score categories were differentially associated with response to subsequent therapies. Thus, individuals with post-MTX biochemical improvements (lower MBDA scores) were more likely to respond to triple therapy than to MTX plus infliximab. According to the authors, if confirmed, these results may help to improve treatment in RA. This study was limited because it was a retrospective analysis. Another limitation is that because of missing data, the authors were unable to analyze 40% of participants who were randomized to second-line therapy causing uncertainty regarding the reliability of the results.

Bouman et al. (2017) evaluated the predictive value of the baseline multi-biomarker disease activity (MBDA) score in long-standing individuals with RA with low disease activity tapering TNF inhibitors (TNFi) for successful tapering or discontinuation, occurrence of flare and major flare, and radiographic progression. Dose Reduction Strategies of Subcutaneous TNF inhibitors (Dutch Trial Register, NTR 3216) is an 18-month non-inferiority randomized controlled trial comparing tapering of TNFi until discontinuation or flaring with usual care (UC) in long-standing individuals with RA with stable low disease activity. MBDA scores were measured at baseline. Radiographs were scored at baseline and 18 months using the Sharp-van der Heijde score. The area under the receiver operating characteristic (AUROC) curve was used to analyze the capability of baseline MBDA score to predict the above-mentioned outcomes. Serum samples and outcomes were available for 171 of 180 individuals from Dose Reduction Strategies of Subcutaneous TNF inhibitors (115 tapering; 56 UC). AUROC analyses showed that baseline MBDA score was not predictive for the above-mentioned clinical outcomes in the taper group but did predict major flare in the UC group. Radiographic progression was minimal and was not predicted by MDBA score. The authors concluded baseline MBDA score was not predictive for successful tapering, discontinuation, flare, major flare or radiographic progression in individuals with RA who tapered TNFi.

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Code	Description
94011	Measurement of spirometric forced expiratory flows in an infant or child through 2 years of age
94012	Measurement of spirometric forced expiratory flows, before and after bronchodilator, in an infant or child through 2 years of age
94013	Measurement of lung volumes (i.e., functional residual capacity [FRC], forced vital capacity [FVC], and expiratory reserve volume [ERV]) in an infant or child through 2 years of age

Spirometry and other pulmonary function tests are unproven and not medically necessary in children under the age of three due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

The 2025 Global Initiative for Asthma (GINA) guidelines specific to children 5 years and younger state that, episodic respiratory symptoms are common in children with and without asthma and it is challenging and may not be possible to assess airflow limitations or response to bronchodilator in this age group. A probability approach based on symptoms during and between viral respiratory infections, family history and physical findings may be helpful to allow individual decision making regarding the use of a trial controller to avoid over or under treating. Any controller treatment trial should have a 2-3 month follow up to assess response. While no tests specifically and definitively diagnose asthma in children 5 years and younger, there are tests such as a therapeutic trial of treatment, allergy testing, chest x-ray, lung function testing, exhaled nitric oxide and risk profiling tools that may be useful adjuncts.

A NICE (2024) asthma guideline addressing diagnosis and monitoring of suspected asthma recommends treating symptoms based on observation and clinical judgement with regular follow up examinations for children under five. If the child is still symptomatic when they turn five, objective tests should be carried out. Measuring the blood eosinophil count or fractional exhaled nitric oxide (FeNO) level is recommended for adults, and young individuals (aged over 16 years) if a diagnosis of asthma is being considered. Asthma control should be monitored at each visit using spirometry or peak flow variability testing for all children aged five and older, young people and adults.

In 2020, the National Heart, Lung, and Blood Institute (NHLBI) National Asthma Education and Prevention Program (NAEPP) updated their 2007 Asthma Management Guidelines and advised that in children ages 0–4 years with recurrent wheezing, the Expert Panel recommended against fractional exhaled nitric oxide (FeNO) measurement to predict the future development of asthma. No updates were made with respect to spirometry testing for children in the ages 0-4 group. In the 2007 guidelines, the Coordinating Committee Expert Panel Work Group recommends that spirometry

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measurements before and after the individual inhales a short-acting bronchodilator should be undertaken for individuals in whom the diagnosis of asthma is being considered, including children 5 years of age or older. For children 0-4 years of age, the panel recommends that the evaluation include the history, symptoms, physical examination, and assessment of quality of life, as diagnosis can be difficult in this age group. A therapeutic trial with medications will also aid in the diagnosis (2007).

The American Thoracic Society (ATS) and European Respiratory Society (ERS) published an updated Technical Statement in 2019 of their 2005 technical standards for spirometry. The guideline indicates that, when the operator administering the spirometry has been specifically trained and is competent to work with young children, a child as young as 2.5 years old with normal cognitive and neuromotor function is able to perform acceptable spirometry when appropriate coaching is given. For children aged six years or younger, they must have at least 0.75 seconds of expiration without glottic closure or cough for acceptable or usable measurement of forced expiratory volume (FEV). The guideline also indicates that one of the contraindications for performing spirometry is an individual's inability to understand the directions or the individual's unwillingness to follow the directions because the results will usually be submaximal. (Graham et al., 2019).

According to Moral et al. (2018), the definition and diagnosis of asthma are the subject of controversy that is particularly intense in the case of individuals in the first years of life, due to reasons such as the difficulty of performing objective pulmonary function tests (PFT) or the high frequency with which the symptoms subside in the course of childhood. As the authors thought that there is no consensus regarding the diagnosis of asthma in preschool children, they conducted a systematic search of the clinical guidelines published in the last 10 years and containing information referred to the concept or diagnosis of asthma in childhood - including the first years of life (infants and preschool children). A series of key questions were established, and each selected guide was analyzed in search of answers to those questions. The review protocol was registered in the international prospective register of systematic reviews (PROSPERO). Twenty-one clinical guidelines were selected: 10 general guides (children and adults), eight pediatric guides and three guides focusing on preschool children. The immense majority accepted that asthma can be diagnosed from the first years of life, without requiring PFT or other complementary techniques. The authors concluded that the response to treatment and the exclusion of other alternative diagnoses are key elements for establishing the diagnosis of asthma in infants and preschool children.

In a clinical guideline on the diagnostic evaluation of infants with recurrent or persistent wheezing, the ATS reported being unable to find any large clinical studies that used consistent case definitions and outcomes. Most of the studies cited were case series, providing the lowest quality of evidence on the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) scale. The guideline development committee did not reach consensus on a clinical recommendation for or against infant PFT, due to the paucity of evidence. They urged that, given the frequency with which infantile wheezing occurs, there is an urgent need for more rigorous research to be conducted in this field (Ren et al., 2016).

The ATS, in a 2013 clinical guideline on the classification, evaluation, and management of childhood interstitial lung disease in infancy, suggests infant PFT be utilized to better characterize physiologic alterations (weak recommendation). However, no controlled clinical trials were identified on this topic and therefore, observational evidence and clinical experience informed judgments were made regarding PFT. Strong recommendations for initial diagnostic testing include echocardiography and thin-section CT using the lowest radiation dose that provides adequate diagnostic information (Kurland et al).

In a 2013 workshop report on the diagnosis and management of chronic pulmonary conditions in children under six years of age, the ATS stated that no evidence yet exists for any lung function monitoring measures as to whether incorporating them into clinical care improves patient outcomes; such studies are urgently needed. They also stated that, despite the lack of empirical evidence, clinical experience suggests that lung function monitoring might be helpful in some clinical settings such as infants and young children with cystic fibrosis, bronchopulmonary dysplasia, or recurrent wheeze (Rosenfeld et al).

In a 2009 guideline, published jointly with the ERS, the ATS addresses lung function tests in children six years of age and older. While they acknowledge that the use of such tests in children younger than six years of age was beyond the scope of their guideline, they state that with appropriate training, preschool children may be able to perform spirometry. Forced oscillation procedures and interrupter resistance (Rint) to measure airway resistance can be applied in children as young as three years of age (Reddel et al).

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Code	Description
A4542	Supplies and accessories for external upper limb tremor stimulator of the peripheral nerves of the wrist
E0734	External upper limb tremor stimulator of the peripheral nerves of the wrist

External upper limb tremor stimulators of the peripheral nerves of the wrist and the related monthly supplies to treat essential tremor or postural and kinetic hand tremor symptoms in adults with Parkinson's disease are unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

External upper limb tremor stimulators of the peripheral nerves of the wrist (e.g., the Cala Health, Inc., Cala Trio™, and Cala kIQ™) deliver non-invasive electrical stimulation to the peripheral nerves of the wrist (Cala Health, Inc. website).

In a 2025 Hayes evolving evidence review, Cala transcutaneous afferent patterned stimulation (TAPS) device (Cala Health Inc.) for temporary relief of essential tremor of the hand prior to performance of activities of daily living (ADL) was found to have minimal support based on 3 poor- to fair-quality studies. Studies included 1 randomized controlled trial, 1 prospective pretest-posttest, and 1 retrospective database review that reported data for 1 month, 3 months, or up to 3 years of intermittent device use, respectively. Nearly half of the participants experienced ≥ 50% hand tremor reduction in the treated limb and/or statistically significant improvement in the ability to perform ADL (2 studies) after treatment sessions; in the RCT, ADL functional improvement was statistically better than the standard care alone. Adverse event/effect rates ranged from 3% to 18%, which tended to be mild to moderate (no serious). Studies lacked comparisons to sham control, active alternative therapies, and to controlled essential tremor medications alone.

In an ECRI clinical evidence assessment (2022, updated 2024), Cala Transcutaneous Afferent Patterned Stimulation (TAPS) was evaluated for essential tremor (ET). ECRI reviewed three randomized controlled trials (RCTs) and three before-and-after studies. ECRI concluded that Cala TAPS therapy is safe, reduces ET severity, and improves activities of daily living (ADLs) for approximately one hour after treatment in most patients with ET at up to three-month follow-up. ECRI noted that studies with follow-up durations longer than three months that report on patient-oriented outcomes are needed to validate findings and whether therapy benefits are sustained beyond three months.

Dai et al. (2023, included in the Hayes and ECRI reviews) conducted a randomized prospective study to evaluate the clinical benefit of adding TAPS treatment to standard of care (SOC) versus SOC alone. The study included 310 patients that received a TAPS device and were randomized to either one month of adding TAPS therapy to usual care or usual care with tremor assessment only. The primary endpoint was the difference in median tremor power for patients in the treatment arm versus SOC arm in the modified intention to treat (mITT). The secondary endpoint was the difference in Bain & Findley activities of daily living (BF-ADL) upper limb score improvement from baseline to the end of the first month for patients in the treatment arm versus SOC in the mITT. Additionally, there was subgroup analysis for patients with

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severe ET who scored a 3 or 4 on at least one of four BF-ADL tasks associated with eating, drinking, or writing at baseline. Of the 310 patients included in the study, 276 patients completed one month of the study. The treatment arm included 119 patients and the SOC arm included 123 patients. There were no statistically significant differences in sociodemographic and baseline clinical characteristics between patients in the treatment and SOC arms. Tremor power in the treatment arm [0.017 ±0.003 $(m/s^2)^2$] was significantly lower than tremor power in the SOC arm [0.08 ±0.014 $(m/s^2)^2$] in the mITT ($p < 0.0001$). Additionally, 134 of the 276 patients completed the BF-ADL ratings at baseline and one month and changes in the score in the treatment arm (1.6 ±0.43, n = 51) were significantly greater than the changes observed in the SOC arm (0.22 ±0.37, n = 83) ($p = 0.0187$) in the mITT. The authors also noted the exploratory end point results included significant improvement of the BF-ADL score from baseline and one month by 2.4 points in the treatment arm whereas there was no significant improvements observed in the SOC arm ($p = 0.55$) as well as the average median tremor power improved in the treatment arm from 0.038 ±0.011 $(m/s^2)^2$) pre-stimulation to 0.017 ±0.004 $(m/s^2)^2$) post-stimulation ($p < 0.0001$). TAPS therapy over one month resulted in 45% of patients experiencing a ≥ 50% tremor power reduction and 25% experiencing a ≥ 70% reduction. Additionally, the authors noted that TAPS significantly improved tremor power in the severe ET subgroup and that those aged 65 and over exhibited a 5-fold greater improvement in tremor power in the treatment arm than the SOC arm ($p < 0.0001$) and a 2.2-point greater change in BF-ADL score improvement in the treatment arm than the SOC arm ($p = 0.0096$). Limitations of the study include bias related to open-label design, unavailability of self-reported medication data, timing of postural holds measurements, missing BF-ADI data, protocol violations by patients (14%), variability in definition and adoption of SOC in ET, placement of device and lack of full measurement at the fingers, elbow or shoulder, and recruitment based on medical claims that may contain misdiagnoses.

