Infertility Diagnosis, Treatment, and Fertility Preservation

Policy Number: 2026T0270NN
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➲ Instructions for Use

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Related Commercial/Individual Exchange Policy

- Preimplantation Genetic Testing and Related Services

Related Optum Clinical Guideline

- Fertility Solutions Medical Necessity Clinical Guideline: Infertility

Application

UnitedHealthcare Commercial

This Medical Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans in all states except for Alabama, Arizona, Florida, Georgia, Indiana, Iowa, Kansas, Michigan, Mississippi, Missouri, Nebraska, New Jersey, New Mexico, North Carolina, Ohio, Oklahoma, South Carolina, Tennessee, Texas, Virginia, Washington, Wisconsin, and Wyoming.

Coverage Rationale

➲ See Benefit Considerations

For medical necessity reviews, refer to the Clinical Guideline titled Fertility Solutions Medical Necessity Clinical Guideline: Infertility.

The following tests or procedures are proven and medically necessary for diagnosing or treating Infertility:

- Antisperm antibodies
- Antral follicle count
- Cryopreservation of sperm, semen, or embryos for individuals who are undergoing treatment with assisted reproductive technologies or are planning to undergo therapies that threaten their reproductive health, such as cancer chemotherapy
- Cryopreservation of surgically derived sperm
- Cryopreservation of mature oocytes (eggs) for women who are undergoing treatment with assisted reproductive technologies or are planning to undergo therapies that threaten their reproductive health, such as cancer chemotherapy
- Cryopreservation of supernumerary embryos or in the setting in which the intent is to freeze all embryos for the purpose of an elective single-embryo transfer

- Genetic screening tests:
  - Cystic fibrosis gene mutations
  - Karyotyping for chromosomal abnormalities
  - Y-chromosome microdeletion testing
- Hormone level tests:
  - Antimüllerian hormone
  - Estradiol
  - Follicle-stimulating hormone
  - Luteinizing hormone
  - Progesterone
  - Prolactin
  - Testosterone (total and free)
  - Thyroid-stimulating hormone
- Hysterosalpingogram
- Diagnostic hysteroscopy
- Diagnostic laparoscopy with or without chromotubation
- Leukocyte count in semen
- Pelvic ultrasound (transabdominal or transvaginal)
- Postejaculatory urinalysis
- Scrotal, testicular, or transrectal ultrasound
- Semen analysis
- Sonohysterogram or saline infusion ultrasound
- Testicular biopsy
- Vasography

Due to insufficient evidence of efficacy, the following are unproven and not medically necessary for diagnosing or treating Infertility:

- Coculture of embryos
- Computer-assisted sperm analysis
- Cryopreservation of immature oocytes (eggs), ovarian tissue, or testicular tissue
- EmbryoGlue®
- Hyaluronan binding assay
- In vitro maturation of oocytes
- Inhibin B
- Postcoital cervical mucus penetration test
- Reactive oxygen species test
- Sperm acrosome reaction test
- Sperm capacitation test
- Sperm DNA integrity/fragmentation tests [e.g., sperm chromatin structure assay, single-cell gel electrophoresis assay (Comet), terminal deoxynucleotidyl transferase dUTP nick end labeling assay (TUNEL), sperm chromatin dispersion, Sperm DNA Decondensation™ Test]
- Sperm penetration assays
- Uterine/endometrial receptivity testing
- Treatments to improve uterine/endometrial receptivity (e.g., immunotherapy, endometrial scratching, uterine artery vasodilation)

Note: For eligibility of Infertility benefits, refer to the member specific benefit plan document.

Benefits are available for fertility preservation for medical reasons that cause irreversible Infertility such as chemotherapy, radiation treatment, and bilateral oophorectomy due to cancer; refer to the member specific benefit plan document. For coding associated with fertility preservation for Iatrogenic Infertility benefit, refer to the Applicable Codes section below; codes are identified with an asterisk (*).

Medical Records Documentation Used for Reviews

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. Medical records documentation may be required to assess whether the

member meets the clinical criteria for coverage but does not guarantee coverage of the service requested; refer to the guidelines titled Medical Records Documentation Used for Reviews.

Definitions

Iatrogenic Infertility: An impairment of fertility by surgery, radiation, chemotherapy, or other medical treatment affecting reproductive organs or processes (Certificate of Coverage, 2018).

Infertility: Several definitions of Infertility exist (ASRM, 2021b; ASRM, 2023; ACOG, 2019; CDC, 2024; WHO, 2025). For the purpose of this policy, Infertility is defined as any of the following:

- The inability to achieve a successful pregnancy due to an individual's medical, sexual, or reproductive history.
- Failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse when the female partner is less than 35 years of age.
- Failure to achieve a pregnancy after 6 months or more of regular unprotected sexual intercourse when the female partner is 35 years or older.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other policies and guidelines may apply.

For the fertility preservation for Iatrogenic Infertility benefit, claims must be submitted with diagnosis code Z31.84 in order for the benefit to apply. Refer to the codes below marked with an asterisk (*).

CPT Code	Description
0253U	Reproductive medicine (endometrial receptivity analysis), RNA gene expression profile, 238 genes by next-generation sequencing, endometrial tissue, predictive algorithm reported as endometrial window of implantation (e.g., pre-receptive, receptive, post-receptive)
0255U	Andrology (infertility), sperm-capacitation assessment of ganglioside GM1 distribution patterns, fluorescence microscopy, fresh or frozen specimen, reported as percentage of capacitated sperm and probability of generating a pregnancy score
52402	Cystourethroscopy with transurethral resection or incision of ejaculatory ducts
54500	Biopsy of testis, needle (separate procedure)
54505	Biopsy of testis, incisional (separate procedure)
55300	Vasotomy for vasograms, seminal vesiculograms, or epididymograms, unilateral or bilateral
55530	Excision of varicocele or ligation of spermatic veins for varicocele; (separate procedure)
55535	Excision of varicocele or ligation of spermatic veins for varicocele; abdominal approach
55550	Laparoscopy, surgical, with ligation of spermatic veins for varicocele
55870	Electroejaculation
58140	Myomectomy, excision of fibroid tumor(s) of uterus, 1 to 4 intramural myoma(s) with total weight of 250 g or less and/or removal of surface myomas; abdominal approach
58145	Myomectomy, excision of fibroid tumor(s) of uterus, 1 to 4 intramural myoma(s) with total weight of 250 g or less and/or removal of surface myomas; vaginal approach
58146	Myomectomy, excision of fibroid tumor(s) of uterus, 5 or more intramural myomas and/or intramural myomas with total weight greater than 250 g, abdominal approach
58321	Artificial insemination; intra-cervical
58322	Artificial insemination; intra-uterine
58323	Sperm washing for artificial insemination
58340	Catheterization and introduction of saline or contrast material for saline infusion sonohysterography (SIS) or hysterosalpingography

CPT Code	Description
58345	Transcervical introduction of fallopian tube catheter for diagnosis and/or re-establishing patency (any method), with or without hysterosalpingography
58350	Chromotubation of oviduct, including materials
58545	Laparoscopy, surgical, myomectomy, excision; 1 to 4 intramural myomas with total weight of 250 g or less and/or removal of surface myomas
58546	Laparoscopy, surgical, myomectomy, excision; 5 or more intramural myomas and/or intramural myomas with total weight greater than 250 g
58555	Hysteroscopy, diagnostic (separate procedure)
58559	Hysteroscopy, surgical; with lysis of intrauterine adhesions (any method)
58660	Laparoscopy, surgical; with lysis of adhesions (salpingolysis, ovariolysis) (separate procedure)
58662	Laparoscopy, surgical; with fulguration or excision of lesions of the ovary, pelvic viscera, or peritoneal surface by any method
58670	Laparoscopy, surgical; with fulguration of oviducts (with or without transection)
58672	Laparoscopy, surgical; with fimbrioplasty
58673	Laparoscopy, surgical; with salpingostomy (salpingoneostomy)
58740	Lysis of adhesions (salpingolysis, ovariolysis)
58752	Tubouterine implantation
58760	Fimbrioplasty
58770	Salpingostomy (salpingoneostomy)
58800	Drainage of ovarian cyst(s), unilateral or bilateral (separate procedure); vaginal approach
58805	Drainage of ovarian cyst(s), unilateral or bilateral (separate procedure); abdominal approach
58920	Wedge resection or bisection of ovary, unilateral or bilateral
*58970	Follicle puncture for oocyte retrieval, any method
58974	Embryo transfer, intrauterine
58976	Gamete, zygote, or embryo intrafallopian transfer, any method
74440	Vasography, vesiculography, or epididymography, radiological supervision and interpretation
74740	Hysterosalpingography, radiological supervision and interpretation
74742	Transcervical catheterization of fallopian tube, radiological supervision and interpretation
76830	Ultrasound, transvaginal
76831	Saline infusion sonohysterography (SIS), including color flow Doppler, when performed
76856	Ultrasound, pelvic (nonobstetric), real time with image documentation; complete
76857	Ultrasound, pelvic (nonobstetric), real time with image documentation; limited or follow-up (e.g., for follicles)
76870	Ultrasound, scrotum and contents
76872	Ultrasound, transrectal
76948	Ultrasonic guidance for aspiration of ova, imaging supervision and interpretation
80415	Chorionic gonadotropin stimulation panel; estradiol response This panel must include the following: Estradiol, total (82670 x 2 on 3 pooled blood samples)
80426	Gonadotropin releasing hormone stimulation panel This panel must include the following: Follicle stimulating hormone (FSH) (83001 x 4) Luteinizing hormone (LH) (83002 x 4)
82397	Chemiluminescent assay
82670	Estradiol; total
83001	Gonadotropin; follicle stimulating hormone (FSH)
83002	Gonadotropin; luteinizing hormone (LH)
83498	Hydroxyprogesterone, 17-d
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified

CPT Code	Description
84144	Progesterone
84146	Prolactin
84402	Testosterone; free
84403	Testosterone; total
84443	Thyroid stimulating hormone (TSH)
84830	Ovulation tests, by visual color comparison methods for human luteinizing hormone
88182	Flow cytometry, cell cycle or DNA analysis
88248	Chromosome analysis for breakage syndromes; baseline breakage, score 50-100 cells, count 20 cells, 2 karyotypes (e.g., for ataxia telangiectasia, Fanconi anemia, fragile X)
88261	Chromosome analysis; count 5 cells, 1 karyotype, with banding
88262	Chromosome analysis; count 15-20 cells, 2 karyotypes, with banding
88263	Chromosome analysis; count 45 cells for mosaicism, 2 karyotypes, with banding
88273	Molecular cytogenetics; chromosomal in situ hybridization, analyze 10-30 cells (e.g., for microdeletions)
88280	Chromosome analysis; additional karyotypes, each study
88283	Chromosome analysis; additional specialized banding technique (e.g., NOR, C-banding)
88285	Chromosome analysis; additional cells counted, each study
*89250	Culture of oocyte(s)/embryo(s), less than 4 days
*89251	Culture of oocyte(s)/embryo(s), less than 4 days; with co-culture of oocyte(s)/embryos
*89253	Assisted embryo hatching, microtechniques (any method)
*89254	Oocyte identification from follicular fluid
89255	Preparation of embryo for transfer (any method)
89257	Sperm identification from aspiration (other than seminal fluid)
*89258	Cryopreservation; embryo(s)
*89259	Cryopreservation; sperm
*89260	Sperm isolation; simple prep (e.g., sperm wash and swim-up) for insemination or diagnosis with semen analysis
*89261	Sperm isolation; complex prep (e.g., Percoll gradient, albumin gradient) for insemination or diagnosis with semen analysis
*89264	Sperm identification from testis tissue, fresh or cryopreserved
*89268	Insemination of oocytes
*89272	Extended culture of oocyte(s)/embryo(s), 4-7 days
*89280	Assisted oocyte fertilization, microtechnique; less than or equal to 10 oocytes
*89281	Assisted oocyte fertilization, microtechnique; greater than 10 oocytes
89290	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); less than or equal to 5 embryos
89291	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); greater than 5 embryos
89300	Semen analysis; presence and/or motility of sperm including Huhner test (post coital)
89310	Semen analysis; motility and count (not including Huhner test)
*89320	Semen analysis; volume, count, motility, and differential
89321	Semen analysis; sperm presence and motility of sperm, if performed
89322	Semen analysis; volume, count, motility, and differential using strict morphologic criteria (e.g., Kruger)
89325	Sperm antibodies
89329	Sperm evaluation; hamster penetration test
89330	Sperm evaluation; cervical mucus penetration test, with or without spinnbarkeit test

CPT Code	Description
89331	Sperm evaluation, for retrograde ejaculation, urine (sperm concentration, motility, and morphology, as indicated)
89335	Cryopreservation, reproductive tissue, testicular
*89337	Cryopreservation, mature oocyte(s)
*89342	Storage (per year); embryo(s)
*89343	Storage (per year); sperm/semen
89344	Storage (per year); reproductive tissue, testicular/ovarian
*89346	Storage (per year); oocyte(s)
89352	Thawing of cryopreserved; embryo(s)
89353	Thawing of cryopreserved; sperm/semen, each aliquot
89354	Thawing of cryopreserved; reproductive tissue, testicular/ovarian
89356	Thawing of cryopreserved; oocytes, each aliquot
89398	Unlisted reproductive medicine laboratory procedure [when used for cryopreservation of ovarian tissue or hyaluronan binding assay]

HCPCS Code	Description
*J0725	Injection, chorionic gonadotropin, per 1,000 USP units
*S0122	Injection, menotropins, 75 IU
*S0126	Injection, follitropin alfa, 75 IU
*S0128	Injection, follitropin beta, 75 IU
*S0132	Injection, ganirelix acetate, 250 mcg
S3655	Antisperm antibodies test (immunobead)
*S4011	In vitro fertilization; including but not limited to identification and incubation of mature oocytes, fertilization with sperm, incubation of embryo(s), and subsequent visualization for determination of development
S4013	Complete cycle, gamete intrafallopian transfer (GIFT), case rate
S4014	Complete cycle, zygote intrafallopian transfer (ZIFT), case rate
S4015	Complete in vitro fertilization cycle, not otherwise specified, case rate
S4016	Frozen in vitro fertilization cycle, case rate
S4017	Incomplete cycle, treatment cancelled prior to stimulation, case rate
S4018	Frozen embryo transfer procedure cancelled before transfer, case rate
S4020	In vitro fertilization procedure cancelled before aspiration, case rate
S4021	In vitro fertilization procedure cancelled after aspiration, case rate
*S4022	Assisted oocyte fertilization, case rate
S4023	Donor egg cycle, incomplete, case rate
S4025	Donor services for in vitro fertilization (sperm or embryo), case rate
S4026	Procurement of donor sperm from sperm bank
*S4027	Storage of previously frozen embryos
S4028	Microsurgical epididymal sperm aspiration (MESA)
*S4030	Sperm procurement and cryopreservation services; initial visit
*S4031	Sperm procurement and cryopreservation services; subsequent visit
S4035	Stimulated intrauterine insemination (IUI), case rate
S4037	Cryopreserved embryo transfer, case rate
*S4040	Monitoring and storage of cryopreserved embryos, per 30 days

Diagnosis Code	Description
E23.0	Hypopituitarism
N46.01	Organic azoospermia
N46.021	Azoospermia due to drug therapy
N46.022	Azoospermia due to infection
N46.023	Azoospermia due to obstruction of efferent ducts
N46.024	Azoospermia due to radiation
N46.025	Azoospermia due to systemic disease
N46.029	Azoospermia due to other extratesticular causes
N46.11	Organic oligospermia
N46.121	Oligospermia due to drug therapy
N46.122	Oligospermia due to infection
N46.123	Oligospermia due to obstruction of efferent ducts
N46.124	Oligospermia due to radiation
N46.125	Oligospermia due to systemic disease
N46.129	Oligospermia due to other extratesticular causes
N46.8	Other male infertility
N46.9	Male infertility, unspecified
N97.0	Female infertility associated with anovulation
N97.1	Female infertility of tubal origin
N97.2	Female infertility of uterine origin
N97.8	Female infertility of other origin
N97.9	Female infertility, unspecified
N98.1	Hyperstimulation of ovaries
*Z31.84	Encounter for fertility preservation procedure

Description of Services

Both male and female factors can contribute to Infertility. Some underlying causes of Infertility include ovulatory dysfunction, decreased ovarian reserve, cervical factors, uterine abnormalities, tubal disease, and male factors. Once a diagnosis is made, treatment falls into three categories: medical treatment to restore fertility, surgical treatment to restore fertility, or assisted reproductive technologies.

Cryopreservation is the process of cooling and storing cells, tissues, or organs at very low or freezing temperatures to save them for future use. It is used to preserve sperm, semen, oocytes (eggs), embryos, ovarian tissue, or testicular tissue as an option for men and women who wish to or must delay reproduction for various reasons, including the need to undergo therapies that threaten their reproductive health, such as cancer treatment. Cryopreservation is also used to preserve unused gametes or zygotes produced through various artificial reproductive techniques for use at a later time.

Fertility preservation is the practice of proactively helping individuals preserve their fertility chances for future reproduction. Established methods of fertility preservation include embryo cryopreservation for men and women, sperm cryopreservation in men, and oocyte cryopreservation in women. A multidisciplinary team approach is encouraged when working with individuals.

Benefit Considerations

Certain plans do not cover Infertility services. Legislative mandates and the member specific benefit plan document must be reviewed when determining benefit coverage for Infertility services.

Infertility Services

When a plan includes coverage for services for the treatment of Infertility, when provided by or under the care or supervision of a physician, the services are limited to the following procedures:

- Ovulation induction (or controlled ovarian stimulation)
- Insemination procedures: Artificial insemination and intrauterine insemination
- Assisted reproductive technologies (ART). Examples of such procedures are:
  - In vitro fertilization (IVF)
  - Gamete intrafallopian transfer (GIFT)
  - Pronuclear stage tubal transfer (PROST)
  - Tubal embryo transfer (TET)
  - Zygote embryo transfer (ZIFT)
- Short-term storage under 1 year
- Pharmaceutical products for the treatment of Infertility that are administered on an outpatient basis in a hospital, alternate facility, physician's office, or the home

To be eligible for benefits, the member must have Infertility not related to voluntary sterilization or to failed reversal of voluntary sterilization.

Gestational Carrier or Surrogate

Refer to the member specific benefit plan document for services related to a gestational carrier or surrogate. A member with an Infertility benefit who is using a gestational carrier/surrogate because of the member's known medical cause of Infertility (this does not include a member who has had a voluntary sterilization or a failed reversal of a sterilization procedure) will have coverage for the following services. These services will be paid per the member's coverage:

- Female members' ovary stimulation and retrieval of eggs are covered when a member is using a surrogate (host uterus) (**Note**: The implantation of eggs, oocytes, or donor sperm into a host uterus is not covered, even if the member has the Infertility benefit.)
- Male member retrieval of sperm

Infertility Services Limitations and Exclusions

When the member's plan includes benefits for Infertility, the following services are not covered:

- Any Infertility services or supplies beyond the benefit maximum [dollars or procedure limit(s)]
- Assisted reproductive technologies, ovulation induction, and insemination procedures are excluded from coverage unless the member has a benefit for Infertility and the criteria listed in the Coverage Rationale section have been met
- Long-term storage (greater than 1 year) of reproductive materials such as sperm, eggs, embryos, ovarian tissue, and testicular tissue
- Infertility treatment when the cause of the Infertility was a procedure that produces sterilization, e.g., vasectomy or tubal ligation
- In vitro fertilization that is not an assisted reproductive technology for the treatment of Infertility; this would include but is not limited to elective fertility preservation or embryo accumulation/banking

When the member's plan does not include benefits for Infertility, the following services are not covered:

- All health care services and related expenses for Infertility treatments, including assisted reproductive technology (see examples listed above), regardless of the reason for the treatment
- Storage and retrieval of all reproductive materials; examples include eggs, sperm, testicular tissue, and ovarian tissue

The following services are excluded on all plans (even when the plan provides benefits for Infertility):

- Donor services for donor sperm, ovum or oocytes (eggs), or embryos
  - Donor eggs: The cost of donor eggs, including medical cost related to donor stimulation and egg retrieval, is excluded. The cost of fertilization (in vitro fertilization or intracytoplasmic sperm injection), embryo culture, and embryo transfer may be covered if the member has an Infertility benefit that allows for assisted reproductive technology.
  - Donor sperm: The cost of procurement and storage of donor sperm is excluded. However, the thawing and insemination are covered if the member has an Infertility benefit that allows for artificial donor insemination.
- Surrogate parenting: Services and treatments for a gestational carrier of a pregnancy who is not our member and all related services, including but not limited to:
  - Fees for the use of a gestational carrier or surrogate.
  - Pregnancy services for a gestational carrier or surrogate who is not a covered person.
- Self-injectable drugs for Infertility (Refer to the exclusion for self-injectable drugs in the member specific benefit plan document; refer to the pharmacy benefit administrator for self-injectable medication benefit information.)

