Autologous Cellular Therapy (for Idaho Only)

Policy Number: CS176ID.C
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➲ Instructions for Use

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Related Policies

- Prolotherapy and Platelet Rich Plasma Therapies (for Idaho Only)
- Spinal Fusion and Bone Healing Enhancement Products (for Idaho Only)

Application

This Medical Policy only applies to the state of Idaho, including Idaho Medicaid Plus plans.

Coverage Rationale

Autologous Cellular Therapy is unproven and not medically necessary for all indications due to insufficient evidence of efficacy.

Definitions

Adipose-Derived Stem Cells (ASCs): Mesenchymal adult cells, isolated from adipose tissue that can expand in vitro in an undifferentiated state and have the capacity to differentiate into multiple cell lineages (Si et al., 2019).

Autologous Adipose-Derived Regenerative Cellular Therapy: A therapy proposed to treat a wide array of conditions using adult stem cells extracted from an individual fat tissue injected into targeted lesion of the same individual. In some cases, the fat-derived stem cells are processed in some fashion prior to reinjection (Si et al., 2019).

Autologous Cellular Therapy: A therapeutic intervention that uses an individual's stem cells, which can be cultured and expanded outside the body, and reintroduced into the donor (Si et al., 2019).

Bone Marrow Mononuclear Stem Cells: A mixed population of blood cells, including stem and progenitor cells, that have been explored in studies of cardiac and vascular repair (Baryeh et al., 2021).

Regenerative Medicine: The branch of medicine that develops methods to regrow, repair or replace damaged or diseased cells, organs, or tissues. Regenerative Medicine includes the generation and use of therapeutic stem cells, tissue engineering, and the production of artificial organs (Baryeh et al., 2021).

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 federal, state, or contractual requirements 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.

CPT Code	Description
*0263T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure including unilateral or bilateral bone marrow harvest
*0264T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure excluding bone marrow harvest
*0265T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; unilateral or bilateral bone marrow harvest only for intramuscular autologous bone marrow cell therapy
*0489T	Autologous adipose-derived regenerative cell therapy for scleroderma in the hands; adipose tissue harvesting, isolation and preparation of harvested cells including incubation with cell dissociation enzymes, removal of non-viable cells and debris, determination of concentration and dilution of regenerative cells
*0490T	Autologous adipose-derived regenerative cell therapy for scleroderma in the hands; multiple injections in one or both hands
*0565T	Autologous cellular implant derived from adipose tissue for the treatment of osteoarthritis of the knees; tissue harvesting and cellular implant creation
*0566T	Autologous cellular implant derived from adipose tissue for the treatment of osteoarthritis of the knees; injection of cellular implant into knee joint including ultrasound guidance, unilateral
*0717T	Autologous adipose-derived regenerative cell (ADRC) therapy for partial thickness rotator cuff tear; adipose tissue harvesting, isolation and preparation of harvested cells, including incubation with cell dissociation enzymes, filtration, washing and concentration of ADRCs
*0718T	Autologous adipose-derived regenerative cell (ADRC) therapy for partial thickness rotator cuff tear; injection into supraspinatus tendon including ultrasound guidance, unilateral
*0999T	Autologous muscle cell therapy, harvesting of muscle progenitor cells, including ultrasound guidance, when performed
*1000T	Autologous muscle cell therapy, administration of muscle progenitor cells into the urethral sphincter, including cystoscopy and post-void residual ultrasound, when performed
*1001T	Autologous muscle cell therapy, injection of muscle progenitor cells into the external anal sphincter, including ultrasound guidance, when performed

Codes that are labeled with an asterisk (*) are not on the State of Idaho Medicaid Fee Schedule and therefore may not be covered by the State of Idaho Medicaid Program. For additional information on non-covered and excluded services, refer to the Idaho Medicaid Provider Handbook, General Information, General Information and Requirements for Providers: Non-Covered and Excluded Services.

Description of Services

Over the past few decades, since the bioengineering revolution, Autologous Cellular Therapy (ACT) has become a rapidly evolving field. Tissue engineering techniques are being developed to improve the efficiency of repair or regeneration of damaged tissues and organs, including musculoskeletal tissues. Tissue engineering focuses on the integration of biomaterials with stem cells and/or bioactive molecules such as growth factors.