Brillman et al. conducted a retrospective, post-marketing, observational study of 321 subjects (average age 71 years, 32% female) diagnosed with essential tremor to evaluate the real-world effectiveness of transcutaneous afferent patterned stimulation (TAPS) delivered by the Cala Trio wrist-worn device. The analysis included subjects who received TAPS therapy for at least 90 days and had a minimum of 10 sessions documented in device logs. Demographic information and tremor history were obtained from the prescription used to obtain the Cala Trio and a voluntary survey sent to subjects after 90 days of TAPS therapy. Usage and effectiveness information were compiled from Cala Trio device logs. These device logs provided session timestamps, device-prompted postural hold tremor accelerometry measurements, and self-ratings of post-session tremor impression (improved, no change, worsened). Of the total number of subjects, 216 had tremor measurements available for analysis and 69 completed the survey. The total use period of TAPS therapy by subjects ranged from 90 to 663 days, with 28% of patients having used the device for greater than one year. Subjects used the Cala Trio 5.4 ±4.5 (mean ±1 standard deviation) times per week. TAPS therapy was found to reduce tremor power, calculated using device postural hold accelerometry data, by 71% (geometric mean) across all sessions. Additionally, 59% of subjects reported experiencing a greater than 50% tremor reduction after TAPS therapy. Of the subjects who returned the voluntary survey, 84% reported improvements in eating, drinking, or writing; and 65% reported improvements in quality of life. Device-related safety complaints were reported as consistent with adverse events reported in prior clinical trials. There were no severe safety events were reported. The authors concluded the study results confirmed TAPS therapy as a safe and effective treatment for essential tremor. However, multi-year safety and effectiveness would be valuable. The authors noted some potential study confounders including the 90-day inclusion criteria and subject self-reported usage and effectiveness analyses could have introduced bias; only subjects who chose to complete the device-prompted postural holds and tremor improvement ratings were included in the analysis and a number of subjects and sessions were not analyzed for effectiveness due to data that was missing or of poor-quality; subjects were prompted to perform postural holds for measuring tremor only immediately before and after stimulation sessions, thus, tremor measurements did not allow for characterization of duration of post-stimulation treatment effect; TAPS efficacy was captured after 1+ years of repeated use for some subjects, which was greater than 90-day efficacy established in prior clinical trials; factors such as caffeine, alcohol and medications are not controlled for in real-world usage; wrist-based accelerometry measures the joint-interaction torques produced by the hand tremor and not the hand tremor itself; and key patient-reported outcomes on activities of daily living were only assessed once and only by the voluntary survey, which may have been subject to recency and respondent-selection bias.

Isaacson et al. (2020, included in the Hayes and ECRI review) performed a prospective, multi-center, open-label, post-clearance, single-arm study to evaluate the efficacy and safety of Transcutaneous Afferent Patterned Stimulation (TAPS) delivered by an FDA-cleared wrist-worn device (Cala Health, Inc.). A total of 263 subjects were enrolled at 26 study sites. Of those, 205 subjects completed the study. Subjects were instructed to use the wrist-worn device for 40 minutes, twice daily, for three months. The co-primary efficacy endpoints were clinician-rated Tremor Research Group Essential Tremor Rating Assessment Scale (TETRAS) and patient-rated Bain & Findley Activities of Daily Living (BF-ADL) dominant hand scores. These endpoints were considered met ($p < 0.0001$), with 62% (TETRAS) and 68% (BF-ADL) of “severe” or “moderate” subjects improving to “mild’ or ‘slight”. Wrist-worn accelerometer recordings of tremor power showed that 92% of subjects improved and 54% of subjects experienced ≥ 50% improvement. Clinical Global Impression (CGI-I) scores showed that clinicians reported tremor improvement in 68% of patients. Patient Global Impression (PGI-I) scores showed

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60% of subjects self-reported tremor improvement. Quality of Life in Essential Tremor (QUEST) surveys completed by subjects also showed improvement (p = 0.0019). Device-related adverse events occurred in 18% of subjects and included wrist discomfort, skin irritation, and pain. There were no device-related serious adverse events reported. The authors concluded that non-invasive neuromodulation therapy used at home over three months is safe and effective to treat patients with ET. This study had some limitations including the open-label, single-arm design; clinical raters were unblinded; while there were statistically significant reductions across the TETRAS and BF-ADL ratings, the extent of those reductions varied; and 58 subjects did not complete the study.

The randomized, controlled, multi-center study to evaluate the safety and efficacy of a wrist-worn peripheral nerve stimulation device (Pahwa et al. 2019, included in the ECRI report) evaluated the safety and efficacy of a wrist-worn peripheral nerve stimulation device (Cala Health, Inc., Cala ONE) in subjects with ET in a single in-office session. A total of 111 subjects were screened at 4 sites. Of those, 93 subjects were randomized to receive treatment (n = 48) or sham stimulation (n = 45). Treatment consisted of a single 40-minute stimulation session. The primary endpoint was the clinician-rated TETRAS Archimedes spiral score. The study showed that subjects who received treatment did not show significantly larger improvements in Archimedes spiral task scores when compared to sham. However, subjects did show significantly greater improvement in upper limb TETRAS tremor scores (p = 0.017). Subject-rated improvements using the BF-ADL scale were significantly greater with treatment (49% reduction) than with sham (27% reduction; p = 0.001). CGI-I showed a greater percentage of ET patients (88%) reported improvement in the stimulation group, as compared to the sham group (62%) (p = 0.019). The adverse event rate was 3% and included significant and persistent skin irritation, sensation of weakness, or stinging pain. The authors concluded that peripheral nerve stimulation to treat ET may provide safe, well-tolerated, and efficacious treatment for transient relief of hand tremor symptoms. This study had some limitations including the evaluation of only a single in-clinic treatment session and a lack of kinematic measurements.

Lin et al (2018, included in the ECRI review) conducted a randomized, sham-controlled pilot trial on non-invasive neuromodulation in essential tremor exploring the extent of relief. The study aims to assess the efficacy of median and radial nerve stimulation as a noninvasive, nonpharmacological treatment to support the symptomatic relief of hand tremor for those with ET. All twenty-three blinded Individuals were randomized to treatment or sham groups at a single site under an institution review board approved protocol. To quantify efficacy the Tremor Research Group's Essential Tremor Rating Assessment Scale (TETRAS) was employed. The treatment group had significant outcome differences compared with sham and starting point, with blinded rater scores enhanced after stimulation versus prestimulation. The sham group scores had no noteworthy change following stimulation versus prestimulation. Although the study proposes that noninvasive neuroperipheral therapy may offer clinically meaningful symptomatic relief of hand tremor, it included too few subjects for sub analyses of the influence of age, medication status, and past medical history. Additional studies are necessary with a greater number of test subjects, examination of response, rate and robustness of the therapy, investigation of chronic utilization effects, and evaluation of quality-of-life. Additionally, future studies can characterize the exact mechanism that enables improvements to therapy.

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Code	Description
E1399	Durable medical equipment, miscellaneous (to report non-invasive bimodal neuromodulation)

Non-invasive bimodal neuromodulation (e.g., Lenire or Neosensory) for tinnitus is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

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Clinical Evidence

There is a lack of quality evidence regarding the effectiveness of non-invasive bimodal neuromodulation for the treatment of tinnitus compared to other recommended therapies. Additional studies are needed comparing it with other recommended tinnitus treatment modalities.

According to the manufacturer, Lenire is a form of noninvasive neuromodulation device intended to provide bimodal (auditory and transmucosal electrical tongue) stimulation to temporarily relieve the symptoms of tinnitus. The treatment is intended to be self-administered at home by the individual following prescription by a healthcare professional who is experienced in the evaluation and management of tinnitus.

The U.S. Food and Drug Administration (FDA) granted De Novo status on March 6, 2023, for the Lenire Device. For additional information, refer to the following website: https://www.accessdata.fda.gov/cdrh_docs/pdf21/DEN210033.pdf. (Accessed April 15, 2025)

According to the manufacturer, Neosensory also known as Neosensory Duo is a wearable device to treat tinnitus through bimodal stimulation using audio tones (individualized to a participants tinnitus frequency) played from a phone application combined with corresponding spatial vibrations.

The TENT-A3 study was a prospective, single-arm multicenter study conducted by Boedts et al. (2024) that evaluated the safety and efficacy of the Lenire device for the treatment of tinnitus. This study involved 112 participants and was designed to compare bimodal neuromodulation (combining sound therapy with electrical stimulation of the tongue) to sound therapy alone. Based on previous trials showing positive outcomes with Lenire's bimodal treatment, participants with a Tinnitus Handicap Inventory (THI) score of at least 38 (indicating moderate or worse tinnitus) were enrolled. Additionally, participants were required to have no more than 40 dB HL hearing loss in frequencies from 250 Hz to 1 kHz, or 80 dB HL in frequencies from 2 to 8 kHz, either in one or both ears. Over 12 weeks, participants used the device for one hour daily, with the first 6 weeks involving sound-only stimulation and the next 6 weeks adding tongue stimulation. In participants with moderate or more severe tinnitus, there was a clinically superior performance of bimodal treatment (58.6%; 95% CI: 43.5%, 73.6%; p = 0.022) compared to sound therapy alone (43.2%; 95% CI: 29.7%, 57.8%), which was not observed in the full cohort across all severity groups. Consistent results were observed for the secondary endpoint based on the Tinnitus Functional Index (bimodal treatment: 45.5%; 95% CI: 31.7%, 59.9%; sound-only stimulation: 29.6%; 95% CI: 18.2%, 44.2%; p = 0.010), where a responder exceeds 13 points. No serious device-related adverse events were reported. Although long-term benefits were not assessed, previous studies (TENT-A1 and TENT-A2) indicated consistent efficacy for up to 12 months post-treatment. Treatment with this device cannot be effectively blinded because both the sound and tongue stimuli are above the threshold of perception and easily noticeable, making a sham control impractical. While the results are promising, additional studies are needed to evaluate the long-term efficacy of this device for the treatment of tinnitus.

A 2024 Hayes evolving evidence review titled “Lenire Bimodal Neuromodulation Device (Neuromod Devices Ltd.) for the Treatment of Tinnitus” indicated that there is minimal support based on clinical studies and systematic reviews to support its clinical utility. Two poor-quality studies were identified that compared different treatment parameters but did not compare with a control group. (RCTs Conlon 2022 and 2020 included below.)

Peratta et al. (2023) conducted an experimental study to determine whether tones combined with vibrations to the wrist reduced the signs of tinnitus. The researchers recruited 45 participants from an online survey. These participants were randomly assigned to the experimental condition (bimodal stimulation with tones + wristband) or a control condition (tones only). Participants in the experimental group (tones paired with simultaneous vibrations of the wristband) showed a clinically significant average improvement in TFI scores of -17.9 (SD = 18.17, n = 22, p < .001, two-tailed dependent t-test). The audio-only control group also showed a statistically significant difference from the group baseline of -7.5 (SD = 15.35; n = 23; p = .03, two-tailed dependent t-test); however, it is important to note that a change in TFI score of less than -13 is not considered clinically significant so while the audio-only control showed a change, it was not clinically meaningful. The difference between the experimental and control groups was statistically significant (t(43) = 2.10, p = .04, two-tailed independent t-test). Participants who started the study with greater severity of tinnitus (as determined by their baseline TFI score) experienced greater improvement from the bimodal stimulation. The difference between the experimental and control groups increased with higher baseline TFI scores: for the subset of participants with baseline TFI scores of 50 or above, the average 8 week drop in TFI score for the experimental group was -21.8 (SD = 14.6; n = 18; p-.24, two- tailed dependent t-test). The absolute difference in TFI score change between the two groups increased to 17.2 (t(32) = 3.39, p = .002, two-tailed independent t-test). The author indicates that this study lays the groundwork for further work into how the different ranges of tones affect the efficacy of this treatment. Larger robust studies are needed to further evaluate this novel treatment. The study is limited by the short duration of the trial, lack of masking or sham comparison, and lack of information on loss to follow-up, missing data, or conflicts of interest.

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In an October 2022 S3 Guideline: Chronic Tinnitus, the German Society for Otorhinolaryngology, Head and Neck Surgery states:

- Bimodal acoustic and electrical stimulation should not be practiced for chronic tinnitus.
- Strength of evidence: 2b (moderate); level of recommendation: recommendation (downgraded because of existing conflicts of interest).
- Classification of consensus strength: strong consensus (100%), 1 abstention (conflict of interest).
- Bimodal acoustic and electrical stimulation is safe to use, but robust evidence for efficacy is not available. A downgrading of the recommendation level of bimodal acoustic and electrical stimulation to a negative recommendation is made due to the lack of robust evidence of the studies and conflicts of interest of the authors in the publications listed in the evidence table.

Conlon et al. (2022) in a randomized double-blind single site trial known as the Treatment Evaluation of Neuromodulation for Tinnitus—Stage 2 (TENT-A2) to further evaluate the findings of the Conlon et al. 2020 TENT-A1 study (included below). This study intended to assess whether the wideband noise component of the sound stimulus was necessary for therapeutic benefit at the 6-week endpoint (arm 1 and arms 2). Both treatment arms exhibited a statistically significant reduction in tinnitus symptoms during the first 6-weeks, which was further reduced significantly during the second 6-weeks by changing the parameter settings (Cohen's *d* effect size for full treatment period per arm and outcome measure ranged from − 0.7 to − 1.4). There were no significant differences between arms, in which tongue stimulation combined with only pure tones and without background wideband noise was sufficient to reduce tinnitus symptoms. These therapeutic effects were sustained up to 12 months after the treatment ended. This study included two additional exploratory arms, including one arm that presented only sound stimuli during the first 6 weeks of treatment and bimodal stimulation in the second 6 weeks of treatment. This arm revealed the criticality of combining tongue stimulation with sound for treatment efficacy. Overall, there were no treatment-related serious adverse events and a high compliance rate (83.8%) with 70.3% of participants indicating benefit. These results showed that adjusting stimulation parameters can be used to achieve greater therapeutic effects and allows more ways to expand stimuli and possibly improve outcomes for individuals with tinnitus. As this study did not include comparison to established therapies or sham interventions, comparative studies are needed to confirm these results.

In 2020, Conlon et al. conducted a randomized control trial, TENT-A1 to evaluate different parameter settings of bimodal neuromodulation in a broad tinnitus population. Bimodal stimulation was delivered using a medical device (known and marketed as Lenire) that pairs sound with electrical stimulation of the tongue. This study enrolled 326 adults at two different sites with chronic subjective tinnitus. Participants were randomized into three parallel arms with different stimulation settings. Clinical outcomes were evaluated over a 12-week treatment period and a 12-month posttreatment phase. For the primary endpoints, participants achieved a statistically significant reduction in tinnitus symptom severity at the end of treatment based on two commonly used outcome measures, Tinnitus Handicap Inventory (Cohen's *d* effect size: -0.87 to -0.92 across arms; $p < 0.001$) and Tinnitus Functional Index (-0.77 to -0.87; $p < 0.001$). Positive results continued for 12 months after treatment for specific bimodal stimulation settings, which had not been found in earlier cohort studies. The treatment also led to higher individual compliance and overall satisfaction with no adverse device effects. The most commonly reported adverse event was increase in tinnitus symptoms; headache and ear or mouth discomfort also occurred in some patients. The authors indicate that a study limitation is that all three arms consisted of bimodal neuromodulation with suprathreshold intensities of sound and tongue stimulation that were required to maintain blinding, and they showed similar improvements in THI and TFI scores at the end of treatment. Although there are positive findings further clinical trials are needed to establish which bimodal neuromodulation stimulation components and parameters are needed and sufficient to treat tinnitus symptoms. The study is limited by lack of comparison to usual care or a sham intervention.