Additional Information

- Assisted reproductive technology services (IVF-in vitro fertilization, GIFT-gamete intrafallopian transfer, ZIFT-zygote intrafallopian transfer, PROST-pronuclear stage tubal transfer, and TET-tubal embryo transfer) requested for reasons other than Infertility must be reviewed in accordance with the member specific benefit plan document (case-by-case determination).
- As a standard, coverage is provided for maternity services (prenatal, delivery, and postnatal pregnancy) for our members. If a female member is pregnant and functioning as a surrogate, coverage is provided for maternity services. Coverage is not provided for maternity services for a surrogate who is not a member. (Refer to the member specific benefit plan document.)
- Even if a plan excludes Infertility services (AI-artificial insemination, ART-assisted reproductive technology, IUI-intrauterine insemination, or ovulation induction), covered health services include procedures to diagnose Infertility and therapeutic (medical or surgical) procedures to correct a physical condition that is the underlying cause of the Infertility (i.e., for the treatment of a pelvic mass or pelvic pain, thyroid disease, pituitary lesions, etc.). These diagnostic and therapeutic services are not considered to be Infertility treatments.

Fertility Preservation for Iatrogenic Infertility

Certain plans may include coverage for fertility preservation for Iatrogenic Infertility. Refer to the member specific benefit plan document to determine if this coverage applies.

Benefits are available for fertility preservation for medical reasons that cause irreversible Infertility such as chemotherapy, radiation treatment, and bilateral oophorectomy due to cancer. Services include the following procedures, when provided by or under the care or supervision of a physician:

- Collection of sperm
- Cryopreservation of sperm
- Ovarian stimulation, retrieval of eggs, and fertilization
- Oocyte cryopreservation
- Embryo cryopreservation

Benefits for medications related to the treatment of fertility preservation are considered under the benefits for Outpatient Prescription Drug or under Pharmaceutical Products - Outpatient. Refer to the member specific benefit plan document for details.

Fertility Preservation for Iatrogenic Infertility Limitations and Exclusions

When the member's plan includes benefits for fertility preservation for Iatrogenic Infertility, the following services are not covered:

- Elective fertility preservation
- Embryo transfer
- Long-term storage costs (greater than 1 year)
- Benefits are further limited to one cycle of fertility preservation for Iatrogenic Infertility per covered person during the entire period of time they are enrolled for coverage under the policy
- Benefits are not available beyond any applicable dollar maximum listed in the member specific benefit plan document

Clinical Evidence

Coculturing of Embryos

Studies describe the different techniques of coculture, but no standardized method of coculturing has been defined. Further studies are necessary to support the effects of coculture on clinical outcomes.

An ECRI (2022) Clinical Evidence Assessment report on endometrial coculture for treating infertility was inconclusive, as there are limited studies that assess its safety. The assessment reviewed all available literature through November 2022 and identified two randomized controlled trials (RCTs), one nonrandomized comparative study, and two case series that reported on 2,684 individuals. The findings suggest that there are insufficient studies to determine whether endometrial coculture improves the chances of assisted reproduction to result in a live birth. The controlled studies suggest that coculture is not effective, but the findings are at a high risk of bias and need validation. In addition, at least one of the studies indicated that the procedure may result in multiple pregnancies.

Le Saint et al. (2019; included in the ECRI 2022 Clinical Evidence Assessment) conducted a randomized double-blinded study in 207 participants undergoing an in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) protocol, which

compared blastocyst quality between autologous endometrial coculture and conventional culture. The study found that autologous endometrial coculture significantly increased the quality of blastocysts compared with a conventional culture medium. However, the analysis was conducted in embryos rather than participants, there was no follow-up in children born following the treatments, and no significant differences were found in pregnancy and live birth rates.

Kattal et al. (2008) evaluated the role of coculture in human IVF in a meta-analysis of 17 prospective randomized trials. The primary outcomes measured were implantation rates and pregnancy rates (clinical and ongoing). The secondary outcomes included evaluation of pre-embryo development based on the average number of blastomeres per embryo. The pooled data of human trials on coculture demonstrate a statistically significant improvement in blastomere number, implantation rates, and clinical and ongoing pregnancy rates. However, the authors acknowledged that confounding factors such as heterogeneity of cell lines and variability in culture media used limit the conclusions.

Computer-Assisted Sperm Analysis

There is insufficient evidence to permit conclusions regarding the use of this sperm function test. Study results to date have demonstrated low specificity, low sensitivity, and a high rate of false positives.

Finelli et al. (2021) conducted a systematic review and sought to compare results from semen evaluation by both computer-aided sperm analyzer (CASA)–based and manual approaches. After meeting the inclusion criteria, 14 articles published within a 10-year period (January 2010 to November 2020) were used in this study. The results concluded that sperm concentration and motility had a high degree of correlation between both approaches, whether manually or by using a CASA system. However, CASA results showed increased variability in low (< 15 million/mL) and high (> 60 million/mL) sperm concentrations. A sperm motility analysis was inaccurate in samples with a higher concentration or in the presence of nonsperm cells and debris due to difficulties with CASA systems distinguishing between immotile sperm, nonsperm cells, and debris. Morphology results were the most difficult parameter to analyze and the least reliable one to assess due to the high amount of heterogeneity seen between the shapes of the spermatozoa, either in one sample or across multiple samples from the same individual. The authors concluded that manual semen analysis is considered the gold standard when performed by highly trained, competent technologists who work in an accredited laboratory and are monitored by external agencies. In addition, the authors suggested that CASA systems are a valid alternative for the evaluation of semen parameters, specifically for sperm concentration and motility. However, further technological improvements are necessary before these devices replace the human operator.

Oehninger et al. (2000) conducted a meta-analysis that used data from 2,906 individuals in 34 prospective controlled studies to evaluate the predictive value of four categories of sperm functional assays, including CASA, for IVF outcome. In this analysis, the combined results of four studies demonstrated a large degree of variability, indicating a poor predictive power for sperm parameters assessed by CASA and IVF results. Predictive statistics demonstrated low specificity and sensitivity and a high rate of false positives.

Cryopreservation

There is insufficient evidence that supports the clinical utility of cryopreservation of immature oocytes (eggs), ovarian tissue, and testicular tissue. Further studies are needed to support improved clinical outcome measures.

Chaudhri et al. (2024) conducted a systematic review and meta-analysis to compare embryonic tissue, oocyte, and ovarian tissue cryopreservation methods by the primary outcome of live birth rates. In total, 23 studies (nine case reports, 10 retrospective cohort studies, three prospective cohort studies, and one questionnaire report) were included in this analysis. The study identified 647 individuals who opted for oocyte cryopreservation, 267 for embryo cryopreservation, and 1,382 for ovarian tissue cryopreservation. When comparing the live birth rate in percentages of the three fertility preservation methods, the highest rate occurred in those who underwent oocyte cryopreservation at a rate of 27% (175 of 647). Following were individuals who underwent ovarian tissue cryopreservation at a rate of 8.76% (121 of 1,382) and then those who underwent embryonic tissue cryopreservation at a rate of 6.74% (18 of 267). The authors concluded that oocyte and embryo cryopreservation/implantation are well-established procedures; however, ovarian tissue cryopreservation is a promising interventional method for prepubertal individuals facing the prospect of fertility loss.

Finkelstein et al. (2024) conducted a systematic review and meta-analysis to investigate the pregnancy outcomes in individuals who had undergone ovarian tissue cryopreservation for nonmalignant indications. Overall, 16 studies (seven cohort studies and nine case series, with 187 individuals) met the inclusion criteria and were reviewed in this meta-analysis. The pooled successful pregnancy rate was 23.52% (16 studies; 95% CI, 6.48%-44.79%). When a subgroup analysis of the study types was performed, the successful pregnancy rate was higher among case series than cohort studies. A sensitivity analysis that was limited to studies at a low risk of bias revealed a similar pooled successful pregnancy rate of 23.35%. The authors concluded that one-quarter of women who underwent ovarian tissue

cryopreservation for nonmalignant indications had a successful pregnancy. Limitations in the study include the small sample size in each study cohort; additionally, the studies did not exclusively dedicate their cohort of individuals to nonmalignant indications.