Stem cells are multipotent cells that possess the ability to differentiate into various cell types and are being used more frequently in the treatment of orthopedic and/or musculoskeletal conditions. There are various types of stem cells which include, but are not limited to embryonic, mesenchymal, and hematopoietic. Embryonic stem cells are isolated from embryonic tissue, while both mesenchymal and hematopoietic cells are isolated using adult bone marrow. While some stem cells are restricted to a few lineages, others may differentiate into a wide variety of cell types. Hematopoietic stem cell transplantation is the only stem cell therapy well-established in clinical practice (Gepstein et al., 2020).

In general, cellular therapies are purported to produce a regenerative effect by promoting growth and differentiation of local cells. Repair and regeneration of human tissue has been studied with a variety of potentially regenerative cells from throughout the body. For example, Autologous Adipose-Derived Regenerative Cellular Therapy (ADRC) has been introduced as a modality to address scleroderma-related hand dysfunction. ADRCs are a mixed population of cells, including adult stem-cells, endothelial progenitor-cells, leukocytes, endothelial cells, and vascular smooth muscle cells. New scientific evidence reveals that ADRCs can potentially counteract inflammation, stimulate new blood vessel formation, prevent cell death, and secrete substances needed for repair and regeneration, which could possibly lead to improvement in hand dysfunction.

Autologous Adipose-Derived Regenerative Cellular Therapy involves the injection of fat-derived cells, either unprocessed or minimally processed, from one part of a person to another part of the same person. This treatment method has been proposed as a treatment of a wide variety of indications, including orthopedic injuries. One commercially available device used to produce this type of therapeutic product is named Lipogems (Lipogems International, Norcross, GA), which is used to produce “microfractionated minimally manipulated adipose tissue.”

Autologous Cellular Therapy has also been proposed as a treatment for peripheral arterial disease (PAD). Theoretically, implantation of bone marrow stem cells into the affected limbs could trigger the growth of new blood vessels, increasing blood flow to the extremities and treating the symptoms and complications of PAD.

Clinical Evidence

The body of evidence in the published peer reviewed scientific literature evaluating ACT is mainly in the form of preliminary animal studies, case reports, case series, and a number of systematic reviews/meta-analysis of these studies. A few nonrandomized comparative trials and randomized controlled trials (RCTs) also exist. Although the evidence base has been steadily increasing, authors indicate that the technology is in an early stage of development. In order to assess the safety and efficacy of orthopedic, vascular, and rheumatological applications of ACT, high-quality RCTs are required that compare patient-centered health outcomes between these and established therapeutic approaches. Additionally, RCTs evaluating long term outcomes are needed to firmly establish safety and efficacy of ACTs.

Some of the more commonly reported conditions under investigation include the following:

Knee Osteoarthritis (KOA)

The use of autologous adipose-derived regenerative cellular therapy, also referred to as autologous cellular implant derived from adipose tissue, has been proposed for knee osteoarthritis (KOA). The bulk of evidence surrounding cellular therapy for orthopedic conditions has focused on regenerating cartilage for individuals with osteoarthritis(OA). Although some conclusions support improvement in pain and function for some individuals, limitations such as heterogeneity of inclusion and exclusion criteria, lack of controls, type of cellular therapies which have been applied in different stages of OA, the use of various quantities of these therapies, and lack of long-term outcomes prohibit strong evidence-based conclusions regarding clinical safety and efficacy.