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Code	Description
E1399	Durable medical equipment, miscellaneous [when used to report robotic lower body exoskeleton device]
K1007	Bilateral hip, knee, ankle, foot (HKAFO) device, powered, includes pelvic component, single or double upright(s), knee joints any type, with or without ankle joints any type, includes all components and accessories, motors, microprocessors, sensors

The use of the robotic lower body exoskeleton device is unproven and not medically necessary for ambulation assistance in all settings/levels of care in patients with conditions which impair the ability to ambulate (e.g., spinal cord injury, stroke, Parkinson's disease, etc.) due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Robotic lower body exoskeletons (also referred to as reciprocating gait orthoses, powered orthoses, robotic orthoses, robotic gait assist devices, wearable exoskeletons, bionic legs, and computerized walking systems) are intended to assist some patients with paraplegia as a result of spinal cord injury (SCI) to stand and move to improve their independence and quality of life (QOL). Some early clinical trials have also evaluated versions of this technology in patients with other conditions including quadriplegia, stroke, multiple sclerosis, and Parkinson's disease.

Liu et al. (2025) conducted a systematic review and meta-analysis to examine the impact of flexible exoskeleton-assisted training (FEAT) compared to conventional therapy on balance, motor functions, and gait parameters in individual's post-stroke. The study included six RCTs with 213 patients. Outcomes such as balance (Berg Balance Scale, BBS), lower limb motor functions (Ten-Meter Walk Test, 10MWT; Six-Minute Walk Test, 6MWT; Functional Ambulation Category, FAC), and gait parameters were evaluated. The authors reported that FEAT significantly enhanced BBS scores, and results on the 10MWT and 6MWT, along with other gait parameters; however, FAC scores did not improve significantly. The authors also reported that subgroup analyses showed that FEAT with hip assistance significantly improved step length, cadence, and gait symmetry ratio, while ankle assistance improved performance on the 10MWT and 6MWT. Finally, the authors reported that FEAT was especially effective in improving step length, cadence, and gait symmetry ratio in patients with a post-stroke duration exceeding three months. The authors concluded that FEAT markedly improved the balance, walking ability, and gait parameters in stroke rehabilitation compared to conventional therapy and that the appropriate type of FEAT needs to be selected in the rehabilitation program based on the individual's specific impairment. Limitations of the study included small sample sizes, limiting the depth and generalizability of findings. Second, this study used aggregate data at the study level rather than individual patient data, which may fail to capture individual variations and treatment effects. The future meta-analysis should aim to include individual patient data to enhance precision, particularly when assessing patient characteristics and treatment responses. Third, methodological differences across studies, such as variations in sample sizes and intervention duration/intensity, may have influenced the findings, compromising the reliability and generalizability of the effects. Future research should validate the effects of FEAT through larger, more standardized randomized controlled trials (RCTs) and investigate its long-term rehabilitation benefits.

Yang et al. (2024) conducted a systematic review and meta-analysis to analyze lower limb robotic exoskeleton training (LRET) efficacy for treating and managing individuals post-stroke based on International Classification of Functioning, Disability, and Health (ICF) scores and to explore the impact of intervention intensities, devices and stroke phases. The review included 34 RCTs with 1166 participants and included a variety of robotic devices, including the Lokomat, Walkbot, HAL, Esko-GT, SMA, BEAR-H1, and MANBUZHE. The authors reported that LRET significantly improved motor control, and gait parameters compared with conventional rehabilitation and that LRET significantly improved walking independence, gait velocity, and balance. The authors also reported that social participation was superior for those receiving LRET compared to conventional rehabilitation and that subgroup analyses showed that LRET improved motor control, gait parameters, gait velocity, and activities of daily living for individuals in the subacute post-stroke phase of recovery while no significant improvement was seen for individuals in the chronic post-stroke phase. When the authors evaluated the exoskeleton devices, they reported that treadmill-based exoskeletons showed significant superiority for balance and activities of daily living while over-ground exoskeletons were more effective for gait parameters and walking independence. Finally, the authors reported that better results may be achieved with daily training intensities of 45 to 60 minutes and weekly training intensities of three hours or more. The authors concluded that their findings offer insight for healthcare professionals to make effective LRET choices based on the individual needs of patients undergoing post-stroke rehabilitation. Limitations of the study include the heterogeneity of RCT protocols, devices being studied, parameters and tools used for measuring outcomes, the small sample size in each included study, and the lack of detailed descriptions of the research protocols in some of the studies [Thimabut et al. (2022) and Yoo et al. (2023) studies previously summarized in this section were included in this systematic review and meta-analysis].

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In their Evidence Analysis Research Brief, Hayes (2024a) found no clinical studies that evaluated the ReWalk Personal Exoskeleton for home-based use following SCI and concluded that there is not enough published peer-reviewed literature to evaluate the use of this device for home-based use following SCI. Hayes also reported that the one position statement that was identified conferred no/unclear support for personal exoskeletons for home use following SCI.

Hayes (2024b) evaluated the ReStore Soft Exo-Suit in another Evidence Analysis Research Brief and reported that, while they found one study (Awad et al. 2020 summarized below) that evaluated treatment guided by the ReStore Soft Exo-Suit, they found no RCTs or studies evaluating this device compared with another technology, sham, or placebo and they concluded that there currently is not enough published peer-reviewed literature to evaluate the evidence related to this device for post-stroke rehabilitation. Hayes also reported that they found three position statements or guidelines; however, none of these documents conferred any support for robotic exoskeleton gait training for post-stroke rehabilitation.

Zhang et al. (2024) conducted a pilot, single-blind RCT to investigate the effect of REX exoskeleton rehabilitation robot training on the balance and lower limb function in individuals with sub-acute stroke. The study included 24 participants with sub-acute stroke ranging from three weeks to three months who were randomized into two groups, a robot group (n = 12, mean age 63.5 years, 83.33% male, stroke duration 46.67 days) who received exoskeleton rehabilitation robot training and a control group (n = 12, mean age 63.83 years, 66.67% male, stroke onset duration 52.50 days) who received upright bed rehabilitation. Both groups underwent training for 60 minutes once a day, five days a week for four weeks. Each participant was evaluated prior to intervention, at two weeks after and four weeks after the intervention with the BBS with secondary assessment done with the Fugl-Meyer Lower Extremity Motor Function Scale (FMA-LE), the Posture Assessment Scale for Stroke Patients (PASS), the Activities of Daily Living Scale (Modified Barthel Index, MBI), the Tecnobody Balance Tester, and lower extremity muscle surface electromyography (sEMG). The authors reported that participants in the robot group showed significant improvements in the primary efficacy index BBS, as well as the secondary efficacy indexes PASS, FMA-LE, MBI, Tecnobody Balance Tester, and sEMG of the lower limb muscles. The authors also reported that there were significant differences in BBS, PASS, static eye-opening or dynamic stability limit evaluation indexes between the two groups. The authors concluded that the REX exoskeleton rehabilitation robot demonstrated superior potential efficacy in promoting the early recovery of balance and motor functions in individuals with sub-acute stroke and recommended future large-scale RCTs and follow-up assessments to validate their findings. Limitations of the study include the small sample size, the single-center design, the short-term follow-up period, the lack of double-blinding and the lack of mechanistic studies balance improvement measurements.

Gavrila Laic et al. (2024) performed a systematic review in effort to synthesize the use of wearable lower limb exoskeletons (LLEs) in alignment with the World Health Organization's Vision on Healthy Aging, examining their impact on intrinsic capacities and functional abilities. The authors conducted a comprehensive literature search in six databases, yielding 36 relevant articles covering older adults (65+) with various health conditions, including sarcopenia, stroke, Parkinson's Disease, osteoarthritis, and more. The interventions, spanning one to forty sessions, utilized a range of LLE technologies such as Ekso®, HAL®, Stride Management Assist®, Honda Walking Assist®, Lokomat®, Walkbot®, Healbot®, Keeogo Rehab®, EX1®, overground wearable exoskeletons, Eksoband®, powered ankle–foot orthoses, HAL® lumbar type, Human Body Posturizer®, Gait Enhancing and Motivation System®, soft robotic suits, and active pelvis orthoses. The findings revealed positive outcomes across diverse health conditions. LLE training led to improvements in key performance indicators, such as the 10MWT, Five Times Sit-to-Stand test, Timed Up and Go (TUG) test, and more. Additionally, enhancements were observed in gait quality, joint mobility, muscle strength, and balance. These improvements were accompanied by reductions in sedentary behavior, pain perception, muscle exertion, and metabolic cost while walking. While longer intervention durations can aid in the rehabilitation of intrinsic capacities, even the instantaneous augmentation of functional abilities can be observed in a single session. The authors concluded that this review demonstrates consistent enhancements in critical parameters across a broad spectrum of health conditions following LLE interventions in older adults. These findings underscore the potential of LLE in promoting healthy aging and enhancing the well-being of older adults. This systematic review has limitations including making outcome comparisons due to the substantial variability in study characteristics and participant profiles among the included studies. The limited number of eligible studies also reflected the scarcity of the literature on lower limb exoskeleton use in older adults, compounded by insufficient details regarding participant heterogeneity, comorbidities, and clinical management. Future investigations should aim to address these variables to mitigate potential biases. Moreover, the authors were not able to study differences in outcomes by training duration and frequency, mainly due to the high heterogeneity among studies. Future studies should focus on further investigating the association between training effects and intervention frequency and duration in older adults.

McGibbon et al. (2024) conducted an open-label, parallel, pilot randomized controlled trial (RCT) to explore the relationship between exercise intensity progression and memory and gait outcomes in people with Parkinson's disease (PwPD) who performed 8 weeks (2 × per week) of progressive exercise with and without a lower-extremity powered exoskeleton, as the planned exploratory endpoint analysis. Adults 50-85 years old with a confirmed diagnosis of

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Parkinson's disease (PD) participated. Twenty-seven participants randomized to exercise with (Exo = 13) or without (Nxo = 14) the exoskeleton were included in this exploratory endpoint analysis. Detailed exercise logs were kept and actigraphy was used to measure activity count*min^{-1} (ACPM) during all exercise sessions. Only participants in the Exo group were able to progressively increase their ACPM over the entire 8-week intervention, whereas the Nxo group plateaued after four weeks. Exercise intensity progression correlated with change in the memory sub-scale of the SCOPA-COG and change in gait endurance from the 6MWT, consistent with the prevailing hypotheses linking high-intensity interval exercise to improved muscle and brain function via angiogenic and neurotrophic mechanisms. The authors concluded that facilitating high-intensity exercise with advanced rehabilitation technology is warranted for improving memory and gait endurance in PwPD. Overground exoskeletons of the type studied here still represent a highly inaccessible technology, which poses an immediate barrier for translating research like this into practice. Most importantly, practice guidelines must be developed that are evidence based. Generally speaking, studies like this in advanced rehabilitation technology are rare. Developers need to employ better knowledge translation practices so that their technology's place in routine clinical practice is driven by the users and recipients. Further investigation is needed before the clinical usefulness of this procedure is proven.

Calafiore et al. (2022) conducted a systematic review and meta-analysis to assess the efficacy of Robot-assisted gait rehabilitation (RAGT) for gait recovery in subacute stroke survivors. A search of studies from inception through January 18, 2021, was performed to identify randomized controlled trials (RCTs) presenting stroke survivors in subacute phase (≤ 6 months) as participants; exoskeleton robotic devices as intervention; conventional rehabilitation as a comparator; and gait assessment, through qualitative scales, quantitative gait scales or quantitative parameters, as outcome measures. In addition, a meta-analysis of the mean difference in the functional ambulation category (FAC) via the random effect method was performed. Out of 3188 records, 14 RCTs were analyzed in this systematic review. The 14 studies have been published in the last 14 years (from 2006 to 2021) and included 576 stroke survivors, of which 306 received RAGT, and 270 underwent conventional rehabilitation. Lokomat® robotic rehabilitation device was the most investigated robotic exoskeleton by the RCTs included (n = 9). The meta-analysis demonstrated an insignificant difference of -0.09 in FAC (95% CI: -0.22.0.03) between Lokomat® and conventional therapy. According to the PEDro scale, 11 (78.5%) were classified as good-quality studies, two as fair-quality studies (14.3%), and one as a poor-quality study (7.1%). The authors concluded the findings showed that RAGT might have a potential role in gait recovery in subacute stroke survivors. However, further RCTs comparing the efficacy of RAGT with conventional physical therapy are still warranted in the neurorehabilitation field. This systematic review provides information on the efficacy of RAGT in allowing subacute stroke patients to perform high-intensity gait training with a lower physical burden on PRM professionals. Limitations of this systematic review include the lack of meta-analysis for all the RAGT interventions assessed. Except for studies that investigated the Lokomat® (with FAC as outcome), all the other RCTs were heterogeneous, adopting different systems for RAGT and studied different outcomes. All studies showed a high heterogeneity of protocol session and duration of intervention. Further investigation is needed before clinical usefulness of this equipment is proven.