Khattak et al. (2022) conducted a systematic review and meta-analysis to review the current evidence of women who received ovarian transplants, including frozen-thawed transplant or fresh or donor graft. The analyzed data included in this review were from 87 studies (n = 735 women). The reproductive outcomes reviewed in this study included pregnancy, live birth, and miscarriage rates. For endocrine outcomes, estrogen, follicle-stimulating hormone (FSH), and luteinizing hormone levels were reviewed. The pooled rates for reproductive outcomes after ovarian tissue transplant was a pregnancy rate of 37% for frozen transplants and 52% for fresh transplants. The live birth rate for frozen transplants was 28% and was 45% for fresh transplants. The miscarriage rate for frozen transplants was 37% and was 33% for fresh transplants. The endocrine function after ovarian tissue transplant pooled mean for pretransplant estrogen was 101.6 pmol/L, which increased post transplant to 522.4 pmol/L. The pooled mean of pretransplant FSH was 66.4 IU/L, which decreased post transplant to 14.1 IU/L. The median time to the return of FSH to a value of < 25 IU/L was 19 weeks. The median duration of graft function was 2.5 years. The authors concluded that ovarian tissue cryopreservation and transplant show promising results in reproductive and hormonal functions in women. However, due to the limitations of the small sample size and heterogeneity of the studies, larger samples of well-characterized populations are required to define the optimal retrieval, cryopreservation, and transplant processes. (Meirow et al., 2016, previously cited in this policy, is included in this systematic review.)

An American Society for Reproductive Medicine (ASRM) guideline covers evidence-based outcomes regarding the efficacy of oocyte cryopreservation for donor oocyte IVF and planned oocyte cryopreservation. The ASRM conducted a literature search from 1986 to 2018 that identified 30 relevant studies. The main outcome measures included clinical pregnancy rate, obstetric and neonatal outcomes, live birth rate, and factors predicting reproductive outcomes. Recommendations were developed regarding neonatal outcomes after using fresh vs cryopreserved oocytes in cases of autologous or donor oocytes. Evidence-based recommendations were developed for predicting factors that may impact live birth rates and predicting the likelihood of live births after planned oocyte cryopreservation, autologous oocyte cryopreservation in infertile women, and donor oocyte cryopreservation. The authors concluded that (1) neonatal outcomes appear similar with cryopreserved oocytes compared with fresh oocytes, (2) ongoing and live birth rates appear to be improved in women who undergo planned oocyte cryopreservation at a younger vs older age, and (3) there were no significant differences in per-transfer pregnancy rates with cryopreserved vs fresh donor oocytes. Additionally, the authors found insufficient evidence to predict live birth rates after planned oocyte cryopreservation and insufficient evidence that the live birth rate is the same with vitrified vs fresh donor oocytes. The authors recommended future studies that compare cumulative live birth rates with long-term outcomes (ASRM, 2021c).

A Hayes report (2019; updated 2021) concluded that a low-quality, limited body of evidence suggests that ovarian tissue cryopreservation and transplant have the potential to restore ovarian function and may result in preserved fertility in individuals who have undergone gonadotoxic cancer treatment. Limitations include an evidence base that is composed of two poor-quality cohort studies, six poor-quality single-arm studies, and one very poor-quality cross-sectional study. Better-quality prospective studies that ensure that all individuals are followed up after receiving a transplant would provide better assurance that the effects of ovarian tissue cryopreservation and subsequent transplant on fertility and pregnancy outcomes are consistent with these findings. Future evidence should evaluate the long-term safety and efficacy in populations that are unable to undergo current standard fertility preservation techniques (e.g., embryo or oocyte cryopreservation). In a Hayes (2022) Health Technology Annual Review, two new abstracts were retrieved, including two single-arm studies. Based on the impact of the newly published studies, there is no change to the current rating.

Meirow et al. (2016) conducted a small, prospective, single-center cohort study to report the results of cryopreserved ovarian tissue in 20 cancer survivors. Participant ages at tissue harvesting ranged from 14 to 39 years. Overall, 15 women had hematologic malignancies, and two had leukemia. Ten participants were exposed to nonsterilizing chemotherapy before ovarian tissue cryopreservation. After transplant, the endocrine recovery rate was 93%. Fourteen participants underwent IVF treatments, with a fertilization rate of 58%. Sixteen pregnancies were achieved (10 after IVF; six spontaneous), resulting in 10 live births, with two (twins) occurring after harvesting from the mother at the age of 37 years. After transplant, 53% of participants conceived, and 32% delivered at least once. One participant conceived four times. Preharvesting chemotherapy exposure was not associated with inferior outcomes. This study is limited by the small participant numbers. Further results from ongoing clinical trials are needed to confirm these findings.

EmbryoGlue

There is insufficient evidence supporting the clinical utility of EmbryoGlue. Further studies are needed to support improved clinical outcome measures.

Greco et al. (2025) conducted a retrospective observational study that included 445 patients (549 cycles) undergoing frozen single euploid blastocyst transfer after preimplantation genetic testing for aneuploidy at a reproductive medicine clinic. Patients were allocated to either a hyaluronan-enriched transfer medium (EmbryoGlue) group or a standard medium control group. All embryos were euploid, confirmed by next-generation sequencing, and the primary outcome was live birth rate. The secondary outcomes of the study were implantation rate, clinical pregnancy, biochemical pregnancy rate, miscarriage rate, and ongoing pregnancy rate. The results indicated that no statistically significant differences were observed between the hyaluronan-enriched transfer medium and control groups in the main reproductive outcomes, including positive human chorionic gonadotropin (hCG) rates (72.27% vs 70.23%; p = 0.648), clinical pregnancy (80.23% vs 84.11%; p = 0.440), live birth rates (66.28% vs 72.85%; p = 0.237), and miscarriage rates (13.95% and 11.26%; p = 0.404). The authors concluded that hyaluronan-enriched transfer medium did not improve reproductive outcomes after single euploid blastocyst transfer. Limitations include the retrospective, single-center design; lack of randomization; potential confounding from clinician-based allocation; and absence of stratification by embryo stage at transfer, collectively reducing internal validity and generalizability.

Bhoi et al. (2024) conducted a retrospective multicenter study to examine the impact of EmbryoGlue, which is a culture medium comprising high-concentration hyaluronan and low-concentration recombinant human albumin, on assisted reproductive technology (ART) outcomes. This study was designed as a two-arm study, in which the standard treatment arm (group A) received conventional medium (n = 649), and the second arm (group B; n = 649) received EmbryoGlue for embryo transfer (ET). In this study, the primary outcome measure was the live birth rate, and the secondary outcome measures were the clinical pregnancy rate and clinical miscarriage rate. The findings identified higher live birth rates (60.6% vs 47.5%) and clinical pregnancies (69.5% vs 57.6%) in the EmbryoGlue group, correlating with factors like patient age and blastocyst transfer. Specifically, EmbryoGlue showed a significant association with higher live birth rates [odds ratio (OR), 1.593; CI, 1.170-2.168; p = 0.003]. Univariate and multivariate analyses identified EmbryoGlue, female age, and blastocyst transfer as predictors of live birth. The authors concluded that the use of EmbryoGlue as an ET medium can result in significantly higher rates of clinical pregnancy, live birth, and multiple live births than conventional culture media. Limitations in the study include its retrospective design and lack of randomization, which could have led to biases and unmeasured confounding factors. Future prospective RCTs are warranted for validation.

Heymann et al. (2022) conducted a systematic review and meta-analysis to determine whether the hyaluronic acid (HA) addition to ET media improves pregnancy outcomes in both autologous and egg donation IVF cycles. Overall, 15 studies, totaling 4,686 individuals, were analyzed. In autologous oocyte cycles, live birth increased from 32% to 39% when ET media contained functional HA concentrations. HA-enriched media increased clinical pregnancy and multiple pregnancy rates by 5% and 8%, respectively. Furthermore, in donor oocyte cycles, HA addition showed little effect on live birth and clinical pregnancy. There was insufficient available information on multiple pregnancy in donor oocyte cycles and on total adverse effects in both groups to draw conclusions. The authors suggested that HA may be valuable in improving the success rate of IVF using autologous oocytes. The combination of HA addition to transfer media in cycles using autologous oocytes and a single-embryo transfer policy might yield the best combination, with higher clinical pregnancy and live birth rates, without increasing the chance of multiple pregnancies. Limitations in the study include limited studies with separate data on donor oocyte cycles and limited information on oocyte quality. Additionally, one-third of the included studies did not include the main outcome, which was live birth rate. (Hazlett et al., 2008, previously cited in this policy, is included in this systematic review.)

Yung et al. (2021) performed a randomized, double-blinded, controlled trial that compared the effects of HA-enriched transfer medium vs those of standard medium on live birth rate after frozen ET. Overall, 550 infertile women, aged 43 years or under, were randomly placed in two groups. The first group used an HA-enriched medium (EmbryoGlue) with an HA concentration of 0.5 mg/mL, while the control group used the conventional G-2 (Vitrolife) medium with an HA concentration of 0.125 mg/mL. The study found that live birth rates in both groups were comparable; however, EmbryoGlue did not improve the live birth rates with frozen ET compared with standard medium.

Heymann et al. (2020) conducted a systematic review to evaluate whether adding adherence compounds to ET media could improve pregnancy outcomes, including improving live birth and decreasing miscarriage, in women undergoing assisted reproduction. Overall, 26 RCTs, with a total of 6,704 individuals, were analyzed. The certainty of evidence was low to moderate overall. Compared with embryos transferred in media containing no or low (0.125 mg/mL) HA, the addition of HA concentrations (0.5 mg/mL) to the transfer media probably increases the live birth rate [risk ratio (RR), 1.21; 95% CI, 1.1-1.31; 10 RCTs; n = 4,066; I^2 = 33%]. This suggests that if the chance of live birth following no HA addition in media is assumed to be 33%, the chance following HA addition would be between 37% and 44%. The addition of HA may slightly decrease miscarriage rates (RR, 0.82; 95% CI, 0.67-1.00; seven RCTs; n = 3,091; I^2 = 66%). Adding HA to transfer media probably results in an increase in both clinical pregnancy (RR, 1.16; 95% CI, 1.09-1.23; 17 studies; n = 5,247; I^2 = 40%) and multiple pregnancy rates (RR, 1.45; 95% CI, 1.24-1.70; seven studies; n = 3,337; I^2 = 36%). The effect of HA added to transfer media on the rate of total adverse events yielded uncertain results. The authors concluded

that the addition of HA as an adherence compound in ET media in ART improved clinical pregnancy and live birth rates; the authors added that (1) HA may slightly decrease miscarriage rates, (2) HA had no clear effect on the rate of total adverse events, and (3) combining an adherence compound and transferring more than one embryo may increase multiple pregnancy rates. The authors recommended further studies of adherence compounds with single-embryo transfers. Limitations include imprecision and/or heterogeneity.