Yanke et al. (2025) conducted a RCT to evaluate the effects of autologous bone marrow aspirate concentrate (BMAC) on the development and progression of OA in participants undergoing meniscectomy by comparing patient-reported outcomes, specifically IKDC scores between participants who receive BMAC post-meniscectomy and those who receive a saline control injection. The study will also compare physical examination, MRI, radiographs, and synovial fluid analysis. There were 95 enrolled participants with 83 (87.4%) included for final analysis. No significant differences were found between the groups with regard to patient characteristics, intraoperative variables, concomitant procedures, preoperative PROM scores, or preoperative radiographic findings. At 1 year postoperatively, the BMAC group failed to demonstrate significantly better IKDC scores (p = .687) or radiographic outcomes (p .05 for all radiographic measures) compared with the control group. Secondary PROM scores also did not significantly differ between the groups (p > .05 for all PROMs). However, there were higher achievement rates of the minimal clinically important difference for the KOOS Sport (100.0% vs 80.0%, respectively; p = .023) and KOOS Symptoms (92.3% vs 68.0%, respectively; p = .038) at 1 year postoperatively in the BMAC group than in the control group. All PROMs, excluding the VR-12 mental score, showed significant improvements compared with baseline at all postoperative time points for both the BMAC and control groups. The study's limitations include restrictive inclusion and exclusion criteria, limiting generalizability to broader populations, especially those outside the specified age range or with different comorbidities. Since this was study was conducted at a single center, the findings may not apply to other healthcare settings with varying individual demographics and clinical practices. The number of eligible individuals who declined participation and their reasons were not recorded. The trial protocol was unpublished before the study began, and due to potential risks, a placebo saline injection was not administered, opting for a sham incision at the ASIS for the control group. Lastly, the follow-up period may not capture long-term outcomes, crucial

for post-meniscectomy individuals, particularly those with preexisting OA. At the 1-year postoperative mark, no significant differences were found in IKDC scores or radiographic outcomes between the BMAC and control groups. Most secondary PROMs showed no significant differences up to 2 years postoperatively, except the BMAC group achieved higher MCID for KOOS Sport and KOOS Symptoms at 1 year. Individuals with meniscal tear symptoms and mild OA may still benefit from arthroscopic debridement, with or without BMAC. Additional research is necessary to evaluate the clinical efficacy of BMAC in OA.

Lee et al. (2024) conducted a systematic review evaluating the efficacy and safety of autologous-cultured adipose-derived mesenchymal stem cells (ADMSCs) and stromal vascular fractions (SVFs) in treating KOA. By including a broad range of recent studies, it provides a comprehensive analysis of 31 studies involving 1,406 participants, with 19 studies and 958 individuals included in a meta-analysis. The review found significant pain reduction with ADMSCs starting at 3 months and with SVF therapy at 12 months. Both treatments showed substantial improvement in knee function at 12 months, with no severe adverse events linked to ADMSC therapy. These findings suggest that ADMSCs may offer faster pain relief, while both ADMSCs and SVF provide long-term benefits in joint function and cartilage regeneration. This review identifies several limitations, such as significant heterogeneity in study designs, injection doses, and outcome measures, which complicate the generalization of findings. The lack of standardized dosing criteria and variability further hinders effective comparison, highlighting the necessity for dose standardization to optimize ADMSC application in clinical settings. Additionally, varied control interventions may have contributed to inconsistencies in reported outcomes. In conclusion, autologous-cultured ADMSCs and SVFs can significantly enhance knee function, alleviate pain, and promote cartilage repair in knee OA individuals. While ADMSCs may offer quicker pain relief, both treatments display strong long-term efficacy in functional improvement and cartilage regeneration. The positive safety profile of ADMSCs supports the use in a clinical setting. Additional research with larger RCTs are needed to refine application methods, clarify dose–response relationships, and establish standardized protocols to fully use the therapeutic potential of both therapies in treating knee OA. (Kim 2020 discussed below in evidence, was included in this systematic review).

Hayes published a health technology assessment evaluating the use of adipose-derived stem cell therapy for KOA. The focus of the Health Technology Assessment is evaluation of the effectiveness and safety of adipose-derived stem cells (ADSC) compared with placebo or other minimally invasive therapies for KOA. An overall low-quality body of evidence suggests that relative to placebo and hyaluronic acid injection, ADSC treatment of KOA is reasonably safe and can provide limited improvements in knee pain and function; however, these improvements were not usually clinically significant and may have been relatively short lived since only 1 study involved more than 1 year of follow-up. Benefits of ADSC therapy were somewhat inconsistent across the studies, which may reflect the low statistical power of smaller studies or the variable effectiveness of divergent protocols for ADSC treatment. Additional randomized controlled trials with long term follow-up are needed to identify the optimal ADSC treatment protocol and determine whether that protocol provides long-term clinically significant relief of KOA. (Hayes, 2024).