Edwards et al. (2022) conducted a randomized controlled trial (RCT) to demonstrate that a 12-week exoskeleton-based robotic gait training regimen can lead to a clinically meaningful improvement in independent gait speed, in community-dwelling participants with chronic incomplete spinal cord injury (iSCI). Multi-site (United States), randomized, controlled trial, comparing exoskeleton gait training (12 weeks, 36 sessions) with standard gait training or no gait training (2:2:1 randomization) in chronic iSCI (> 1 year post injury, AIS-C, and D), with residual stepping ability was completed. The primary outcome measure was change in robot-independent gait speed (10-meter walk test, 10MWT) post 12-week intervention. Secondary outcomes included: TUG, 6MWT, Walking Index for Spinal Cord Injury (WISCI-II) (assistance and devices), and treating therapist NASA-Task Load Index. Twenty-five participants completed the assessments and training as assigned (n = 9 Ekso, n = 10 Active Control, n = 6 Passive Control). Mean change in gait speed at the primary endpoint was not statistically significant. The proportion of participants with improvement in clinical ambulation category from home to community speed post-intervention was greatest in the Ekso group (> 1/2 Ekso, 1/3 Active Control, 0 Passive Control, $p < 0.05$). Improvements in secondary outcome measures were not significant. The authors concluded that 12 weeks of exoskeleton robotic training in chronic SCI participants with independent stepping ability at baseline can improve clinical ambulatory status. Improvements in raw gait speed were not statistically significant at the group level, which may guide future trials for participant inclusion criteria. While generally safe and tolerable, larger gains in ambulation might be associated with higher risk for non-serious adverse events. The simple randomization method in the present study resulted in non-significant statistical difference in baseline features between the three groups. Future clinical trials should also consider (1) sufficient sample size to detect a statistical difference in group mean data, (2) anticipating a small increase in gait speed in the Passive Control group potentially a repeated assessment on the 10MWT or association with a gait clinical trial, (3) participant characteristics (clinical features) that might limit the response to this form of training, (4) restricting the number of assessments on a given day to avoid testing fatigue, and (5) including patient-reported outcome measures that detect potentially small outcome differences in domains not easily measured by the usually applied clinical assessments. Further investigation is needed before the clinical usefulness of this exoskeleton gait training is proven.

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Tamburella et al. (2022) conducted a systematic review to provide a general overview of the effects of commercial overground powered lower limb exoskeletons (EXOs) (i.e., not EXOs used in military and industry applications) for medical purposes in individuals with spinal cord injury (SCI). This systematic review was conducted following the PRISMA guidelines, and it referred to MED-LINE, EMBASE, SCOPUS, Web of Science and Cochrane library databases. The studies included were Randomized Clinical Trials (RCTs) and non-RCT based on EXOs intervention on individuals with SCI. Out of 1296 studies screened, 41 met inclusion criteria. Among all the EXO studies, the Ekso device was the most discussed, followed by ReWalk, Indego, HAL and Rex devices. Since 14 different domains were considered, the outcome measures were heterogeneous. The most investigated domain was walking, followed by cardiorespiratory/metabolic responses, spasticity, balance, quality of life, human–robot interaction, robot data, bowel functionality, strength, daily living activity, neurophysiology, sensory function, bladder functionality and body composition/bone density domains. There were no reports of negative effects due to EXOs training and most of the positive effects were noted in the walking domain for Ekso, ReWalk, HAL and Indego devices. Ekso studies reported significant effects due to training in almost all domains, while this was not the case with the Rex device. Not a single study carried out on sensory functions or bladder functionality reached significance for any EXO. It is not possible to draw general conclusions about the effects of EXOs usage due to the lack of high-quality studies as addressed by the Downs and Black tool, the heterogeneity of the outcome measures, of the protocols and of the SCI epidemiological/neurological features. However, the strengths and weaknesses of EXOs are starting to be defined, even considering the different types of adverse events that EXO training brought about. The authors concluded EXO training showed to bring significant improvements over time, but whether its effectiveness is greater or less than conventional therapy or other treatments is still mostly unknown. High-quality RCTs are necessary to better define the pros and cons of the EXOs available today.

Zhang et al. (2022) performed a systematic review and meta-analysis to assess locomotor abilities in patients with spinal cord injuries (SCI) with two different types of robotic-assisted gait training (RAGT) programs, Lokomat and wearable exoskeleton-assisted walking (EAW) training. Of 319 studies identified, 12 studies published between 2013 and 2021 were included in this review. The study included evaluation of locomotor abilities with a 10-MWT, 6-MWT, TUG test, and WISCI-II in patients with SCI. The authors findings concluded that wearable EAW showed notable increase in distance and speed in the 10-MWT [distance: 0.85 (95% CI = 0.35, 1.34); speed: −1.76 (95% CI =−2.79, −0.73)]. In findings for the 6-MWT and TUG test, they also concluded notable increase; 6-MWT distance [−1.39 (95% CI = −2.01, −0.77)] and TUG test [(1.19 (95% CI = 0.74, 1.64)]. However, the WISCI-II did not have a notable distinction [−0.33 (95% CI = −0.79, 0.13)]. In the author's findings for Lokomat, the 10-MWT and WISCI-II revealed notable increases. The 10-MWT distance was [−0.08 (95% CI = −0.14, −0.03)] and WISCI-II was [1.77 (95% CI = 0.23, 3.31)]. Overall, the two types of RAGT had beneficial effects on locomotion abilities but EAW had better outcomes in speed compared to Lokomat. However, there were limitations in the study based on the small sample size of articles. According to the authors, further studies are necessary to understand if the intensity of training affects RAGT success, and by which RAGT techniques enhanced walking recovery capabilities.

Yip et al. (2022) performed a scope review on overground exoskeleton effectiveness, preclusions on secondary health complications, quality of life (QOL) changes, and the outcomes on the independence of individuals with spinal cord injury (SCI) in community settings. The purpose of the review was to identify gaps in the current literature, and to make recommendations on future study areas and research methods. In this systematic review, an initial search of 654 articles were identified, and 50 articles met the inclusion criteria. The authors concluded that overground exoskeletons show promise in health benefits, pragmatic outcomes in secondary health complications, enhancing QOL in individuals with SCI and favorable probability of regaining their previous roles in the community. There were limitations identified which include limited types of exoskeletons, variability on study design, distinct study populations, and diverse training programs, which future studies can address. The authors also recommend future studies in cardiovascular health, body mass density, body composition changes and applicability of exoskeleton toward independence and functional gain.

Calabro et al. (2021) conducted a systematic review to determine the scope, quality, and consistency of guidelines for robotic lower limb rehabilitation after stroke, in order to provide clinical recommendations. Stroke rehabilitation guideline recommendations between January 1, 2010, and October 31, 2020, were reviewed. Two independent reviewers used the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument, and brief syntheses were used to evaluate and compare the different recommendations, considering only the most recent version. From a total of 1219 papers screened, ten eligible guidelines were identified from seven different regions/countries. Four of the included guidelines focused on stroke management, the other six on stroke rehabilitation. Robotic rehabilitation is generally recommended to improve lower limb motor function, including gait and strength. Unfortunately, there is still no consensus about the timing, frequency, training session duration and the exact characteristics of subjects who could benefit from robotics. The authors concluded their systematic review shows that the introduction of robotic rehabilitation in standard treatment protocols seems to be the future of stroke rehabilitation. However, robot assisted gait training (RAGT) for stroke needs to be improved with new solutions and in clinical practice guidelines, especially in terms of applicability. Guidelines development groups have used different methods to create recommendations, leading to variability in both quality and scope.

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International guidelines are needed to overcome this issue. Further research with randomized controlled trials is needed to validate these findings.

In Duddy et al. (2021), a systematic review of studies was conducted to examine the effects of powered exoskeleton training on cardiovascular function and gait performance. Out of a 65-article search conducted between April 2020 to February 2021, 23 studies were included in this review. The researchers examined cardiovascular function variables which included volume of oxygen (VO2), heart rate (HR), rate of perceived exertion (RPE), metabolic equivalent of task (MET), physiological cost index (PCI), respiratory exchange ratio (RER), energy expenditure and blood pressure (BP). In gait performance the researchers evaluated a variety of assessment protocols which include 6 MWT, 10 MWT, TUG test, 25-foot walk test (25 FWT), 2-minute walk test (2 MWT), 30-minute walk test (30 MWT), total steps, distance and walking speed. The researchers concluded that powered exoskeleton assisted training may increase oxygen and HR when compared to non-exoskeleton walking. In comparison to non-exoskeleton walking and wheelchair propulsion, the MET and PCI of exoskeleton assisted walking demonstrated three to four times greater. In addition, carbohydrate utilization in RER was higher during exoskeleton walking. As for energy expenditure with exoskeleton assisted walking it was slightly less than non-exoskeleton walking and the RPE was equivalent to moderate intensity. When evaluating gait performance, the studies indicated improvements in all gait assessment protocols except for the 30 MWT. The 30 MWT identified that between ReWalk exoskeleton assistance and an unpowered KAFO the KAFO showed greater distance than the ReWalk. In conclusion, the researchers identified that powered exoskeleton training is a safe and effective way to improve cardiovascular function and gait performance. However, there were limitations in the study which include the limited sample size from some of the selected studies. According to the researchers, future studies are warranted with larger sample sizes, exploration of studies with control groups for further comparisons and to explore longitudinal effects of cardiovascular function with exoskeleton gait training, walking capabilities and secondary health conditions with longer durations.

In a clinical evidence assessment, ECRI (2021, updated in 2023) evaluated wearable powered exoskeletons for personal use after a spinal cord injury (SCI) in the home and community settings. The analysis included 19 individuals from two case series and one case report. The assessment stated that the evidence was inconclusive related to its safety and effectiveness in aiding individuals with SCI perform ambulatory functions in the home and community setting as there was too few data although the evidence suggested that short-term use of ReWalk and Ekso improved physical, social, and mental health in some individuals with SCIs but that it was unclear whether these benefits were sustained or whether exoskeletons improved the individuals' abilities to perform activities of daily living. The authors concluded the studies contained a high risk of bias along with a small number of participants and that additional comparative studies with larger sample sizes assessing long-term outcomes and adverse effects were warranted to determine the benefit of these devices.

Rodríguez-Fernández et al. (2021) completed a systematic review of 87 clinical studies that gathered information and measured the outcomes of wearable lower-limb exoskeletons while gait training overground for individuals with neuromuscular impairments. There were 25 exoskeletons included with only 6 containing FDA approval and/or commercially available. The results of the literature survey revealed that wearable exoskeletons have potential for a number of applications including early rehabilitation, promoting physical exercise, and carrying out daily living activities both at home and in the community. Likewise wearable exoskeletons may improve mobility and independence in non-ambulatory people may reduce secondary health conditions related to sedentariness. However, the use of this technology is still limited by heavy and bulky devices, which require supervision and the use of walking aids. In addition, evidence supporting their benefits is still limited to short-intervention trials with few participants and diversity amongst clinical protocols. Wearable lower-limb exoskeletons for gait rehabilitation are still in the early stages of development and RCTs are needed to demonstrate their clinical efficacy.

According to NICE's guideline (2020; updated 2023) on stroke rehabilitation in adults, the standard of care for managing movement difficulties after stroke includes physiotherapy and fitness, strength and repetitive task training. Walking therapy is recommended for people who have had a stroke and who are able to walk, with or without assistance. Electromechanical gait training should only be used as part of a research study.

Awad et al. (2020) conducted a multi-site clinical trial that included 44 patients with post-stroke hemiparesis to study the safety, reliability and feasibility of the ReWalk Restore soft robotic exosuit for post-stroke gait rehabilitation. The patients trained for five days with the Restore soft exosuit and 16 patients required an assistive device [Ankle foot orthosis (AF0), cane, ankle brace, walker] on the treadmill and overground. During the five days of training, each visit consisted of 20 minutes of overground and 20 minutes treadmill walking practice while wearing the Restore exosuit motor at the waist as it transmitted mechanical forces to points located proximally attached around the calf and distally to a shoe insole. During the study eight patients dropped out for various reasons. Of the 36 patients that finished the study, they found the Restore soft exosuit clinically feasible, less than 10% had safety issues ranging from mild to severe, no falls, and the device

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malfunctioned for 11.6%. After five days of training 61% of the patients increased their maximum walking speed. The authors concluded that the ReStore soft exosuit is safe and reliable for use in post-stroke gait rehabilitation with the supervision of licensed physical therapist for support. These findings are motivation for further efficacy trials of soft robotic exosuits.

Moucheboeuf et al. (2020) conducted a meta-analysis to investigate the effects of robot-assisted gait training after stroke and to elucidate the observed heterogeneity of results in previous meta-analyses. All RCTs investigating exoskeletons or end-effector devices in adult patients with stroke were searched in databases from inception to November 2019, as were bibliographies of previous meta-analyses, independently by two reviewers. Variables collected before and after the rehabilitation program included gait speed, gait endurance, Berg Balance Scale (BBS), Functional Ambulation Classification (FAC) and TUG scores. In addition, data on randomization method, blinding of outcome assessors, drop-outs, intention (or not) to treat, country, number of participants, disease duration, mean age, features of interventions, and date of outcomes assessment were extracted. A total of 33 studies involving 1466 participants were included. On analysis by subgroups of intervention, as compared with physiotherapy alone, physiotherapy combined with body-weight support training and robot-assisted gait training conferred greater improvement in gait speed [+0.09m/s, 95% confidence interval (CI) 0.03 to 0.15; p = 0.002], FAC scores (+0.51, 95% CI 0.07 to 0.95; p = 0.022) and BBS scores (+4.16, 95% CI 2.60 to 5.71; p = 0.000). A meta-regression analysis suggested that these results were underestimated by the attrition bias of studies. The authors concluded that the use of RAGT associated with CT and BWST would improve the efficiency of walking rehabilitation after stroke, with significant gait speed, FAC and BBS improvements. The findings of this study need to be validated by well-designed studies. Further investigation is needed before the clinical usefulness of this procedure is proven.