Hyaluronan Binding Assay

There is insufficient evidence supporting the clinical utility of hyaluronan binding assay testing as an advanced sperm selection technique. More studies are needed to support improved outcomes (e.g., increased successful pregnancies with delivery of live-born children).

Alegre et al. (2025) conducted a prospective, randomized, triple-blinded study and sought to demonstrate whether the physiological intracytoplasmic sperm selection (PICSI) technique, as a sperm selection method, increased live birth rate and improved the results of IVF techniques. The study was conducted at a single center and included 277 infertile couples participating in an oocyte donation program. Couples were randomly assigned to conventional intracytoplasmic sperm selection (ICSI; n = 135) or PICSI (n = 142), with sperm selection in the PICSI group performed using HA-coated plates. The study evaluated fertilization rate, blastocyst formation, embryo quality, pregnancy, miscarriage, and live birth rates. The primary outcome, live birth rate, was similar between the PICSI (52.88%) and ICSI (57.28%) groups for fresh cycles ($p > 0.05$), with logistic regression showing an OR of 0.755 (95% CI, 0.425-1.340) for PICSI vs ICSI. The authors concluded that sperm selection with HA did not improve live birth rates compared with conventional ICSI, although PICSI cycles showed higher overall efficiency in cumulative pregnancy rates and may be advantageous in egg donation programs or recurrent pregnancy failure. Limitations identified by the authors include the single-center design; limited sample size, affecting generalizability; and absence of a sibling oocyte cohort design that could have strengthened comparisons.

West et al. (2022) conducted the Hyaluronic Acid Binding Sperm Selection phase 3 RCT (2014-2018), which enrolled 2,772 couples across 16 UK centers, to compare HA-based sperm selection (PICSI) with standard ICSI. A mechanistic cohort of 1,247 couples, enriched for miscarriage outcomes, was analyzed for sperm DNA quality using multiple assays and HA binding score. Baseline semen parameters, sperm DNA quality, and treatment outcomes were assessed using correlation and logistic regression models. The primary outcome, live birth, was significantly associated with treatment allocation (OR, 2.167; 95% CI, 1.084-4.464; $p = 0.03$) and female age (OR, 0.301; 95% CI, 0.113-0.761; $p = 0.013$). Live birth rates were 31.1% for ICSI and 36.0% for PICSI ($p = 0.078$), with PICSI mitigating the negative effect of female age on live birth (OR, 0.58; 95% CI, 0.40-0.82; $p = 0.002$ per decade). Fertilization rates were slightly lower with PICSI (68%) than ICSI (71%; $p = 0.007$), but miscarriage rates were reduced in the PICSI arm, and declining sperm DNA quality was associated with reduced predicted live birth rates regardless of treatment allocation. The authors concluded that selecting sperm with lower DNA damage through HA-based PICSI likely reduced miscarriage risk and mitigated age-related declines in live birth rates, suggesting that HA-based sperm selection could be considered for older individuals undergoing assisted conception. Limitations identified by the authors include the retrospective mechanistic cohort without full randomization, use of residual samples rather than HA-selected sperm, high variability in DNA quality data due to multicenter sampling, and exclusive use of a solid-state PICSI version, limiting generalizability.

Lepine et al. (2019) conducted a systematic review to evaluate the safety and effectiveness of advanced sperm selection techniques, including the ability to bind to HA, on ART outcomes. Two RCTs compared the effects of HA selected sperm-ICSI vs those of ICSI on live birth rates. The evidence suggests that sperm selected by HA binding may have little or no effect on live birth or clinical pregnancy but may reduce miscarriage. However, the quality of the evidence was low. Further high-quality studies, including data from ongoing trials, are required to evaluate whether advanced sperm selection techniques, such as HA binding, can be recommended for use in routine practice.

Miller et al. (2019) compared the success rates of ICSI and hyaluronan-based sperm selection for ICSI (PICSI) for improving live birth rates among couples undergoing fertility treatment. A parallel two-group RCT was performed. Between February 2014 and August 2016, 2,772 couples were randomly assigned to receive either the PICSI (n = 1,387) or ICSI (n = 1,385). Compared with standard ICSI, PICSI did not increase the term live birth rate, and there was no difference found in either premature birth or clinical pregnancy. A significant reduction in miscarriage with PICSI was noted compared with standard ICSI.

Beck-Fruchter et al. (2016) conducted a systematic review of seven studies and concluded that the use of HA binding sperm selection techniques yielded no improvement in fertilization and pregnancy rates. The results did not support the routine use of HA binding assays in all ICSI cycles. Identification of individuals who might benefit from this technique needs further study.

In Vitro Maturation of Oocytes

Although preliminary results with in vitro maturation (IVM) are promising, studies to date show that implantation and pregnancy rates are significantly lower than those achieved with standard IVF. Further evidence from well-designed trials is needed to determine the long-term safety and efficacy of the procedure.

Bartolacci et al. (2024) conducted a systematic review and meta-analysis evaluating the developmental competence of oocytes matured following rescue IVM compared with in vivo–matured sibling oocytes. Overall, 24 observational studies published between 1991 and 2022 were included, encompassing 74,136 oocytes [59,144 metaphase II (MII); 11,326 metaphase I (MI); and 3,666 germinal vesicle (GV)]. The primary outcomes were fertilization and blastulation rates, analyzed using random-effects models with ORs and 95% CIs. Oocytes that matured following rescue IVM had significantly reduced fertilization rates (MI to MII: OR, 0.49, 95% CI, 0.41-0.59, $p < 0.00001$; GV to MII: OR, 0.53, 95% CI, 0.38-0.74, $p = 0.0002$). Blastulation rates were also significantly lower (MI to MII: OR, 0.27, 95% CI, 0.21-0.34, $p < 0.0001$; GV to MII: OR, 0.23, 95% CI, 0.12-0.48, $p = 0.0001$). The authors concluded that oocytes matured through rescue IVM have lower developmental competence than in vivo–matured oocytes and that rescue IVM is not recommended for individuals with a good prognosis but may be considered for poor responders to increase oocyte or embryo numbers. Limitations identified by the authors include the observational nature of included studies, significant statistical heterogeneity, and inability to separately analyze abnormal fertilization conditions, limiting causal inference and precision of pooled estimates.

Vuong et al. (2023) conducted a systematic review to evaluate the effectiveness and safety of IVM compared with those of conventional ovarian stimulation (COS) in women with predicted hyperresponse to gonadotropins. The authors searched for relevant studies comparing any IVM protocol with any COS protocol followed by IVF or ICSI. From a total of 1,472 potentially relevant records screened, three studies (two RCTs and one retrospective cohort study) met the inclusion criteria and were used in the analysis. The live birth rate was not significantly lower after IVM vs COS [OR (95% CI) of 0.56 (0.32-1.01) overall; 0.83 (0.63-1.10) for hCG-triggered IVM; and 0.45 (0.18-1.13) for non–hCG-triggered IVM], irrespective of the stage of transferred embryos. Data from nonrandomized studies generally showed either significantly low or statistically comparable rates of live birth with IVM vs COS. Most studies have not identified any significant difference between IVM and COS with respect to the rates of obstetric or perinatal complications, apart from a potentially higher rate of hypertensive disorders during pregnancy. The development of offspring from IVM and COS with IVF or ICSI appears to be similar. The authors concluded that data are not yet sufficient to draw definitive conclusions about the relative merits of IVM compared with COS in terms of reproductive outcomes. The authors identified that there is a clear need for additional data on IVM to allow more robust comparisons with current ART strategies. (Zheng et al., 2022, previously cited in this policy, is included in this systematic review.)

Zheng et al. (2022) conducted a single-center open-label RCT and sought to assess the effectiveness of IVM in noninferior cumulative live birth rates compared with that after standard IVF in infertile women with polycystic ovary syndrome (PCOS). In total, 351 women were randomly selected to receive one cycle of unstimulated IVM (n = 175) or one cycle of standard IVF with a gonadotropin-releasing hormone antagonist protocol and hCG as an ovulatory trigger (n = 176). Both groups received a freeze-all and single blastocyst transfer strategy. The researchers concluded that one cycle of IVM without ovarian stimulation is inferior to IVF with ovarian stimulation in women with infertility and PCOS in terms of 6-month cumulative ongoing pregnancy rates (22.3% vs 50.6%; rate difference, -28.3%; 95% CI, -37.9% to -18.7%). To evaluate the effectiveness and safety of other IVM protocols or multiple cycles of IVM compared with IVF, further RCTs should be evaluated due to limitations in the study. The limitations include IVM protocol constraint, decline in participant participation, primary outcome transfer time frames, and ovarian stimulants.

Siristatidis et al. (2018) conducted a systematic review and meta-analysis of RCTs to compare outcomes associated with IVM followed by IVF or ICSI vs conventional IVF or ICSI in women with PCOS undergoing ART. Although the results are promising, there is still no evidence from RCTs upon which to base any practice recommendations regarding IVM before IVF or ICSI for women with PCOS. Clinical trials are ongoing.

Inhibin B

There is insufficient evidence to permit conclusions regarding the use of inhibin B as a measure of ovarian reserve. More studies are needed to support improved outcomes (e.g., increased successful pregnancies with delivery of live-born children) with the use of this test.

Postcoital Cervical Mucus Penetration Test

There is insufficient evidence supporting the predictive value or clinical utility of this test. More studies are needed to support improved outcomes (e.g., increased successful pregnancies with delivery of live-born children).

Reactive Oxygen Species Test

There is insufficient evidence supporting the predictive value or clinical utility of this test. Additional studies are needed to support improved clinical outcomes.