Kim et al. (2022) published the results of an RCT assessing intra-articular injection of ADMSC after medial open-wedge high tibial osteotomy (MOWHTO) compared to medial open-wedge high tibial osteotomy (MOWHTO). The primary outcome was the serial changes of cartilage defect on periodic magnetic resonance imaging (MRI) evaluation using valid measurements until postoperative 24 months. Secondary outcomes included two stage arthroscopic evaluation for macroscopic articular cartilage status and postoperative functional improvements reported by the participants. At 24 month follow up both serial MRIs and arthroscopic evaluation demonstrated that the experimental group had significantly better cartilage regeneration compared with the high-tibial osteotomy group. The authors concluded that injection of adipose-derived mesenchymal stem cells is a potential disease modifying treatment for the treatment of KOA without any safety issue. Limitations include small sample population and short-term outcomes.

In a systematic review of 14 RCTs to evaluate the use of autologous mesenchymal stem cell (MSC) therapy for the treatment of KOA, Wiggers et al (2021) concluded that there was a positive effect with the use of MSC when compared to control treatments on patient-reported outcome measures and disease severity although the certainty of the evidence was low to very low. The study populations ranged between 10-40 individuals per trial with a total of 408 individuals who were treated with a variety of stem cells with another 300 individuals allocated to a control arm. The included studies were done to evaluate the efficacy of MSC compared with other treatments, observation, or no treatment on patient-reported outcome measures (PROMs) on knee function, knee pain and knee-related quality of life at 1 year follow up. Bone marrow was the most frequently used source of stem cells (8 out of 14 studies; 57%), while adipose tissue was used in 5 trials (36%) and one trial (7%) used MSCs from activated peripheral blood. Most trials (n = 11; 79%) performed 1 MSC injection, 2 trials (14%) did 2 MSC injections, and 1 trial (7%) did 3 MSC injections. In four trials (29%), MSC injections were given in addition to surgical interventions. Hyaluronic acid (HA) was given as concomitant therapy in three trials (21%) and platelet-rich plasma (PRP) injections were given in three trials (21%). The control interventions were HA injection in six of the trials (43%), PRP-injection in four of the trials (29%), saline-injection in three trials (21%), dexamethasone injection in one trial (7%) and conservative treatment/exercise in two trials (14%). They reported that

most outcomes were considered as high risk of bias (84%), with another 14% considered as some concerns and 2% as low risk. The sources of bias identified by the authors included the randomization procedures, the adherence to intervention, the measurement tools used to assess outcomes and the risk of bias in selection of the reporting results. The GRADE summary findings by the authors for all combinations of MSC therapy and control interventions in the included RCTs were evaluated on clinical outcome measures (14/14; 100%), pain score (10/14; 71%) and an MRI scoring system (6/14; 43%). They reported that the certainty of evidence for clinical outcome measures was considered low to very low and that the evidence was downgraded for risk of bias, inconsistency, and imprecisions. The authors indicated that there is a positive effect of autologous MSC therapy in KOA on clinical outcome measures (28/43; 65%) and radiological (MRI) outcome measures (5/6; 83%) with clinical outcome measures 1 year after MSC therapy showing improvement in 19/26 (73%) of cases. They noted that adverse events during the follow-up of the trials were mild, and no serious adverse events were reported in individuals treated with MSCs during a maximum follow-up of 4 years. Limitations of the systematic review included the inability of the authors to do a meta-analysis due to the high clinical heterogeneity among the trials, the inclusion of all grades of KOA, the heterogeneity of the interventions in the studies and the variety of sources for the stem cells from bone marrow, adipose tissue and activated peripheral blood. They recommend additional RCTs with long-term follow-up to address these areas.

Gong et al. (2021) systematically reviewed the evidence for the efficacy of mesenchymal stem cell (MSC) injections in improving OA-related structural outcomes. Ovid Medline and EMBASE were searched from their inceptions to April 2020 using MeSH terms and key words. Independent reviewers extracted data and assessed methodological quality. Qualitative evidence synthesis was performed due to the heterogeneity of interventions and outcome measures. Thirteen randomized controlled trials (phase I or II) were identified: 10 in OA populations and 3 in populations at risk of OA, with low (n = 9), moderate (n = 3), or high (n = 1) risk of bias. Seven studies used allogeneic MSCs (4 bone marrow, 1 umbilical cord, 1 placenta, 1 adipose tissue) and 6 studies used autologous MSCs (3 adipose tissue, 2 bone marrow, 1 peripheral blood). Among the 11 studies examining cartilage outcomes, 10 found a benefit of MSCs on cartilage volume, morphology, quality, regeneration, and repair, assessed by magnetic resonance imaging, arthroscopy, or histology. The evidence for subchondral bone was consistent in all 3 studies in populations at risk of OA, showing beneficial effects. The authors concluded that the systematic review of early-phase clinical trials demonstrated consistent evidence of a beneficial effect of intraarticular MSC injections on articular cartilage and subchondral bone. The authors indicated that due to the heterogeneity of MSCs, modest sample sizes, methodological limitations, and potential for publication bias, further work is needed before this therapy is recommended in the management of OA.