The exoskeleton hybrid assistive limb (HAL) is controlled voluntarily by the patient's own muscle signals detected by surface electrodes. Sczesny-Kaiser et al. (2019) conducted a monocentric, controlled, randomized, two-period crossover study to test the efficacy of HAL-assisted body weight supported treadmill training (BWSTT) compared to conventional physiotherapy (CPT) on walking parameters in chronic stroke patients. A total of 18 chronic stroke patients participated in this study. Treatment consisted of 30 CPT sessions and of 30 sessions of BWSTT with a double leg type HAL exoskeleton successively in a randomized, crossover study design. Primary outcome parameters were walking time and speed in 10MWT, TUG test and distance in 6MWT. Secondary outcome parameters were the functional ambulatory categories (FAC) and the BBS. Data were assessed at baseline, at crossover and at the end of the study, all without using and wearing HAL. The study demonstrated neither a significant difference in walking parameters nor in functional and balance parameters. When HAL-BWSTT was applied to naïve patients it led to an improvement in walking parameters and in balance abilities. Pooling all data, the authors showed a significant effect in 10MWT, 6MWT, FAC and BBS, both therapies sequentially applied over 12 weeks. Thereby, FAC improved from dependent to independent category (3 to 4). One patient dropped out of the study due to intensive fatigue after each training session. The authors concluded that HAL-BWSTT and mixed-approach CPT were effective therapies in chronic stroke patients. However, compared with CPT, HAL training with 30 sessions over six weeks was not more effective. The combination of both therapies led to an improvement of walking and balance functions. Robotic rehabilitation of walking disorders alone still lacks proof of superiority in chronic stroke. Robotic treatment therapies and classical CPT rehabilitation concepts should be applied in an individualized therapy program.

A VA/DoD joint clinical practice guideline for rehabilitation after stroke states that evidence supporting the use of robotics for stroke rehabilitation is weak. The quality of current evidence suggests offering robot-assisted movement therapy as an adjunct to conventional therapy in patients with deficits in upper-limb function to improve motor skill. In addition, there is insufficient evidence to recommend for or against the use of robotic devices during gait training (Sall et al., 2019).

Cheung et al. (2017) completed a systematic review and meta-analysis to investigate the effects of robot-assisted training on the recovery of people with SCI. The survey considered all randomized controlled trials (RCTs) and quasi-RCTs. Only studies involving people with SCIs were considered. Studies were included if the intervention involved robot-assisted training, including both upper limb robotic training and robot-assisted BWSTT. 11 articles met the inclusion criteria. Four articles were identified as reporting investigations of the effect of robotic training on walking speed and walking endurance. Two studies provided sufficient data for analysis. Together they involved 158 participants. The robotic group showed no significant improvement in walking speed. The pooled mean difference (fixed effects model) was only .08 seconds. The robot-trained group showed improvements in endurance, which were highly significant in both statistical and practical terms. The pooled mean difference (fixed effects model) was 53.32m (95% CI, −73.15 to −33.48; p ≤ .00001; I^2 = 0%). Two articles reporting the effect of robotic training on walking independence were identified. A total of 158 participants were included. The robotic group showed better improvement in walking independence compared with the control group. The pooled mean difference (fixed effects model) was 3.73 (95% CI, −4.92 to −2.53; p < .00001; I^2 = 38%). Lower limb robot-assisted training was also found to be as effective as other types of BWSTT. The authors concluded that robot-assisted training is an adjunct therapy for physical and functional recovery for patients with SCI. Future high-quality

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studies are warranted to investigate the effects of robot-assisted training on functional and cardiopulmonary recovery of patients with SCI.

Fisahn et al. (2016) completed a systematic review to determine if powered exoskeletons are effective as assistive and rehabilitation devices in improving locomotion in patients with SCI. Eleven publications were included in the review, 10 utilized the robotic exoskeleton Lokomat and the remaining study utilized the robotic exoskeleton MBZ-CPM1 [ManBuZhe (TianJin) Rehabilitation Equipment Co. Ltd., PR China]. Nine of the included randomized trials were of parallel design, and two were of crossover design. Most studies were of moderately high risk of bias. The authors of the review identified no comparison studies evaluating exoskeletons as an assistive device. Nine comparison studies (11 publications) evaluated the use of exoskeletons as a rehabilitative device. The 10MWT velocity and Spinal Cord Independence Measure scores showed no difference in change from baseline among patients undergoing exoskeleton training compared with various comparator therapies. The remaining primary outcome measures of 6MWT distance and WISCI-II and Functional Independence Measure–Locomotor scores showed mixed results, with some studies indicating no difference in change from baseline between exoskeleton training and comparator therapies, some indicating benefit of exoskeleton over comparator therapies, and some indicating benefit of comparator therapies over exoskeleton. The authors of this review concluded that there is no data to compare locomotion assistance with exoskeleton versus conventional knee-ankle-foot orthoses (KAFOs). The authors also concluded that there is no consistent benefit from rehabilitation using an exoskeleton versus a variety of conventional methods in patients with chronic spinal cord injury and that trials comparing later-generation exoskeletons are needed.

In 2016, Miller et al. completed a systematic review with meta-analysis on the clinical effectiveness and safety of powered exoskeletons in SCI patients. A total of 14 studies (eight ReWalk™, three Ekso™, two Indego®, and one unspecified exoskeleton) representing 111 patients were included in the analysis. Training programs were typically conducted three times per week, 60–120 minutes per session, for one to24 weeks. Ten studies utilized flat indoor surfaces for training and four studies incorporated complex training, including walking outdoors, navigating obstacles, climbing and descending stairs, and performing activities of daily living. Following the exoskeleton training program, 76% of patients were able to ambulate with no physical assistance. The weighted mean distance for the 6-minute walk test was 98 m. The physiologic demand of powered exoskeleton-assisted walking was 3.3 metabolic equivalents and rating of perceived exertion was 10 on the Borg 6–20 scale, comparable to self-reported exertion of an able-bodied person walking at three miles per hour. Improvements in spasticity and bowel movement regularity were reported in 38% and 61% of patients, respectively. No serious adverse events occurred. The incidence of fall at any time during training was 4.4%, all occurring while tethered using a first-generation exoskeleton and none resulting in injury. The incidence of bone fracture during training was 3.4%. Limitations to the meta-analysis included considerable variation in the consistency of outcome reporting among studies. It is also noted that the research for this analysis was supported by ReWalk Robotics, Inc. the manufacturer of the ReWalk™ exoskeleton.

Louie and Eng (2016) completed a literature review surrounding the use of robotic exoskeletons for gait rehabilitation in adults' post-stroke. Articles were included if they utilized a robotic exoskeleton as a gait training intervention for adult stroke survivors and reported walking outcome measures. Of 441 records identified, 11 studies involving 216 participants met the inclusion criteria. The study designs ranged from pre-post clinical studies (n = 7) to controlled trials (n = 4); five of the studies utilized a robotic exoskeleton device unilaterally, while six used a bilateral design. Participants ranged from sub-acute (less than seven weeks) to chronic (more than 6 months) stroke. Training periods ranged from single-session to 8-week interventions. Meaningful improvement with exoskeleton-based gait training was more apparent in sub-acute stroke compared to chronic stroke. Two of the four controlled trials showed no greater improvement in any walking outcomes compared to a control group in chronic stroke. The authors concluded that clinical trials demonstrate powered robotic exoskeletons can be used safely as a gait training intervention for stroke. Preliminary findings suggest that exoskeletal gait training is equivalent to traditional therapy for chronic stroke patients, while sub-acute patients may experience added benefit from exoskeletal gait training. According to the authors of this review, efforts should be invested in designing rigorous, appropriately powered controlled trials before powered exoskeletons can be translated into a clinical tool for gait rehabilitation post-stroke.

Guidelines on adult stroke rehabilitation and recovery published by the AHA and ASA state that no benefit was seen with robotic-based interventions compared with more traditional approaches. Robot-assisted movement training to improve motor function and mobility after stroke in combination with conventional therapy may be considered however, further studies are needed to clarify the optimal device type, training protocols, and patient selection to maximize benefits (Winstein, et al., 2016).

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Code	Description
E2001	Suction pump, home model, portable or stationary, electric, any type, for use with external urine and/or fecal management system

Female external urine management systems (including but not limited to QiVi™ Female External Urine Management System, CareDry® System, PrimaFit External Urine Management Device, PureWick™ System, Versette ® external catheter) are unproven and not medically necessary for managing urinary incontinence due to insufficient evidence of efficacy.

Clinical Evidence

Female external urinary management systems are intended to reduce the risk of indwelling catheter-associated urinary tract infections (CAUTIs), and skin irritation associated with incontinence pads and diapers. The systems consist of a wicking fabric that is placed against the female urinary tract external genitalia and is connected to continuous low suction to divert urine into a collection vessel (Lopez, 2024). Despite its unique design, studies are conflicting regarding the efficacy of these devices to lower CAUTI's, further research is needed to demonstrate the superior nature of these devices.

Baxter et al. (2025) conducted a randomized, prospective, multi-center, quality improvement study to evaluate the incidence of skin-related complications attributable to incontinence-associated dermatitis (IAD) from the use of an external female urinary catheter device used for urinary incontinence. The study included 381 females (mean age 76.3 years) from 57 inpatient care units at a 40-hospital integrated academic healthcare system in central and western Pennsylvania over a nine-month period. Participants were randomized to receive one of two commercially available external female urinary catheter devices [catheter A (n = 158) and catheter B (n = 205)]. There were 15 participants who utilized both catheters in the study and seven who did not utilize either device. Median catheter duration was three days in both groups, and the number of catheters used was two in the catheter A group and three in the catheter B group. The authors reported that the frequency of new or worsening skin breakdown was 19 (4.9%) in the Intention to Treat analysis, 19 (5.1%) in the As Treated analysis, and 14 (4.1%) events in the Per Protocol analysis. According to the authors, both devices were associated with an overall low risk (5%) of new or worsening skin breakdown. The authors also reported that participants who were randomized to the catheter A group had a higher switch rate at 16.9% (31 of 193 participants) than did those who were randomized to the catheter B group (12.1%, 26 of 215 participants). There was a nominal decrease in CAUTI rates after implementation, according to the authors, in 29 (50.9%) hospital units, a nominal increase in 21 (36.8%) units and no change in seven (12.3%) units with a median decrease of 0.31 CAUTI events per 1000 catheter days. Regarding the adverse events reported on 15 participants, seven arrived with baseline skin intact and subsequently developed new skin breakdown mostly in the buttocks region, five participants arrived with baseline IAD primarily in the buttocks region that worsened or spread to new skin regions and three participants arrived with baseline coccyx pressure injuries that became worse. Limitations of the study included the inclusion of only hospital units that agreed to participate, the honor system adherence for the randomized allocation, the inclusion of women who could cooperate with care, and the homogenous participant population. The authors concluded that external urinary catheter use in hospitalized female patients with urinary incontinence was associated with low risk of new or worsening overall skin breakdown.

Pryor et al. (2024) conducted a systematic review and meta-analysis to assess the clinical risks and benefits of female external urine wicking devices (FEUWDs) as alternatives to indwelling urinary catheters (IUCs). The systematic review included 50 non-randomized intervention studies, of which 49 were based in the United States. Fourteen of these studies provided sufficient methodological information and interventional in design to be evaluated for quality, of which seven provided adequate outcomes data required for inclusion in meta-analyses; however, all seven demonstrated a moderate or serious risk of bias overall. The authors reported that IUC utilization rates decreased 14% following FEUWD implementation and indwelling CAUTI rates decreased (non-significantly) up to 32%, while the incidence rate of indwelling CAUTIs decreased significantly up to 54% when the authors limited their review to only studies that described protocols for implementation. The authors concluded that FEUWDs non-significantly reduced indwelling CAUTI rates overall, though the reductions were significant among studies describing FEUWD implementation protocols. The authors recommended that standard definitions be developed for consistent reporting of non-dwelling CAUTI complications such as FEUWD-associated UTIs, skin injuries, and mobility-related complications. Limitations of the study include the heterogeneity of the studies involved, the lack of randomization and controls in the studies, the low number of available studies for the meta-analyses, the moderate to serious risk of bias in all the studies, the introduction of FEUWDs alongside existing interventions focusing on reducing CAUTIs, and the lack of accountability for confounding interventions. This systematic review included the Beeson, et al. (2023), Eckert et al. (2020), Lem, et al. (2022), Jasperse, et al. (2022), Warren, et al. (2021) and Zavodnick, et al. (2020) studies summarized below.

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ECRI (2024) published an Evidence Analysis on female external urine collection systems for reducing CAUTIs and found that there was a very-low-quality body of evidence that did not enable conclusions about whether these systems reduce CAUTI rates or how their safety and effectiveness for reducing CAUTIs compares with those of indwelling catheters or other methods for reducing CAUTIs. ECRI reviewed full text of nine studies (one systematic review, seven pre/post implementation studies, and one clinical implementation study) that reported on over 10, 000 patients. The report stated that these studies all had a high risk of bias, reported mixed findings on CAUTI rates, or reported no statistical difference in CAUTI rates between female external urine collection systems and indwelling catheters. The report also found no studies that compared the use of female external urine collection systems with other methods intended to reduce CAUTI incidence. In their search for guidelines, position, and consensus statements, ECRI found no published guidelines that discussed female external urine collection systems for reducing CAUTIs. This analysis included the Pryor, et al. (2024), Beeson, et al. (2023), Lem, et al. (2022), Jasperse, et al. (2022), Warren, et al. (2021) and Zavodnick, et al. (2020) studies included below.