Sanyal et al. (2023) conducted a systematic review to assess the clinical utility of available advance sperm function tests in predicting male fertility potential. In total, 110 articles met the inclusion criteria and were included in this review. The majorly investigated sperm function tests are the hypo-osmotic swelling test, acrosome reaction test, sperm capacitation test, hemizona binding assay, sperm DNA fragmentation (SDF) test, seminal reactive oxygen species (ROS) test, mitochondrial dysfunction test, antisperm antibody test, and nuclear chromatin decondensation test. The different advance sperm function tests analyze different aspects of sperm function. The authors concluded that any one test may not be helpful to appropriately predict male fertility potential. Currently, the unavailability of high-quality clinical data, robust thresholds, complex protocols, and high cost are the limiting factors and prohibit current sperm function tests from reaching clinics. Further multicentric research efforts are required.

Chen et al. (2013) studied the influence of ROS on sperm physiology and pathology. Low levels of ROS serve a critical function in normal sperm physiology, such as fertilizing ability and sperm motility. Increased levels of ROS are considered to be a significant contributing factor to male infertility/subfertility due to sperm DNA damage and reduced motility. Some studies have shown that antioxidant therapy significantly improves sperm function and motility; however, the overall effectiveness remains controversial due to nonstandardized assays for measuring levels of ROS and sperm DNA damage. Further development of standardized tests is needed.

Sperm Acrosome Reaction Test

There is insufficient evidence supporting the predictive value or clinical utility of this test. More studies are needed to support improved outcomes (e.g., increased successful pregnancies with delivery of live-born children).

Xu et al. (2018) performed a meta-analysis to determine whether sperm acrosome function scoring can predict fertilization rate in vitro. The study included 737 couples undergoing IVF. Although a significant correlation was found between acrosome function scoring and fertility rate, the study revealed that acrosome function assays were not specific or highly sensitive. Additional studies of sperm functional assays are needed in clinical settings to better predict fertilization outcomes in IVF.

Sperm Capacitation Test

There is insufficient evidence supporting the predictive value or clinical utility of this test. Additional quality studies are needed to support improved clinical outcomes.

A Hayes (2023) Precision Medicine Research Brief examined the published, peer-reviewed literature to evaluate the evidence related to the Cap-Score™ test for the evaluation of sperm capacitation. Conclusions on the safety and clinical utility of this health technology cannot be made in this report, as there is currently not enough published, peer-reviewed literature to evaluate the evidence related to the Cap-Score test for sperm capacitation evaluation in a full assessment.

Sharara et al. (2020) analyzed data in a multicentric, prospective observational study (n = 128; six clinics) to test a previously published relationship between the probability of generating pregnancy (PGP) within three cycles of intrauterine insemination (IUI) and percentage of fertilization-competent capacitated spermatozoa (Cap-Score). A logistic regression of total pregnancy outcomes (n = 252) assessed fit. Cap-Scores in 2,155 men questioning their fertility (MQF) from 22 clinics were compared with those in 76 fertile men in the cohort comparison. New outcomes (n = 128) were rank ordered by Cap-Score and divided into quintiles (25-26 per group); chi-squared testing revealed no difference between predicted and observed pregnancies ($p = 0.809$). Total outcomes (n = 252; 128 new and 124 previous) were pooled and the model recalculated, yielding an improved fit ($p < 0.001$). Applying the Akaike information criterion showed that the optimal model used Cap-Score alone. Semen analysis data were available for 1,948, and Cap-Scores were performed on 2,155 men. To compare fertilizing ability, men were binned by PGP (≤ 19%, 20%-29%, 30%-39%, 40%-49%, 50%-59%, and ≥ 60%). Distributions of PGP and the corresponding Cap-Scores were significantly lower in MQF vs fertile men ($p < 0.001$). Notably, 64% of MQF with normal volume, concentration, and motility (757 of 1,183) had a PGP of 39% or less (Cap-Scores ≤ 31) vs 25% of fertile men. The authors concluded that sperm capacitation prospectively predicted male fertility, and many MQF with normal semen analysis results had impaired capacitation. Limitations noted include the logistic relationship between Cap-Score and male fertility in the form of PGP, as it is predicated on a fertile female partner. Additionally, the authors stated that some participating physicians reported modifying their clinical practices when receiving the result of a low Cap-Score that could have led to bias. The authors cautioned of interpretation of outcomes data stratified by maternal age and noted that no data regarding comorbidities were included in the MQF group.

Schinfeld et al. (2018) conducted a prospective observational study to determine whether Cap-Score can predict male fertility, with the outcome being clinical pregnancy within three or fewer IUI cycles. The initial exclusion criteria for men included having fewer than 10×10^6 motile sperm on an initial count. The fertility of female partners was examined, but findings of female factor that did not preclude attempts at IUI were not considered grounds for exclusion. Only couples who pursued IUI were included in the study. A Cap-Score and semen analysis were performed in 208 men, with outcomes available in 91 men. The chance of generating pregnancy was predicted in the men using previously defined Cap-Score ranges: low (n = 47) or high (n = 44). Absolute and cumulative pregnancy rates were reduced in men predicted to have low pregnancy rates vs high (absolute: 10.6% vs 29.5%, p = 0.04; cumulative: 4.3% vs 18.2%, 9.9% vs 29.1%, and 14.0% vs 32.8% for cycles 1-3; n = 91, 64, and 41; p = 0.02). The Cap-Score differed significantly between outcome groups. A logistic regression evaluated Cap-Score and semen analysis results relative to PGP in men who were successful in or who completed three IUI cycles (n = 57). Cap-Score was significantly related to PGP (p = 0.01). The model fit was then tested with 67 additional participants (n = 124; five clinics); the equation changed minimally, but fit improved (p < 0.001; margin of error, 4%). The authors concluded that the Akaike information criterion found that the best model used the Cap-Score as the only predictor and that Cap-Score provided a predictive assessment of male fertility. The authors noted that further investigation is required to assess the decline in success in the third IUI cycle of men with normal-range Cap-Scores. Limitations include the potential variation in IUI techniques and participant characteristics from multiple sites; additionally, minimal tests for female factor infertility were defined.

Cardona et al. (2017) assessed whether G_{M1} localization patterns (Cap-Score) that were previously studied in animal models would correspond with male fertility in humans in two different settings. One study (number 1) was a post hoc association between capacitation and involved couples pursuing assisted reproduction in a tertiary care fertility clinic. The second study (number 2) involved fertile men vs those questioning their fertility at a local urology center. In study 1, various thresholds were examined vs the clinical history of 42 individuals; 13 had Cap-Scores of ≥ 39.5%, with 12 of them (92.3%) achieving clinical pregnancy by natural conception or three or fewer IUI cycles. In study 2, Cap-Scores in 76 men with known recent fertility were obtained (cohort 1, pregnant partner or recent father) and compared with those in 122 men seeking fertility assessment (cohort 2). Cap-Score values were normally distributed in cohort 1, with 13.2% having Cap-Scores more than 1 SD below the mean (35.3 ±7.7%). More men in cohort 2 had Cap-Scores greater than 1 SD below the normal mean (33.6%; p = 0.001). Minimal or no relationship was found between Cap-Score and standard semen analysis parameters. The authors concluded that the data provided reference ranges for fertile men that could be used to guide couples toward the most appropriate fertility treatment and that Cap-Score testing could be used as a complement to standard semen analysis parameters. Study limitations include small sample sizes.

Sperm DNA Integrity/Fragmentation Tests

There is insufficient evidence supporting the predictive value or clinical utility of this test. Prospective studies directly evaluating the impact of DNA fragmentation testing on the management of infertility are needed.

Wan et al. (2026) conducted an umbrella meta-analysis evaluating the association between SDF and ART outcomes, including clinical pregnancy, pregnancy loss, and live birth rate. Systematic searches across major databases identified reviews of infertile couples undergoing IVF, ICSI, or IUI, comparing high vs low SDF measured by validated assays such as sperm chromatin structure assay, sperm chromatin dispersion, TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labeling assay), and Comet. Included in the study were eight meta-analyses that encompassed over 25,000 ART cycles, and pooled RRs were calculated using fixed- or random-effects models, depending on heterogeneity. Elevated SDF was significantly associated with reduced clinical pregnancy in IVF (relative risk, 0.662; 95% CI, 0.547-0.801) and IUI (relative risk, 0.467; 95% CI, 0.242-0.900), while a weak borderline association was observed in ICSI (relative risk, 0.886; 95% CI, 0.764-0.985). High SDF was strongly associated with increased pregnancy loss in ICSI (relative risk, 2.286; 95% CI, 1.383-3.779), but evidence for live birth rate was limited and inconclusive (relative risk, 0.848; 95% CI, 0.717-1.003). The authors concluded that elevated SDF adversely affects ART outcomes and shows consistent negative associations in IVF and IUI, a weak effect in ICSI, and a strong link to miscarriage in ICSI. The authors stated that SDF testing should be considered an adjunctive, context-dependent tool for counseling and selected clinical scenarios. The authors also identified that the certainty of evidence was graded as low due to heterogeneity, imprecision, and methodological limitations. Limitations identified by the authors include heterogeneous cutoff definitions and assay variability; small sample sizes; low methodological quality; substantial heterogeneity and predominance of retrospective designs; and limited assessment of publication bias and study overlap.

Lourenco et al. (2023) conducted a systematic review and sought the impact that SDF has on embryos from ARTs. The study included 20 articles that met the inclusion criteria, which were cohort and case-control articles. The SDF increase proved to be a limiting potential for ARTs. In IVF, clinical outcomes such as reduced fertilization rate, blastocyst rate, embryo quality, reduced implantation rate, and increased abortion rates were observed. In ICSI, outcomes such as reduced blastocyst production rate, embryo quality, implantation, and live birth rate were verified. Furthermore, in IUI, results of reduced pregnancy rates were observed. However, the mechanisms that lead to these deleterious effects on

ARTs are still unclear, so more studies are needed to identify the effects of SDF on ARTs. Limitations in the study include the absence of individuals as healthy controls; additionally, the 5-year period limited the number of articles obtained. The authors concluded that SDF was a potential limiting factor for ARTs.