In a systematic review and meta-analysis of RCTs, Dai et al. (2021) evaluated the efficacy and safety of intra-articular mesenchymal stromal cells (MSCs) injections for KOA treatment. A systematic literature search in PubMed, Embase, Scopus, and the Cochrane Library through April 2020 to identify level I randomized controlled trials (RCTs) that evaluated the clinical efficacy of MSCs versus control treatments for knee OA. Outcomes were analyzed on an intention-to-treat basis with random-effects models. A total of 13 RCTs were included in the meta-analysis. Compared with placebo, there was no significant difference in visual analogue scale (VAS) for pain [mean difference (MD) 1.62, 95% confidence interval (CI -0.60 to 3.85)], WOMAC pain score (MD 1.88, 95% CI -0.21 to 3.98), WOMAC function score (MD -0.67, 95% CI -6.54 to 5.19), or WOMAC stiffness score (MD 0.64, 95% CI -0.86 to 2.14) for MSCs. Moreover, the smallest treatment effect of VAS for pain, WOMAC pain score, WOMAC function score, and WOMAC stiffness score did not exceed the minimum clinically important difference (MCID). Additionally, there was no significant difference in percentage of individuals crossing the MCID threshold between MSC and placebo groups for VAS for pain [relative risk (RR) 0.93, 95% CI 0.55 to 1.57] or WOMAC total score (RR 0.40, 95% CI 0.13 to 1.21). Compared with hyaluronic acid (HA), MSC injection was associated with significantly better improvement in VAS for pain (MD 2.00, 95% CI 0.94 to 3.07), WOMAC pain score (MD 4.58, 95% CI 0.49 to 8.67), WOMAC total score (MD 14.86, 95% CI 10.59 to 19.13), and WOMAC stiffness score (MD 1.85, 95% CI 0.02 to 3.69). However, the smallest treatment effect of VAS for pain, WOMAC pain score, WOMAC function score, and WOMAC stiffness score did not exceed the MCID. Moreover, there was no significant difference in percentage of individuals crossing the MCID threshold between MSC and HA groups for WOMAC total score (RR 0.57, 95% CI 0.21 to 1.55). The authors also found that MSCs did not increase adverse events compared with HA and placebo. The authors concluded that intra-articular MSC injection was not found to be superior to placebo in pain relief and functional improvement for individuals with symptomatic knee OA. According to the authors, additional direct testing, and combination trials of different types of cells, doses, and number of injections of MSCs are required to further enhance clinical decision making for individuals with symptomatic knee OA.

In a systematic review, Prodromos et al. (2020) evaluated autologous mesenchymal stem cell therapy as treatment of KOA. The authors conducted a PubMed search for human clinical studies using autologous mesenchymal stem cell injections (AMSCI) for the treatment of OA and a second search for placebo arms of injectate OA treatment. The review included 34 studies entered into three subgroups of studies: Group I included WOMAC and VAS score outcomes (n = 29), Group 2 included studies that measured outcomes using other than WOMAC or VAS scores (n = 5) and Group 3 included randomized trials using 1-3 injections of saline as a placebo arm (n = 18). All AMSCI cohorts showed improvement at

mean 15.3 months post-treatment. Mean WOMAC and VAS scores improved at 6-months and at final follow-up ($p < 0.0001$ for all). Scores > 2 years were also significant (WOMAC $p = 0.001$/VAS $p = 0.004$). Results exceeded the minimal clinically important difference (MCID) at each time point. AMSCI improvement also substantially exceeded the previously published 6-month placebo-treatment improvement. No dose-response relationship was seen. AMSCI cohorts showed continuing improvement ≥ 6 months and continued upward at one year. Placebo scores were already trending downward by 6 months. The authors concluded that AMSCI is a consistently significantly effective treatment for OA, and it should no longer be stated that data is insufficient to establish AMSCI efficacy for OA. According to the authors, given its excellent safety profile, AMSCI should be widely used for the treatment of OA. The limitations of this review are the limited number of cohorts available for analysis. The heterogeneity of the studies also limited the ability to compare treatment types.