Beeson et al. (2023) conducted a prospective, observational, quasi-experimental study to examine the effectiveness of an external female urinary management system [external urinary device for female anatomy (EUDFA)] in critically ill women unable to self-toilet and to identify rates of indwelling catheter use, catheter-associated urinary tract infections (CAUTIs), urinary incontinence (UI), and incontinence-associated dermatitis (IAD) before and after the introduction of the EUDFA. The sample included 50 adult female patients in 4 critical/progressive care units using an EUDFA at a large academic hospital in the Midwestern United States. All adult patients in these units were included in the aggregate data. The device studied was the Sage PrimaFit External Urine Management System for the Female Anatomy (Sage Products, a business unit division of Stryker, Cary, Illinois). This system is placed in the perineal area between the labia, against the urethra conforming to the female anatomy, and connected to low continuous suction providing a sump mechanism to divert urine into an external canister. Prospective data collected from the adult female patients over 7 days included urine diverted from the device to a canister and total leakage. Aggregate unit rates of indwelling catheter use, CAUTIs, UI, and IAD were retrospectively examined during 2016, 2018, and 2019. Means and percentages were compared using t tests or chi-square tests. EUDFA successfully diverted 85.5% of patients' urine. Indwelling urinary catheter use was significantly lower in 2018 (40.6%) and 2019 (36.6%) compared with 2016 (43.9%) ($p < .01$). The rate of CAUTIs was lower in 2019 than in 2016, but not significantly (1.34 per 1000 catheter-days vs 0.50, $p = .08$). The percentage of incontinent patients with IAD was 69.2% in 2016 and 39.5% in 2018-2019 ($p = .06$). The authors concluded that EUDFA was effective in diverting urine from critically ill female incontinent patients and indwelling catheter utilization. This study was limited by impacts of the COVID-19 pandemic, which interrupted and complicated patient enrollment and imposed significant burdens on staff. Additionally, data on IAD prevalence reflect only a single month in each observation year. Finally, the study time frame coincided with a period when the quality focus was on decreasing use of indwelling catheters and implementing a nurse-driven internal urinary catheter removal protocol. While the use of an effective EUDFA played a pivotal role in these initiatives, not all reductions in indwelling catheter use or CAUTIs can be attributed to the EUDFA. Further research with randomized controlled trials is needed to validate these findings.

Jasperse et al. (2022) reviewed the records of 848 adult female patients in a retrospective, single center cohort study to compare the catheter associated urinary tract infection (CAUTI) rate and the number of indwelling urinary catheter (IUC) days before and after the PureWick® external urinary collection device (EUCD) was introduced in the internal medicine, family medicine, and neurology units of their facility, There were 848 female patients who received an IUC and/or an EUDC between 2017 and 2018 that were included in the study. The participants were divided into two groups, with the PRE group including 259 females who received an IUC in the 3 months before PureWick was introduced and the second group (POST group) included 292 female patients who had an EUCD and 397 patients who received an IUC who were admitted 12 months after PureWick became available. The authors reported that there were no differences in the cohorts regarding age, body mass index (BMI) and comorbidities and that the POST cohort had a greater number of IUC days (median 3 versus 2 days), a higher rate of CAUTI (9.3 versus 2.3 infections per 1000 patient days), and a longer duration of hospitalization (median, 6 versus 5 days), while the overall UTI rate was similar between cohorts (infections per 1000 patient days, 15.5 versus 21.4). Limitations include the retrospective, single-center design, missing data, inconsistencies in charting, potential for reporting bias, the increase in the number of urine cultures ordered in the POST cohort, the lack of a procedure protocol which left the application to provider discretion and the small number of patients included in the study. The authors concluded that, while EUCDs appear to be a promising alternative to IUCs for female patients, their study found that both the median number of IUC days and the CAUTI rate increased after introduction of the PureWick EUCD.

A Hayes Evolving Evidence Review (2022, updated 2024) examined external female catheters for managing urinary incontinence (UI). Five clinical studies were identified but authors concluded they were of poor quality due to lack of simultaneous comparison groups and comparison to historical data. No systematic reviews were identified. In the 2024 update, one newly published prospective cohort study was identified; however, Hayes concluded that there was no change to their previous guidance. The report continues to state that there is a minimal level of support for using female

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external urinary catheters (FEUCs) for managing UI. (Studies by Eckert et al., 2020, Warren et al., 2021, and Zavodnick et al., 2020 which are discussed in this policy, were included in this Evolving Evidence Review.)

Lem et al. (2022) conducted a retrospective study to compare CAUTI rate and the median number of days an indwelling urethral catheter (IUC) was used before and after availability of this female external urinary catheter device (EUCD) for surgical patients. This retrospective analysis consisted of adult female surgical patients admitted to a single academic institution who received an IUC and/or EUCD was performed. Patients who received an IUC three months before (PRE) EUCD availability (08/2017 – 10/2017) were compared to patients receiving an IUC and/or EUCD 12 months after (POST) (11/2017 – 11/2018). Of 906 surgical patients receiving an IUC/EUCD, 127 received an EUCD in the POST cohort. Compared to the PRE, the POST had a higher rate of CAUTIs (infections per 1000 catheter days, 11.2 vs. 4.6, p = 0.017) and overall, UTI rate (infections per 1000 catheter days, 5.4 vs. 4.8, p = 0.036), whereas IUC days were similar between cohorts (median, two vs. two days, p = 0.18). The POST cohort rate of EUCD UTI was 4.6 infections per 1000 device days. The authors concluded while EUCDs appear to be a promising alternative to IUCs for female surgical patients, this study found increased CAUTIs after introduction of an EUCD. Further research is needed to clarify if female EUCDs are effective in decreasing CAUTI prior to widespread adoption. This may be related to selection bias, with EUCDs being ordered for patients who would not have otherwise received any urinary collection device. The dermatologic injury from the pressure and stiffness of the device also should be taken into account when considering using an EUCD. This study suggests that future prospective randomized controlled trials with explicit indications for EUCD usage are needed to validate these findings.

ECRI's (2022) Clinical Evidence Assessment on the Versette Female External Catheter device and on the UriCap Female External Urine Collection Device (TillaCare) identified no published studies on either device that examined the device's safety and effectiveness for reducing CAUTIs.

In their Clinical Evidence Assessment on the use of the Purewick Female External Catheter for reducing CAUTI's, ECRI 2018; updated 2024) concluded that the evidence for reducing CAUTIs via use of the Purewick Female External Catheter was inconclusive due to very low-quality studies. ECRI reviewed eight pre-post intervention studies where Purewick was used in a subset of hospitalized patients with no direct comparison made between patients who received a Purewick catheter and those who received other types of urinary catheters. ECRI reported that the studies suggested that Purewick may reduce CAUTI, however, due to retrospective design, lack of randomization, nonconcurrent controls, and single-center focus, further prospective, controlled studies that compare Purewick to standard care are needed to address these gaps. (Studies by Eckert et al., 2020, Warren et al., 2021, and Zavodnick et al., 2020 which are summarized below, are included in this report).

Warren et al. (2021) conducted a retrospective study analyzing the impact of a hospital-wide implementation of an external female urinary catheter. The investigators compared a 12-month period before and after device implementation to assess the impact on indwelling urinary catheter utilization and CAUTI rate. The study included female patients with a combined patient stay of 220,000 days,10,000 external urinary catheter days and 33,000 indwelling urinary catheter days. The authors concluded that an increase in external female urinary catheter utilization coincided with a decline in patient CAUTI rate, but only in intensive care units (ICUs). Limitations of this study included lack of documentation regarding the catheter type used by the patients and lack of direct correlation of CAUTI decline with use of FEUCs, especially outside of the ICU setting. Further studies are needed to correlate usage of FEUCs versus indwelling catheters (IDCs) and the impact on the CAUTI rate.

ECRI's 2024 updated Clinical Evidence Assessment (2021) on the efficacy of the PrimaFit Female External Urine Management System for reducing CAUTIs included one newly identified observational study that provided insufficient evidence and did not enable conclusions about the device's safety and effectiveness for reducing CAUTIs. ECRI stated that large, multicenter, RCTs comparing CAUTI rates with and without PrimaFit are needed to demonstrate whether the device reduces CAUTI risk across hospital units caring for critically ill patients. The Beeson et al., (2023) study included in this report is summarized above.

Zavodnick et al. (2020) conducted a retrospective, observational study that included nine adult ICUs to investigate CAUTIs rates in adult females. The study compared the use of FEUCs versus IDCs. The participants had a combined total of 89,856 patient stay days. CAUTI rates and indwelling catheter days were obtained before and after the introduction of the devices. The study shows that CAUTI rates decreased from 3.14 per 1000 catheter days to 1.42 per 1000 catheter days (p = 0.013). The number of days participants needed an indwelling catheter decreased; however, the ICU days of stay increased. The authors concluded that FEUCs are associated with a significant decrease in the CAUTI rate among female intensive care participant, and they may prevent the need for indwelling catheters. Further studies are needed with a larger sample-size along with equal usage of both FEUCs and IDCs over the same number of patient days of stay.

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Eckert et al. (2020) conducted a quality improvement, single center study comparing the use of an FEUC device with wall suction as an alternative to IDC. The outcomes were to determine if FEUCs reduced the risk of CAUTI rates. The FEUC device was trialed September 2015 through December 2015, using 60 FEUC devices on 30 female patients. Data collection on these patients for one year period after use of FEUC. In 2015, before the use of the FEUC device, the baseline female IDC utilization rate was 31.7% (7181 IDC device-days/22,656 patient stay days) and the female CAUTI rate was 1.11 (8 cases/7181 IDC device-days) per 1000 stay days. After implementing use of the FEUC device both IDC utilization and CAUTI rates declined. In 2016, the IDC utilization rate was 29.7% (p = .000) and the CAUTI rate was 0% (p = .005). In 2017 there was a reduction in IDC utilization rates of 26% (p = .000) but the CAUTI rate of 0.90% was not significantly different from the prior year rate (p = .726). The authors concluded they need to continue to prioritize the use of FEUCs over IDCS. Limitations of this study include lack of consistent sample size, short follow-up and lack of equal comparisons of FEUC and IDC patient usage.

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Code	Description
L8699	Prosthetic implant, not otherwise specified [when used to report three-dimensional (3-D) printed cranial implants]

Three-dimensional (3-D) printed cranial implants are unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Note: 3D printing of implants may be performed with other procedures such as 3D rendering with interpretation and reporting of imaging. For additional information regarding these imaging procedures, refer to the UnitedHealthcare Community Plan: Radiology Prior Authorization and Notification. (Accessed April 16, 2025).

Clinical Evidence

Custom craniofacial implants are used to repair skull bone defects after trauma or surgery. Cranial implants must fit precisely within all borders of a defect to restrict movement and successfully restore natural cranial shape. Currently, cranial implants are designed and produced by third-party suppliers, which can be time consuming and expensive. Recent advances in additive manufacturing (3-D) make point of care fabrication of personalized implants feasible (Li et al., 2021).

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Most of the currently published research is limited to studies with a small number of participants, case series, and technical publications.

In a 2024 systematic review, Di Cosmo et al. evaluated the efficacy of 3D-printed titanium and polyetheretherketone (PEEK) implants versus standard non-3D-printed implants in cranial reconstructions following craniectomy. The review included nine studies with 942 participants, of which 318 received 3D-printed implants and 624 underwent standard cranioplasties. The meta-analysis revealed no statistically significant difference between the total complication rates of 3D-printed vs. non-3D-printed cranial reconstruction [OR: 0.58, 95% CI: (0.27-1.23), p-value = 0.1571]. When comparing 3D-printed titanium implants to standard implants, the total complication rates were significantly reduced (5.8% complication rate in titanium and 21.6% in standard) [OR = 0.261, 95% CI: (0.118-0.578), p-value = 0.0009]. The authors noted no statistically significant difference in total complication rates between 3D-printed PEEK implants to standard implants (36.5% in PEEK and 28.9% in standard) [OR = 1.02, 95% CI; (0.412-2.51), p-value = 0.972]. When evaluating for infection rates, the 3D-printed implant group infection rate was 1.7% compared to the standard implant group which was 6.6% which revealed a significant relationship between the type of cranioplasty and the infection rate [OR = 0.327, 95% CI: (0.124-0.862), p-value = 0.0238]. The authors note that while PEEK did not differ meaningfully from the standard treatment in infection rates, titanium exhibited a promising trend towards reducing infection rates, though this did not achieve statistical significance [OR = 0.34, 95% CI: (0.10-1.18), p-value = 0.0893]. While reported complications varied across the included studies, five studies demonstrated 3D-printed implants to significantly increase the risk of effusion [OR = 2.20, 95% CI: (1.20-4.02), p-value = 0.0103]. Additionally, no significant differences were observed between 3D-printed and traditional implants in the rates of hematoma, epilepsy, and dehiscence. Limitations of the study include high heterogeneity and small sample sizes in the 3D-printed PEEK implants, variations in follow-up times, nature of cranial lesions (size and location), differences in implant production methods, and absence of randomized control trials which increases the risk of confounding variables related to patient-selection bias and surgeon bias. The authors note that due to the limited quality of existing literature on 3D-printed implants in cranioplasty which consists of small, single-center cohort studies, prospective randomized controlled trials are essential to validate these results and to further evaluate the risks and benefits of 3D-printed cranial implants.

In a 2021 ECRI Clinical Evidence Assessment on AccuShape PEEK, patient-specific Cranial Implants (MedCAD) for Cranial reconstruction were evaluated. The report focused on determining the product's safety and efficacy for cranial reconstruction. No published studies addressed the technologies safety and efficacy for cranial reconstruction.