Chen et al. (2022) conducted a meta-analysis study to analyze the effect of the sperm DNA fragmentation index (DFI) on the outcomes of IVF and ICSI. Overall, 12 cohort studies (four retrospective, five prospective, and three bidirectional cohort studies) between 2005 and 2020 were included and analyzed using a random-effects model. The results indicated that the high-DFI group was statistically inconsequential compared with the low-DFI group with the IVF fertilization rate (relative risk, 0.94; 95% CI, 0.77-1.14; p = 0.61), pregnancy rate (relative risk, 0.83; 95% CI, 0.57-1.21; p = 0.32), and live birth rate (relative risk, 0.53; 95% CI, 0.16-1.80; p = 0.31). The association between DFI and ICSI with the fertilization rate (relative risk, 0.79; 95% CI, 0.52-1.18; p = 0.25), pregnancy rate (relative risk, 0.89; 95% CI, 0.74-1.06; p = 0.18), and live birth rate (relative risk, 0.89; 95% CI, 0.70-1.14; p = 0.36) was also not statistically significant. The authors concluded that the study showed no significant association between sperm DFI and assisted reproductive outcomes. Therefore, further studies of multicenter, large-sample clinical trials should be carried out to conclusively determine the significance of DNA damage on assisted reproduction outcomes. Several limitations were identified in the study. First, age-considered subgroup analyses were not examined. Second, only sperm chromatin structure assay studies using DFI detection were used and introduced biases that do not reflect the overall DFI. Finally, no differences were identified in sperm DFI in assisted reproductive outcomes, although the threshold between high and low DFI was 15% to 30%, which is relatively large.

Sperm Penetration Assays

There is insufficient evidence supporting the clinical utility of this test in lieu of newer technologies for treating male infertility.

Oehninger et al. (2000) conducted a meta-analysis study using data from 2,906 individuals in 34 prospective controlled studies to evaluate the predictive value of four categories of sperm functional assays, including sperm penetration assays, for IVF outcome. In this analysis, the sperm-zona pellucida binding assay and the induced-acrosome reaction assay had a high predictive value for fertilization outcome. Sperm penetration assays had a relatively high positive predictive value (more than 70%), but the negative predictive value was variable, ranging from 11% to 100%, with most studies reporting a negative predictive value of less than 75%. The authors noted that this assay is limited by the need for standardization.

Uterine Receptivity Testing and Treatment

There is insufficient evidence supporting the safety and efficacy of uterine receptivity testing and/or treatment. More studies are needed to support improved outcomes such as successful pregnancies with delivery of live-born children.

Xu et al. (2025) conducted a retrospective cohort study to evaluate the clinical efficacy of endometrial receptivity analysis (ERA)–guided personalized ET (pET). The study included 3,605 patients with previous failed ET cycles treated at a single reproductive medicine center between January 2016 and October 2022. Patients were categorized into non-recurrent implantation failure (RIF; n = 2,045) and RIF (n = 1,560) groups, with 782 patients receiving ERA and pET. The primary outcome was clinical pregnancy, defined as ultrasound detection of a gestational sac 4 weeks after transfer, with live birth rate also assessed. The study's findings identified that in patients without RIF, pET achieved higher clinical pregnancy (64.5% vs 58.3%; p = 0.025) and live birth rates (57.1% vs 48.3%; p = 0.003) than non-pET. In patients with RIF, after propensity score matching, pET resulted in higher clinical pregnancy (62.7% vs 49.3%; p < 0.001) and live birth rates (52.5% vs 40.4%; p < 0.001) than non-pET. The authors concluded that pET guided by ERA improved clinical pregnancy and live birth rates, particularly in patients with RIF, and reduced early abortion rate in patients without RIF; additionally, an appropriate serum E2/P ratio benefits endometrial receptivity, while a displaced window of implantation increases with age and the number of previous failed cycles. Limitations identified by the authors include the incomplete exclusion of immunologic factors; potential confounding from additional treatments and endometrial scraping; retrospective design, with selection bias; and possible discrepancy between biopsy and transfer cycle receptivity.

Zolfaroli et al. (2023) conducted a systematic review and meta-analysis evaluating the influence of ERA on ET outcomes in individuals undergoing IVF. Searches across multiple databases up to December 2022 identified 12 studies that included 14,224 individuals pooled using a random-effects model. Eligible studies compared ERA testing vs no testing prior to ET, with live birth as the primary end point. The analysis included RCTs and cohort studies assessing live births, clinical pregnancies, and related outcomes. For the primary outcome of live births, no significant difference was found between the ERA and non-ERA groups (OR, 1.00; 95% CI, 0.63-1.58; I^2 = 92.7%). The pooled data indicated that ERA testing did not improve live birth rates compared with standard ET protocols. The authors concluded that pET guided by ERA was not associated with significant differences in pregnancy outcomes compared with standard protocols and that the utility of ERA in IVF should be revisited. Limitations identified by the authors include the lack of individual-level data,

which restricted assessment of baseline characteristics; inconsistent outcome definitions, which reduced reliability; and the invasiveness of ERA biopsy, which introduced potential adverse effects and treatment delays.

Arian et al. (2023) conducted a systematic review and meta-analysis to investigate the impact of ERAs before frozen ET in individuals undergoing IVF. Eight studies (2,784 individuals; 831 who had undergone the ERA and 1,953 who had not undergone the ERA) were found to be eligible for this meta-analysis. The live birth or ongoing pregnancy rate in the ERA group was not significantly different compared with that in the non-ERA group; no difference was seen in subgroup analyses based on the number of previous failed ETs. The rates of implantation, biochemical pregnancy, clinical pregnancy, and miscarriage were also comparable between the ERA and the non-ERA groups. After separate analyses according to the study design and adjustment for confounding factors, overall pooled estimates remained statistically nonsignificant. Limitations in the study include the combination of randomized trials with non-RCT studies, separate subgroup analyses, heterogeneity of different types of ERA kits and testing modalities, different types of endometrial preparations, and lack of control for causes of implantation failure. The authors concluded that the meta-analysis did not reveal a significant change in the rate of pregnancy after IVF cycles using the ERA; it is not clear whether the ERA can increase the pregnancy rate or not. The authors suggested that further well-designed RCTs must prove the utility of ERA testing on clinical pregnancy rates and ongoing pregnancy rates in general and in certain subgroups of individuals with infertility.

Papanikolaou et al. (2023) conducted a systematic review and meta-analysis to investigate the impact of endometrial scratching during hysteroscopy before ET on pregnancy rates. Twelve studies (n = 2,213) met the inclusion criteria and were used in this analysis. The authors identified that hysteroscopy and concurrent endometrial scratching before ET resulted in a statistically significant improvement in clinical pregnancy rate (RR, 1.50; 95% CI, 1.30-1.74; $p < 0.0001$) and live birth rate (RR, 1.67; 95% CI, 1.30-2.15; $p < 0.0001$), with no statistically significant difference in miscarriage rate (RR, 0.80; 95% CI, 0.52-1.22; $p = 0.30$). Limitations in the study include poor-quality studies, a limited number of studies, the timing of the interventions, and the different instruments used. The authors concluded that hysteroscopy with concurrent endometrial scratching may be offered in IVF before ET as a potentially improving manipulation. The authors suggested that future randomized trials comparing different groups of individuals would also provide more precise data on that issue to clarify specific criteria in the selection of individuals.

A Hayes (2022) Precision Medicine Research Brief examined the published, peer-reviewed literature to evaluate the evidence related to the ERA test. The safety and clinical utility of this health technology could not be made in this report, as it would require a full-text review of the evidence. A full review of evidence may be justified, depending on whether the health technology of interest is emerging, evolving, controversial, or disruptive and the degree to which it is a priority to individuals.

Liu et al. (2022) conducted a systematic review and meta-analysis to determine the prevalence of a displaced window of implantation in infertile women and the clinical utility of pET guided by the ERA on IVF/ICSI outcomes. The study included 11 published articles after the studies met the inclusion criteria. The intervention consisted of ERA testing of endometrial biopsies collected on 7 days after the spontaneous surge of the luteinizing hormone in natural cycles or 5 days post administration with progesterone during hormone replacement treatment cycles to determine receptivity status, followed by pET for nonreceptive results. The primary outcomes were the prevalence of a displaced window of implantation and the ongoing pregnancy/live birth rate. The pooled prevalence of a displaced window of implantation was 38% (95% CI, 19%-57%) in good-prognosis individuals and 34% (95% CI, 24%-43%) in individuals with RIF. In good-prognosis individuals, ongoing pregnancy/live birth rates did not differ between ERA-guided and standard ET (39.5% vs 53.7%; OR, 1.28; 95% CI, 0.92-1.77; $p = 0.49$; $I^2 = 0\%$). In individuals with RIF, ongoing pregnancy/live birth rates were similar between personalized and standard transfer (40.7% vs 49.6%; OR, 0.94; 95% CI, 0.70-1.26; $p = 0.85$; $I^2 = 0\%$). The authors concluded that approximately one-third of infertile women may have a displaced window of implantation and that ERA-guided pET may improve pregnancy chances for nonreceptive individuals with RIF of endometrial origin but not for good-prognosis individuals. Limitations include the heterogeneity in individuals' characteristics and IVF protocols, inconsistent biopsy-to-transfer intervals, unconfirmed embryo euploidy, invasive testing requirements, need for vitrification, and variable definitions of RIF across studies.