In a multisite prospective double-blinded randomized placebo-controlled clinical trial, Garza et al. (2020) evaluated if participants receiving intra-articular stromal vascular fraction (SVF) would show greater improvement than patients receiving placebo injections. Adult patients with symptomatic knee OA were eligible. Thirty-nine participants were randomized to high-dose SVF, low-dose SVF, or placebo (1:1:1). SVF was obtained via liposuction, processed to create the cellular implant, and injected during the same clinical visit. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores and magnetic resonance images were obtained preoperatively and at 6 and 12 months after injection. The Wilcoxon rank sum nonparametric test was utilized to assess statistical significance, and the Hodges-Lehmann location shift was used to assess superiority. The median percentage change in WOMAC score at 6 months after injection for the high-dose, low-dose, and placebo groups was 83.9%, 51.5%, and 25.0%, respectively. The high- and low-dose groups had statistically significant changes in WOMAC scores when compared with the placebo group (high dose, $p = .04$; low dose, $p = .02$). The improvements were dose dependent. The median percentage change in WOMAC score from baseline to 1 year after injection for the high-dose, low-dose, and placebo groups was 89.5%, 68.2%, and 0%, respectively. The high- and low-dose groups displayed a greater percentage change at 12 months when compared with the placebo group (high dose, $p = .006$; low dose, $p = .009$). Magnetic resonance image review revealed no changes in cartilage thickness after treatment. No serious adverse events were reported. The authors concluded that intra-articular SVF injections can significantly decrease knee OA symptoms and pain for at least 12 months. The authors indicated that the efficacy and safety demonstrated in this placebo-controlled trial support its implementation as a treatment option for symptomatic knee OA. According to the authors, the trial had the following limitations: participants were unblinded after 6 months, potentially biasing the 1-year results. Additionally, there was considerable attrition in the control group at 1 year, which may have biased the results. Further research is needed to assess the efficacy of SVF treatment in participants with other comorbidities and long-term outcomes and delay or elimination of progression to total knee arthroplasty after SVF treatment should also be investigated.

An updated ECRI report for autologous mesenchymal stem cell (MSC) therapy for chronic knee or ankle pain from OA indicated that meta-analyses suggests that intra-articular autologous MSC infusions are safe and may reduce chronic pain in knee OA, but pain reduction varies across MSC therapies and pain etiologies; also, the effects are modest, and overall pain relief may not be clinically significant. According to ECRI, differences across studies in MSC dose, source, processing methods, number of injections and OA severity prevented them from drawing conclusions about comparative effectiveness. They also found data heterogeneity which led to uncertainty about MSC therapy's value compared with other nonsurgical treatments for chronic knee OA joint pain. ECRI recommended large, multicenter RCTs with standardized methods of MSC preparation, dose, and administration to determine how best to use MSC to treat joint OA. as well as additional studies to assess MSC therapies in specific patient groups and to compare MSCs with other pharmacologic or biologic therapies, such as hyaluronic acid, growth factors, and non-stem cells (ECRI, 2019; updated January 2022).

Hayes published an updated health technology assessment evaluating the use of autologous microfragmented adipose tissue (MFAT) injection for treatment of OA. The evidence base for the 2022 Hayes assessment included 4 observational small studies (n = 17, 17, 20 and 35) without experimentally designed non-MFAT comparison groups. The Lipogems System was the only device specifically noted in the clinical studies reviewed in this report. Hayes indicated that the overall quality of the body of evidence for MFAT for KOA remains very low. The primary limitation of the evidence is the lack of direct comparative evidence. According to Hayes, due to the limited comparative evidence, the evidence base does not sufficiently inform whether MFAT provides better, worse, or equivocal care as any other intervention or sham control (Hayes, 2020; Updated February 2022).