Maricevich et al. (2019) evaluated the symptomatic and aesthetic improvement of patients with cranial defects secondary to decompressive craniectomies after cranial reconstruction with customized polymethyl methacrylate (PMMA) prostheses produced by 3D impression molds. This prospective study included 63 patients who underwent cranioplasties that were performed using customized PMMA prosthesis produced by 3D impression molds. All patients underwent a functional and aesthetic evaluation questionnaire in the preoperative period and in the sixth postoperative month. The mean area of the defect was 147 cm^2. The mean postoperative follow-up of the patients was 21 months, ranging from 6 to 33 months. Fifty-five patients attended the 6-month postoperative consultation. All patients presented symptomatic improvement after reconstruction of the skull. The infection rate was 3.2%, 4.8% of extrusion, 1.6% of prosthesis fracture, 7.9% of extradural hematoma, 17.4% of reoperation, 5% of wound dehiscence, and 4.8% of removal of the prosthesis. The authors concluded that cranioplasty, with a customized PMMA prosthesis, improved the symptoms and aesthetic appearance of all operated patients. The use of prototypes to customize cranial prostheses facilitated the operative technique and allowed the recovery of a cranial contour very close to normal. Limitations of this study include its case series design, the use of simple direct questions by the team that performed the cranioplasties to assess cognitive, motor, and QOL rather than the use of validated assessment tools, and the short follow-up period. Additional prospective, randomized controlled trials with longer follow-up are needed to examine the safety and efficacy of 3D printed cranial implants.

Francaviglia et al. (2017) conducted a case series analysis to present their preliminary experience with a custom-made cranioplasty, using electron beam melting (EBM) technology, in ten patients. EBM is a new sintering method for shaping titanium powder directly in 3D implants. According to the authors, this is the first report of a skull reconstruction performed by this technique. In a 1-year follow-up, no postoperative complications were observed, and good clinical and esthetic outcomes were achieved. According to the authors, a longer production process, and the greater expertise needed for this technique are compensated by the achievement of most complex skull reconstructions with a shorter operative time. This study was limited by its design, a small population and short follow-up period. Additional prospective studies with comparison groups, larger sample sizes and longer follow-up periods are needed.

Park et al. (2016) conducted a case series analysis to evaluate the efficacy of custom-made 3D-printed titanium implants for reconstructing skull defects. From 2013 to 2015, 21 patients (age range, 8-62 years; mean, 28.6 years) with skull defects were treated. Total disease duration ranged from 6 to 168 months. The size of skull defects ranged from 84×104 to 154×193mm. Custom-made implants were manufactured using 3D computed tomography data, Mimics software, and

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an electron beam melting machine. The team reviewed several different designs and simulated surgery using a 3D skull model. During the operation, the implant was fit to the defect without dead space. Operation times ranged from 85 to 180 minutes. Operative sites healed without any complications except for 1 patient who had red swelling with exudation at the skin defect, which was a skin infection and defect at the center of the scalp flap reoccurring since the initial head injury. This patient underwent reoperation for skin defect revision and replacement of the implant. Twenty-one patients were followed for 6 to 24 months (mean,14.1 months). The patients were satisfied and had no recurrent wound problems. Head computed tomography after operation showed good fixation of titanium implants and satisfactory skull-shape symmetry. According to the authors, for the reconstruction of skull defects, the use of autologous bone grafts has been the treatment of choice. However, bone use depends on availability, defect size, and donor morbidity. The authors stated that as 3D printing techniques are further advanced, it is becoming possible to manufacture custom-made 3D titanium implants for skull reconstruction. This study was limited by a small study population, lack of a comparison group, and short follow-up time.

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Code	Description
L8701	Powered upper extremity range of motion assist device, elbow, wrist, hand device with single or double upright(s), includes microprocessor, sensors, all components and accessories, custom fabricated
L8702	Powered upper extremity range of motion assist device, elbow, wrist, hand, finger , single or double upright(s), includes microprocessor, sensors, all components and accessories, custom fabricated

The use of the upper limb orthotic known as the MyoPro® is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

The MyoPro (Myomo, Inc.) is a powered orthosis designed to help restore function to arms and hands paralyzed or weakened by stroke, brachial plexus injury, cerebral palsy or other neuromuscular disease or injury. The brace works by noninvasively reads the faint myoelectric signals generated by the muscles from the surface of the skin. Small motors are then activated to move the arm and hand without electrical stimulation (Hayes, 2023; annual review 2025).

Hayes conducted an evolving evidence review regarding the MyoPro for upper extremity paralysis or paresis after stroke. The review included four studies reporting on 80 individuals. A review of full-text clinical studies suggested minimal support for using the MyoPro for upper extremity paralysis or paresis after stroke. Of note, no relevant systematic reviews, clinical practice guidelines, position statements, or guidance were identified. Hayes concluded the current evidence does not indicate that the MyoPro provided benefits over repetitive task practice (RTP) alone. Limitations of the current evidence base include a lack of comparisons with other assistive devices, a younger age than typical for individuals recovering from stroke, a small sample size, and an absence of long-term outcomes. During the most recent annual review, Hayes identified no new relevant systematic reviews, clinical practice guidelines, position statements, or guidance. However, two new clinical studies were identified. Based on a review of abstracts, Hayes concluded the newly published studies conferred minimal support for using the MyoPro for upper extremity paralysis or paresis after stroke (Hayes, 2023; annual review, 2025).

ECRI performed a clinical evidence assessment regarding the MyoPro 2+ orthosis for individuals with upper arm neuromuscular impairment. The assessment included eight studies reporting on 98 individuals. The results of the assessment revealed there were no published studies available that specified use of the MyoPro 2+ orthosis. ECRI

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concluded that evidence from four small case series, two observational cohort studies, and two case series that primarily reported on the MyoPro Motion-G, suggested there was improved motor control and function for individuals with long-term muscle weakness and paralysis. However, the evidence was too limited in quantity and quality to be conclusive. It was also unclear how the MyoPro Motion-G compared with other therapies intended to improve arm and hand impairment. Larger controlled trials that report on patient-oriented outcomes are needed to compare the MyoPro 2+ with a control in different populations and standardized settings (ECRI, 2017; revised, 2024).

Chang et al. (2024) evaluated the outcomes and clinical benefits of the MyoPro orthosis for upper limb impairment secondary to chronic stroke. The study included 19 participants, 65 years and older, who had completed a patient-reported Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire prior to using a MyoPro for at least 6 months. After enrollment, a generalized estimating equation model was used to analyze pre-MyoPro and 6-month post-MyoPro DASH scores obtained during a virtual follow-up visit. The study results revealed that all 19 participants had a mean improvement (decrease) in DASH score of 18.07 points (95% Confidence Interval: -25.41 to -10.72), adjusted for eight covariates. This change in DASH score was determined to be statistically significant and clinically meaningful. The authors concluded that the MyoPro increased independence in functional tasks for older participants with chronic stroke, as reported by the validated DASH outcome measure. The authors also noted several study limitations including the small sample size, multiple external variables, and varying completion timelines for the 6-month DASH scores (6.8-17.4 months). Use of the MyoPro, home exercise programs, and medications were also not controlled as part of the study and this could have affected participant reports of functional change. Additionally, pre-study DASH questionnaires were administered by various clinical staff, potentially causing rater variability or bias.

Pundik et al. (2022) performed a prospective single arm mixed cohort interventional pilot study to evaluate the MyoPro as a tool for motor learning-based therapy for participants with chronic upper limb weakness. The study included 13 participants with chronic moderate/severe arm weakness due to either stroke (n = 7) or traumatic brain injury (TBI) (n = 6). The study consisted of two phases. The in-clinic phase included 18 sessions (twice per week, 27 hours of face-to-face therapy) plus a home exercise program. The home phase included practice of the home exercise program. Outcomes were collected at baseline and at weeks 3, 5, 7, 9, 12, 15, and 18. The study results reported that statistically significant and clinically meaningful Fugl-Meyer Assessment improvements were observed (+7.5 points). Gains were observed at week 3, increased through the in-clinic phase and were maintained during the home phase. Changes in the Modified Ashworth Scale, Range of Motion, and Chedoke Arm and Hand Activity Inventory were observed early during the in-clinic phase and also reported as statistically significant. Satisfaction with the MyoPro was demonstrated throughout the study using an Orthotic and Prosthetic User's Survey. Both cohorts, participants with a history of stroke and participants with a history of TBI, responded to the intervention. The authors concluded that MyoPro might be a useful tool for motor learning in individuals with chronic stroke and TBI. Reduction in impairment, gains in function, and satisfaction with the device were observed in response to the intervention. Further studies using a randomized controlled design is warranted.

Page et al. (2020) conducted a single-blind, RCT to compare the efficacy of the Myomo brace and/or RTP in participants exhibiting chronic, moderate, stable, post-stroke, upper extremity hemiparesis. The study included 34 participants randomly assigned to therapy consisting of the Myomo brace combined with RTP, RTP only, or the Myomo brace only. All three groups were supervised by a therapist and treatment was administered for one hour each day, three days per week, for eight weeks. The primary outcome measure was the upper extremity section of the Fugl-Meyer Impairment Scale. The secondary outcome measure was the Arm Motor Activity Test (AMAT). The study results revealed that the three groups exhibited similar score increases of approximately 2 points. There were no differences in the amount of change on the Fugl-Meyer Impairment Scale ($H = 0.376$; $p = 0.83$) or AMAT ($H = 0.978$; $p = 0.61$). The authors concluded that a therapeutic approach including the Myomo brace yielded highly comparable outcomes to those derived from RTP only. Due to its equivalent efficacy to RTP in this population, the Myomo brace could be used as an alternative for labor-intensive upper extremity training. The study is limited by small sample size and short follow-up period. (This study is included in the evolving evidence review by Hayes, 2023; annual review, 2025.)

McCabe et al. (2019) conducted a retrospective study to demonstrate the feasibility of utilizing the MyoPro motion-G for the treatment of persistent moderate upper limb impairment following stroke. The study included nine patients greater than 6 months post stroke. Group therapy using the MyoPro motion-G was provided at a frequency of 1-2 sessions per week (60-90 minutes per session). Patients were also instructed to utilize the MyoPro motion-G at home on non-therapy days and to continue with use of the device after completion of the group training period. Outcome measurements included change in Fugl-Meyer Upper Limb Assessment and modified Ashworth Scale after 12 weeks. The study reported a clinically important and statistically significant improvement ($p = 0.0005$) on a measure of motor control impairment during participation in group training. Muscle tone was also observed to improve for some patients. It was also determined that utilization of the MyoPro motion-G was feasible in a group setting using a ratio of one therapist to four patients. The authors concluded the MyoPro motion-G is feasible in a group clinic setting and for home-use in this patient population. Clinically important motor control gains were observed for seven of nine patients who participated in training. Limitations

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of the study include the single center, retrospective design, and small sample size. The authors also noted there was variability in treatment doses across different patients and inconsistent timing with which testing was completed. More robust studies are needed to determine how the MyoPro motion-G impacts patient care and functional performance. (This study is included in the clinical evidence assessment by ECRI, 2017; revised, 2024.)

Peters et al. (2017) performed an observational cohort study to determine the immediate effect of the MyoPro Motion-G on paretic upper extremity impairment. The study included 18 participants exhibiting chronic, moderate, stable, poststroke, upper extremity hemiparesis. Outcome measurements included the upper extremity section of the Fugl-Meyer Scale, four functional tasks developed for the study, and the Box and Block Test. Assessments were performed without and while wearing the MyoPro Motion-G. The study results revealed significantly reduced upper extremity impairment while wearing the MyoPro Motion-G ($p < 0.0001$). Increased quality in performing all functional tasks was also observed. Three subtasks, feeding (grasp), feeding (elbow), and drinking (grasp) also showed significant increases in quality ($p = 0.024$, $p = 0.003$, and $p = 0.001$, respectively). Additionally, significant decreases in the time taken to grasp a cup ($p = 0.016$) and increased gross manual dexterity ($p < 0.001$) were also reported. The authors concluded the study results suggested that upper extremity impairment, as measured by the Fugl-Meyer Scale, was significantly reduced with the MyoPro Motion-G. These changes exceeded the clinically important difference threshold. Furthermore, the MyoPro Motion-G significantly increased gross manual dexterity and performance of certain functional tasks. Limitations of the study include the single center design and small sample size. The authors also noted another potential limitation, the use of functional tasks for which psychometrics has not been established, necessitating future multicenter studies to formally investigate the validity of the measure with a larger sample. (This study is included in the evolving evidence review by Hayes, 2023; annual review, 2025; and the clinical evidence assessment by ECRI, 2017; revised, 2024.)

Willigenburg et al. (2017) compared the efficacy of an 8-week regimen combining RTP with the Myomo brace to RTP only in participants with paretic upper extremity and history of a single stroke. The study included 12 participants, seven were administered RTP plus Myomo therapy and five were administered RTP only. Both groups received individualized, 45-minute therapy sessions, 3 days per week, over an 8-week period. The main outcome measures were arm, hand ability, activities of daily living, and perceptions of recovery subscales using the Stroke Impact Scale (SIS), as well as upper extremity reaching kinematics, assessed before and after the intervention. The study results revealed that participants in the RTP plus Myomo therapy group showed greater improvements on all SIS subscales. The recovery scale reached statistical significance ($p = 0.03$). Participants in the RTP-only group showed a greater increase in hand velocity in the reach up task ($p = 0.02$). However, no changes were observed in the range of shoulder flexion or elbow extension during reaching. None of the changes observed for the kinematic outcome measures significantly correlated with any of the changes in SIS subscales. The authors concluded that RTP integrating the Myomo brace may be more beneficial than RTP only for improving self-reported function and perceptions of overall recovery. However, there were no observed changes in the range of elbow extension, nor relationship between self-reported improvements and changes in reaching kinematics. This study is limited by small sample size and short follow-up period. (This study is included in the evolving evidence review by Hayes, 2023; annual review, 2025.)

Page et al. (2013) conducted a pilot RCT to compare the efficacy of an RTP regimen that included the Myomo brace to RTP alone in participants with chronic, moderate upper extremity impairment. The study included 16 participants, eight in the RTP with Myomo brace group and eight in the RTP only group. Both groups were supervised by a therapist and underwent targeted therapy, 30 minutes in duration, 3 days per week, for eight weeks. The main outcome measures included the upper extremity Fugl-Meyer, Canadian Occupational Performance Measure, and SIS. The study results revealed both groups showed the same Fugl-Meyer score increase of ≈2.1 points. However, the RTP with Myomo brace group exhibited larger score changes on all but one of the Canadian Occupational Performance Measures and SIS, including a 12.5 point increase on the recovery subscale. The authors concluded that a therapist supervised RTP regimen that included the Myomo brace is as efficacious as RTP alone in this population. This study is limited by small sample size and short follow-up period. (This study is included in the evolving evidence review by Hayes, 2023; annual review, 2025.)