Van Hoogenhuijze et al. (2021) conducted a nonblinded RCT (SCRaTCH trial) in women with one failed IVF/ICSI cycle to evaluate whether a single endometrial scratch using an endometrial biopsy catheter would lead to a higher live birth rate after the subsequent IVF/ICSI treatment compared with no scratch. Cumulative 12-month ongoing pregnancy leading to live birth rate was a secondary outcome. The women were randomized between January 2016 and July 2018; in total, 933 participants of 1,065 who were eligible were included in the study that took place in eight academic and 24 general hospitals. After the fresh transfer, 4.6% more live births were observed in the scratch than the control group (110 of 465 vs 88 of 461, respectively). These data are consistent with a true difference of between -0.7% and +9.9% (95% CI), indicating that while the largest proportion of the 95% CI is positive, scratching could have no or even a small negative

effect. Biochemical pregnancy loss and miscarriage rate did not differ between the two groups; in the scratch group, 27 of 153 biochemical pregnancy losses and 14 of 126 miscarriages occurred, while this was 19 of 130 and 17 of 111 in the control group. After 12 months of follow-up, 5.1% more live births were observed in the scratch group (202 of 467 vs 178 of 466), of which the true difference most likely lies between 1.2% and +11.4% (95% CI). The authors noted that the results of this study are an incentive for further assessment of the efficacy and clinical implications of endometrial scratching; additionally, if a true effect exists, it may be smaller than previously anticipated or may be limited to specific groups of women undergoing IVF/ICSI. The authors concluded that at present, endometrial scratching should not be performed outside clinical trials and recommended further studies with larger sample sizes. Limitations include the nonblinding of participants.

Lensen et al. (2019) conducted a multicenter, open-label RCT evaluating the impact of endometrial scratching prior to IVF. Participants were randomly assigned in a 1:1 ratio to either endometrial scratching (n = 690) or no intervention (n = 674). The primary outcome was live birth. The frequency of live birth was 180 (26.1%) in the endometrial scratching group and 176 (26.1%) in the control group (adjusted OR, 1.00; 95% CI, 0.78-1.27). There were no significant between-group differences in the rates of ongoing pregnancy, clinical pregnancy, multiple pregnancy, ectopic pregnancy, or miscarriage.

Nastri et al. (2015) conducted a review of RCTs comparing intentional endometrial injury before ET in women undergoing ART vs a sham procedure or no intervention. Fourteen trials were included (n = 1,063 in the intervention groups and n = 1,065 in the control groups). One study compared endometrial injury on the day of oocyte retrieval vs no injury, and 13 studies compared endometrial injury performed between day 7 of the previous cycle and day 7 of the ET cycle vs no injury. In studies comparing endometrial injury performed between day 7 of the previous cycle and day 7 of the ET cycle vs no intervention or a sham procedure, endometrial injury was associated with an increase in live birth or ongoing pregnancy rate (RR, 1.42; 95% CI, 1.08-1.85; p = 0.01). There was no evidence of an effect on miscarriage. Endometrial injury was also associated with an increased clinical pregnancy rate (RR, 1.34; 95% CI, 1.21-1.61; p = 0.002). This suggests that if 30% of women achieve clinical pregnancy without endometrial injury, between 33% and 48% will achieve clinical pregnancy with this intervention. Endometrial injury was associated with increased pain. One study reported pain on a visual analog scale, two studies reported the number of pain concerns after the procedure, one recorded no events in either group, and the other reported that endometrial injury increased pain concerns. Results from the only RCT comparing endometrial injury on the day of oocyte retrieval vs no injury reported that this endometrial injury markedly decreased live birth and clinical pregnancy. The authors concluded that (1) the procedure is mildly painful; (2) there is no evidence of effect on miscarriage, multiple pregnancy, or bleeding; and (3) a reduction in clinical and ongoing pregnancy rates is associated with endometrial injury on the day of oocyte retrieval. Additionally, moderate-quality evidence indicates that endometrial injury performed between day 7 of the previous cycle and day 7 of the ET cycle is associated with an improvement in live birth and clinical pregnancy rates in women with more than two previous ETs. The authors stated that although current evidence suggests benefit of endometrial injury, more evidence from well-designed trials that avoid instrumentation of the uterus in the preceding 3 months, do not cause endometrial damage in the control group, stratify the results for women with or without RIF, and report live birth are needed.

Clinical Practice Guidelines

American Society for Reproductive Medicine (ASRM)

An ASRM committee opinion on IVM of oocytes states that initial results suggest the potential for clinical application. However, at this time, implantation and pregnancy rates are significantly lower than those with standard IVF. Because only a small number of children have been conceived with IVM, information on the safety of the procedure with regard to malformation and developmental outcomes cannot be accurately assessed. IVM should only be performed as an experimental procedure in specialized centers in carefully selected patients (ASRM, 2021a).

An ASRM committee opinion on fertility evaluation of infertile women states that the postcoital test of cervical mucus is no longer recommended for evaluating infertility because the test is subjective, has poor reproducibility, rarely changes clinical management, and does not predict the inability to conceive. Additionally, inhibin B and the clomiphene challenge test are not helpful tools to assess ovarian reserve and are not recommended (ASRM, 2021b).

In an ASRM committee opinion on testing and interpreting measures of ovarian reserve, it states that markers of ovarian reserve tests are neither beneficial in predicting the likelihood of unaided pregnancy in women with infertility nor do they predict the reproductive potential of women with undocumented fertility. Markers of ovarian reserve can be useful predictors of oocyte yield but weak independent predictors of reproduction potential and should not be used as a fertility test (ASRM, 2020).

An ASRM committee opinion states that ovarian tissue banking is an acceptable fertility preservation technique and is no longer considered experimental. However, data on the efficacy, safety, and reproductive outcomes after ovarian tissue

cryopreservation are still limited. Given the current body of literature, ovarian tissue cryopreservation should be considered an established medical procedure, with limited effectiveness, that should be offered to carefully selected patients (ASRM, 2019).

The ASRM (2018) recommends the following with regard to cryopreservation and fertility preservation:
- Sperm cryopreservation is an established method of fertility preservation in men
- Oocyte cryopreservation in women is an established method
- Embryo cryopreservation is an established method of fertility preservation in women and men
- Cryopreservation of ovarian tissue remains investigational (refer to ASRM, 2019, above for updated information)
- Cryopreservation of testicular tissue in prepubescent male patients remains investigational

American Society of Clinical Oncology (ASCO)

In a 2018 ASCO clinical practice guideline on fertility preservation in patients with cancer, an updated summary states a recommendation for ovarian tissue cryopreservation and transplant. At the time of publication of this guideline, ovarian tissue cryopreservation remains experimental. However, ASCO indicates that ovarian tissue cryopreservation is advancing rapidly and may evolve to become standard therapy in the future. Sperm, embryo, and oocyte cryopreservation continue to be standard practice. Testicular tissue cryopreservation is still considered to be investigational. In a 2025 ASCO clinical practice guideline on fertility preservation in patients with cancer, an update addresses ovarian tissue cryopreservation and transplant. The recommendation states that ovarian tissue cryopreservation for future transplant may be provided to patients with cancer as an established method of fertility preservation. This option can be considered either as an alternative or as a complement to embryo or oocyte cryopreservation. Decisions about ovarian tissue cryopreservation should take into account patient preferences, clinical factors, and individual circumstances, including future flexibility, success rates, and relevant legal considerations (Oktay et al., 2018; updated Su et al., 2025).

American Urological Association (AUA)/American Society for Reproductive Medicine (ASRM)

The AUA/ASRM 2020 society guideline on the diagnosis and treatment of infertility in men states that SDF analysis is not recommended in the initial evaluation of the infertile couple. There are no prospective studies that have directly evaluated the impact of DNA fragmentation testing on the clinical management of infertile couples (Schlegel et al., 2021a; Schlegel et al., 2021b).

An AUA/ASRM 2020 guideline on the diagnosis and treatment of infertility of men states that patients with pyospermia should be evaluated for the presence of infection. Elevated semen white blood cells may secrete cytokines and generate free radicals in the semen (ROS) that may be detrimental to sperm function; this is not a test of fertility (Schlegel et al., 2021a).

National Institute for Health and Care Excellence (NICE)

A NICE clinical guideline addresses the evaluation and management of infertility, including ART, and recommends:
- For people with cancer who wish to preserve fertility:
  - When using cryopreservation to preserve fertility in people diagnosed with cancer, use sperm, embryos, or oocytes
  - Offer sperm cryopreservation to men and adolescent boys who are preparing for medical treatment for cancer that is likely to make them infertile
  - Offer oocyte or embryo cryopreservation, as appropriate, to women of reproductive age (including adolescent girls) who are preparing for medical treatment for cancer that is likely to make them infertile if:
    - They are well enough to undergo ovarian stimulation and egg collection; and
    - This will not worsen their condition; and
    - Enough time is available before the start of their cancer treatment
  - In cryopreservation of oocytes and embryos, use vitrification instead of controlled rate freezing if the necessary equipment and expertise are available
- The use of inhibin B testing for predicting any outcome of fertility treatment is not recommended
- No recommendation for the routine use of postcoital testing of cervical mucus for evaluating infertility because the test has no predictive value on pregnancy rate

(NICE, 2013; updated 2017)

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Many tests and procedures used in the diagnosis and treatment of infertility are not subject to FDA regulation. Refer to the following website to search for specific products: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed February 19, 2026)

For tests regulated under the Clinical Laboratory Improvement Amendments of 1988, premarket approval from the FDA is not required.

Products and media used for cryopreservation of reproductive tissue are too numerous to list. Refer to the following website for more information (use product code MQL). Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed February 19, 2026)

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Policy History/Revision Information

Date	Summary of Changes

06/01/2026	**Coverage Rationale**
	• Replaced reference to "deoxynucleotidyl transferase-*mediated* dUTP nick end labeling assay (TUNEL)" with "*terminal* deoxynucleotidyl transferase dUTP nick end labeling assay (TUNEL)"
	Definitions
	• Removed definition of:
	  ○ Preimplantation Genetic Testing (PGT)
	  ○ Therapeutic Donor Insemination (TDI)
	Applicable Codes
	• Removed HCPCS code J3355
	Supporting Information
	• Updated *Benefit Considerations*, *Clinical Evidence*, and *References* sections to reflect the most current information
	• Archived previous policy version 2026T0270MM

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, check the member specific benefit plan document and any applicable federal or state mandates. 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.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. 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.