Hayes also updated their comparative effectiveness review of stem cell therapy for joint pain which involves injection of stem cells into the knee, hip, shoulder, or spinal disc to promote repair of defects in the joint cartilage or the gelatinous material within the spinal disc to reduce or eliminate joint pain. The 2021 updated review included six RCTs evaluating stem cell therapy for knee OA and found that they had conflicting results. The review indicated that there is low-quality evidence (due to inconsistency and individual study limitations) that suggests some benefits of stem cell therapy compared with alternative therapies for pain and other outcomes in 3 of 6 studies that evaluated autologous or allogeneic

bone marrow or peripheral blood stem cells for knee OA. There were no or unclear benefits of stem cell therapy in the remaining 3 studies and a lack of evidence on long-term outcomes. For stem cell therapy for spinal disc or hip disorders, knee cartilage defects and rotator cuff repair the evidence was low quality and did not support improved outcomes. The 2022 update indicated that based on the new evidence there was an unlikely change from the 2018 Hayes review findings (Hayes, 2018; Updated August 2021).

Peripheral Arterial Disease

Autologous intra-arterial or intra-muscular bone marrow cell transplantation for peripheral PAD and other occlusive conditions is an emerging technology. While the existing evidence to-date shows some potential benefit of autologous cellular therapy (ACT) for PAD, this evidence is from predominately small, uncontrolled, non-blind, nonrandomized studies. Furthermore, the data from available RCTs is somewhat contradictory. There are significant outstanding questions regarding optimal selection criteria for treatment candidates and cell types, methods of administration, and whether or not similar benefits can be derived with the treatment of lower and upper extremities. Further investigation in the form of well-done, large scale, RCTs are needed to answer these questions and before definitive conclusions can be made regarding the safety and efficacy of this treatment.

In 2022 Moazzami et al. published an updated Cochrane review evaluating local intramuscular transplantation of autologous mononuclear cells for critical lower limb ischemia (CLI) that was initially published in 2011. Four randomized controlled trials (RCTs), with a combined total of 176 individuals, met the inclusion criteria. Participants were randomized to receive either intramuscular cell implantation of bone marrow mononuclear cells (BMMNCs) or control. The review was unable to draw conclusions to support the use of local intramuscular transplantation of BMMNC for improving clinical outcomes in people with CLI due to the very low- to low-certainty evidence and limited data. Evidence from larger RCTs are needed in order to provide adequate statistical power to assess the role of this procedure.

In a meta-analysis of RCTs on the therapeutic efficacy and safety of ACT for atherosclerosis obliterans (ASO), Pu et al (2022) reviewed 12 RCTs including the Lindeman, et al. 2018 study that was previously included in this policy. The studies included 630 individuals from Europe, Asia, and North America with an age range of 58.2 to 75 years and Rutherford classification scores of 1 to 6. Stem cells were derived from bone marrow and peripheral blood after granulocyte colony stimulating factor (G-CSF) stimulation with individuals in one study receiving ACT repeatedly while individuals in the other 11 studies received cell products only once. Follow-up ranged from one month up to 12 months. The authors used the Cochrane Collaboration tool to measure the risk of bias for each study and found that most studies were considered to be at low risk of bias in random sequence generation with incomplete outcome data while several studies did not mention the details of the allocation concealment. They also found that some studies lacked blinding for participants and providers, or outcome assessment and some studies had issues with selective reporting of partial outcomes at the endpoints. The authors determined that ACT therapy may provide benefit for some individuals in limb salvage, limb blood perfusion and rest pain alleviation. The RCTs they reviewed included intervention groups who received autologous cell implantation, and control groups who received placebo administration of substances such as normal saline, diluted autologous peripheral blood or a matrix of cell products, or standard care that consisted of risk factor management, exercise therapy and/or pharmacotherapy. The results of their analysis showed that ACT significantly improved total amputation, major amputation, ankle-brachial index, transcutaneous oxygen tension, and rest pain scores compared with placebo or standard care while ACT was not superior to placebo or standard care in all-cause death and ulcer size. The authors noted that their analysis was limited by the number of included studies and individuals, inclusion of some studies that were deemed to be relatively low quality, the number of studies included in subgroup analyses were too small and the inherent heterogeneity of the included trials due to the diversity of source and dosage of the cell products, route of administration, follow up duration, treatments for the control groups, and the broad spectrum of severity of limb ischemia. They recommend larger RCTs with long-term follow-up to confirm the efficacy and safety of ACT for the treatment of ASO.