The U.S. Food and Drug Administration (FDA) initially cleared the e100 (Myomo, Inc.) for marketing through the 510(k) process on April 12, 2007. Additional information is available at: https://www.accessdata.fda.gov/cdrh_docs/pdf6/K062631.pdf. (Accessed April 30, 2025)

The MyoPro (Myomo, Inc.) is currently considered by the FDA to be a 510(k) exempt device. Refer to the following website for more information and search by either Owner/Operator Name or Proprietary Name: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/rl.cfm. (Accessed April 30,2025)

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Code	Description
P2031	Hair analysis (excluding arsenic)

Hair analysis is unproven and not medically necessary for evaluating any disorder or condition due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Hair analysis has been proposed as an aid in the diagnosis of several conditions including but not limited to dietary deficiencies, allergies, hair loss, autism, schizophrenia, mood disorders, and environmental contamination. Hair has also been used as a specimen source for drug testing. Currently, in federally regulated programs, only urine and oral specimens are collected for drug testing (SAMHSA). There are no widely accepted standards that specify how hair samples should be collected, stored, and analyzed, making results unreliable and inconsistent (ATSDR).

Künzel et al. (2024) conducted a systematic review and meta-analysis on maternal hair cortisol concentration (HCC) and the associated risk of pre-term birth due to stress before and during pregnancy. Eleven prospective and retrospective cohort design studies met the inclusion criteria. There was a high level of heterogeneity across all studies, with the results showing marginal and imprecisely measured higher levels of HCC among preterm deliveries, and no conclusive evidence of higher incidence of preterm birth.

In a 2023 systematic review and meta-analysis, Ramazani et al. investigated the differences in cadmium (Cd) and mercury (Hg) concentrations between children with autism spectrum disorder (ASD) and controls in different biological samples, including hair. Twenty eight studies analyzed Cd in blood, urine and hair, and forty studies assessed Hg. Most studies had a case-controlled design. For hair levels of Cd, 15 studies with 779 children with ASD, and 705 health controls were analyzed and showed no differences in the concentration between the two groups. With regard to Hg levels in hair, twenty-nine studies with 1543 and 1294 children in ASD and control groups respectively were analyzed. These results also showed no significant differences in concentration. The authors concluded that there are many variations and confounding factors that may have influenced these results and they included diet, nutritional status, exposure levels, medication and socioeconomic status. Furthermore, there is a broad range of ASD types resulting in heterogeneity across studies.

Hardy et al. (2021) conducted a pilot cohort study to compare the information obtained from the analysis of urine versus hair for exposure to pesticides. In ninety-three pregnant women, one urine and one hair sample were collected simultaneously. Samples were analyzed using GC-MS/MS analytical methods allowing for the detection of both parent pesticides and metabolites and designed to be as similar as possible between urine and hair for reliable inter-matrix comparison. Fifty-two biomarkers of exposure were targeted, including parents and metabolites of organochlorines, organophosphates, pyrethroids, carbamates, phenylpyrazoles and other pesticides. The results showed the number of different compounds detected ranged from 16 to 27 (median = 22) in hair, and from 3 to 22 (median = 12) in urine. In hair, 24 compounds were found in > 40% of the individuals, whereas only 12 compounds presented the same frequency of detection in urine. Among the chemicals detected in > 80% of both hair and urine samples, only one (pentachlorophenol) showed a signification correlation between hair and urine concentrations. The authors concluded that these results highlight multiple exposures and suggest that hair provides more comprehensive information on pesticide exposure than

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urine analysis and supports the relevance of hair analysis in future epidemiological studies investigating association between exposure and adverse health effects.

In a 2019 systematic review and meta-analysis, Huang et al. sought to identify whether magnesium levels are lower in children with ADHD. A total of twelve studies were included. The results showed magnesium levels in the hair of children diagnosed with ADHD were significantly lower than those in controls (k = 4, Hedges' g = -0.713, 95% CI = -1.359 to -0.067, p = .031). In this meta-analysis, the authors found that children diagnosed with ADHD have lower serum and hair magnesium levels than children without ADHD. The authors concluded that further study is needed to investigate the behavioral influence on ADHD due to lower magnesium levels, the association between brain and serum magnesium levels, and the effects brought about by larger longitudinal cohort studies.

Khajuria et al. (2018) conducted a review designed to investigate the efficacy of chromatography for detection of drugs of abuse in hair. A comprehensive review of articles from last two decades on hair analyses via PubMed and similar resources was performed. The results showed a hair sample may be chosen over traditional biological samples such blood, urine, saliva, or tissues due to its inimitable ability to provide a longer time frame for drug detection. Its collection is almost non-invasive, less cumbersome and does not involve any specialized training/expertise. Recent advances in analytical technology have resulted in better sensitivity, reproducibility, and accuracy, thus providing a new arena of scientific understanding and test interpretation. The authors concluded that although recent studies have yielded insights into drug binding and drug incorporation in hair, the major challenge in hair analysis lies in the interpretation of results, which may be affected by external contamination and thus lead to false positives. Therefore, there is a need for more sensitive and selective analysis methods to be developed.

Mikulewicz et al. (2013) completed a systematic review to investigate the reference values of minerals in human hair. The five studies that met inclusion criteria reported reference ranges for the content of elements in hair: macro elements, microelements, toxic elements and other elements. Reference ranges were elaborated for different populations in the years 2000–2012. The analytical methodology differed, in particular sample preparation, digestion and analysis, as a result, the levels of hair minerals reported as reference values varied. The authors concluded standardization of procedures and detailed methodology are needed to validate hair mineral analysis. Only then it would be possible to provide meaningful reference ranges and take advantage of the potential that lies in Hair Mineral Analysis (HMA) as a medical diagnostic technique.

A 2011 guideline for food allergy in children and young people from the National Institute for Health and Care Excellence (NICE) recommends against the use of hair analysis in the diagnosis of food allergy.

In their 2010 guidelines, the National Institute of Allergy and Infectious Diseases (NIAID) states that hair analysis for food allergies is non-standard and unproven. Additionally, the utility of these tests has not been validated for the diagnosis of FA and may result in false positive or false negative diagnoses.

In a 2014 joint practice parameter by the American Academy of Allergy, Asthma & Immunology (AAAAI), the American College of Allergy, Asthma & Immunology (ACAAI), and the Joint Council of Allergy, Asthma & Immunology (JCAAI), hair analysis is listed as an unproven test for the evaluation of food allergies.

A practice parameter from the Quality Standards Subcommittee of the American Academy of Neurology and the Child Neurology Society states that there is insufficient evidence to support the use of hair analysis for the diagnosis and evaluation of autism (Filipek et al., 2000. Reaffirmed August 2014).

In 2013, the American Society of Addiction Medicine (ASAM) published a document titled, Drug Testing: A White Paper of the American Society of Addiction Medicine. This document indicates that hair sample benefits include difficulty in falsifying sampling and a longer period of detection. However, the ASAM noted that recent exposures cannot be detected in hair samples, and hair coloring can cause modest degradation of drugs in the matrix. The ASAM notes that one distinct disadvantage to hair testing is that some drug classes (e.g., benzodiazepines) are poorly detected in hair.

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Policy History/Revision Information

Date	Summary of Changes
02/01/2026	**Definitions** • Updated definition of "Unproven Service(s)" **Coverage Summary** • Added notation to indicate the bracketed language following the unlisted code descriptions was added by UnitedHealthcare to indicate the intended use of the code within this policy **Coverage Rationale** • Added coverage guidelines for: ***Histotripsy (CPT codes 0686T and 0888T)*** ○ Added language to indicate histotripsy is unproven and not medically necessary for treating malignant liver and renal tumors due to insufficient evidence of safety and/or efficacy ***Oncology, Quantitative Enzyme-Linked Immunosorbent Assay (ELISA) (CPT codes 0558U and 0559U)*** ○ Added language to indicate the use of oncology, quantitative enzyme-linked immunosorbent assay (ELISA) for protein biomarkers (e.g., IGoCheck using BF7 antigen or MammoCheck using BF9 antigen) to monitor therapy and/or disease progression/regression response is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy • Revised coverage guidelines for: ***Ablative Laser Treatment for Wound Healing (CPT code 17999)*** ○ Replaced language indicating "ablative laser treatment (*non-contact*, full field, and fractional ablation) for wound healing is unproven and not medically necessary" with "ablative laser treatment (full field and fractional ablation) for wound healing is unproven and not medically necessary" ***Cardiac Resynchronization Therapy (CRT) With Wireless Left Ventricular (LV) Endocardial Pacing (CPT codes 0515T, 0516T, 0517T, 0518T, 0519T, 0520T, 0521T, 0522T, 0861T, 0862T, and 0863T)*** ○ Replaced language indicating "cardiac resynchronization therapy (CRT) with wireless left ventricular (LV) endocardial pacing is unproven and not medically necessary *for the treatment of cardiac arrhythmias, heart failure (HF), or for the prevention of HF as a*

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Date	Summary of Changes
	consequence of right ventricular pacing due to insufficient evidence of efficacy and/or safety" with "cardiac resynchronization therapy (CRT) with wireless left ventricular (LV) endocardial pacing is unproven and not medically necessary due to insufficient evidence of efficacy and/or safety" ***Chronic Baroreceptor Stimulation of the Carotid Sinus (CPT codes 0266T, 0267T, 0268T, 0269T, 0270T, 0271T, 0272T, and 0273T)*** ○ Updated language pertaining to FDA approval of the Barostim neo™ device for treatment of heart failure ***Implantable Wireless Pulmonary Artery Pressure (PAP) Sensor (CPT/HCPCS codes 33289, 93264, C2624, and G0555)*** ○ Updated list of examples of implantable wireless PAP sensors; added "Cordella®" ***Laboratory Measurement of Antidrug Antibodies and Serum Levels of Biologic Agents and Biosimilars (CPT codes 80145, 80230, 80280, and 80299)*** ○ Removed CPT code 84999 ○ Replaced language indicating "laboratory measurement of antibodies and serum levels of biologic agents (e.g., infliximab, adalimumab, vedolizumab, ustekinumab, certolizumab pegol, golimumab) for *treating* inflammatory bowel disease (including ulcerative colitis and Crohn's disease) is unproven and not medically necessary" with "laboratory measurement of *antidrug* antibodies and serum levels of biologic agents *and biosimilars* (e.g., infliximab, adalimumab, vedolizumab, ustekinumab, certolizumab pegol, golimumab) for *assessing treatment response for ankylosing spondyloarthritis, hidradenitis suppurativa,* inflammatory bowel disease (including ulcerative colitis and Crohn's disease), *juvenile rheumatoid arthritis/rheumatoid arthritis, plaque psoriasis, and psoriatic arthritis* is unproven and not medically necessary" ***Remote Monitoring of an External Continuous Pulmonary Fluid Monitoring System (CPT codes 0607T and 0608T)*** ○ Replaced language indicating "remote monitoring of an external continuous pulmonary fluid monitoring system, including measurement of radiofrequency derived pulmonary fluid levels, heart rate, respiration rate, activity, posture, and cardiovascular rhythm (e.g., ECG data), transmitted to a remote 24 hour attended surveillance center as well as the analysis of data received and transmission of *reports to the physician or other* qualified health care professional is unproven" with "remote monitoring of an external continuous pulmonary fluid monitoring system, including measurement of radiofrequency derived pulmonary fluid levels, heart rate, respiration rate, activity, posture, and cardiovascular rhythm (e.g., ECG data), transmitted to a remote 24 hour attended surveillance center as well as the analysis of data received and transmission of *data to a* qualified health care professional is unproven" ***Transcutaneous Magnetic Stimulation (tMS) (CPT codes 0766T and 0767T)*** ○ Revised description for CPT codes 0766T and 0767T ○ Updated language pertaining to the FDA approval of electromagnetic stimulator devices for pain relief • Removed coverage guidelines for: ***Antiprothrombin Antibody Testing for Antiphospholipid Syndrome (CPT code 86849)*** ○ CPT code 86849 no longer requires clinical review ***Biomechanical Mapping Using Vaginal Tactile Imaging Techniques (CPT code 58999)*** ○ CPT code 58999 no longer requires clinical review ***Fallopian Tube Occlusion With a Degradable Biopolymer Implant (CPT code 58999*** ○ CPT code 58999 no longer requires clinical review ***Kinesio Taping (CPT/HCPCS codes 29799, 97139, 97799, and A9999)*** ○ CPT/HCPCS codes 29799, 97139, 97799, and A9999 no longer require clinical review ***Pulse-Echo Ultrasound Bone Density Measurement (CPT code 76999)*** ○ CPT code 76999 no longer requires clinical review ***Rhinophototherapy (CPT code 30999)***

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Date	Summary of Changes
	○ CPT code 30999 no longer requires clinical review ***Sonosalpingography (CPT code 58999)*** ○ CPT code 58999 no longer requires clinical review • Updated list of applicable CPT/HCPCS codes for: ***Radiofrequency Ablation (RFA) for the Treatment of Joint Pain (CPT codes 64624 and 64999)*** ○ Removed 23929, 27299, and 27599 ***Radiofrequency (RF) Therapy (CPT codes 0672T, 53860, and 53899)*** ○ Removed 58999 ***Robotic Lower Body Exoskeleton Devices (CPT/HCPCS codes E1399 and K1007)*** ○ Removed 97799 and L2999 ***Ultrafiltration (Aquapheresis) (CPT codes 0692T and 90999)*** ○ Removed 37799 **Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version CS087PA.AA

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

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