Sharma et al. (2021) evaluated the safety and efficacy of angiogenesis induced by intraarterial autologous bone marrow-derived stem cell (BMSC) injection in individuals with severe PAD. Eighty-one individuals with severe PAD (77 men), including 56 with critical limb ischemia (CLI) and 25 with severe claudication, were randomized to receive sham injection (group A) or intraarterial BMSC injection at the site of occlusion (group B). Primary endpoints included improvement in ankle-brachial index (ABI) of > 0.1 and transcutaneous pressure of oxygen (TcPO2) of > 15% at mid- and lower foot at 6 mo. Secondary endpoints included relief from rest pain, > 30% reduction in ulcer size, and reduction in major amputation in individuals with CLI and > 50% improvement in pain-free walking distance in individuals with severe claudication. Technical success was achieved in all individuals, without complications. At 6 months, group B showed more improvements in ABI of > 0.1 [35 of 41 (85.37%) vs 13 of 40 (32.50%); p < .0001] and TcPO2 of > 15% at the midfoot [35 of 41 (85.37%) vs 17 of 40 (42.50%); p = .0001] and lower foot [37 of 41 (90.24%) vs 19 of 40 (47.50%); p < .0001]. No individuals with CLI underwent major amputation in group B, compared with 4 in group A (p = .0390). No significant difference was observed in relief from rest pain or > 30% reduction in ulcer size among individuals with CLI or in > 50%

improvement in pain-free walking distance among individuals with severe claudication. The authors concluded that intraarterial administration of autologous BMSCs results in significantly greater improvement in hemodynamic parameters such as ABI and TcPO2 in individuals with severe PAD. Issues related to inadequate numbers and function of progenitor cells in elderly individuals and individuals with comorbidities and the occurrence of cytokine and angiogenic factors need to be addressed. The authors indicated that large-scale RCTs addressing these issues would help in the institution of an evidence-based stem cell therapy protocol in the management of individuals with severe PAD.

In a systematic review and meta-analysis, Gao et al. (2019) evaluated the efficacy and safety of autologous implantation of stem cells in individuals with PAD, compared with active controls and placebo. RCTs of autologous implantation of stem cells compared with placebo and control for PAD were included. Electronic medical databases including MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), the Chinese Biomedical Literature Database, China National Knowledge Infrastructure (CNKI), and ClinicalTrials.gov were searched from initial period to September 2018. Independently, two reviewers screened citations, extracted data, and assessed the risk of bias according to the criteria of the Cochrane handbook. The quality of evidence was evaluated by GRADE evidence profile. The primary outcomes consisted of amputation rate, major amputation rate, ulcer healing rate, and side effects. The second outcome included ankle-brachial index (ABI), transcutaneous oxygen tension (TcO2), pain-free walking distance (PFWD), and rest pain score. Statistical analysis was conducted via RevMan 5.3 and Stata 12.0. According to the twenty-seven RCTs, 1186 individuals and 1280 extremities were included, and the majority of studies showed a high risk of bias. Meta-analysis indicated that autologous stem cell therapy was more effective than conventional therapy on the healing rate of ulcers [OR = 4.31 (2.94, 6.30)]. There was also significant improvement in ABI [MD = 0.13 (0.10, 0.17)], TcO2 [MD = 0.13 (0.10, 0.17)], and PFWD [MD = 178.25 (128.18, 228.31)] while significant reduction was showed in amputation rate [OR = 0.50 (0.36, 0.69)] and rest pain scores [MD = -1.61 (-2.01, -1.21)]. But the result presented no significant improvement in major limb salvage [0.66 (0.42, 1.03)]. Besides, stem cell therapy could reduce the amputation rate [OR = 0.50 (0.06, 0.45)] and improve the ulcer healing rate [OR = 4.34 (2.96, 6.38)] in DM subgroup. Eight trials reported the side effects of autologous stem cell therapy, and no serious side effects related to stem cells were reported. GRADE evidence profile showed all the quality evidence of outcomes were low. Based on the review, the authors concluded that autologous stem cell therapy may have a positive effect on "no-option" individuals with PAD but presented no significant improvement in major limb salvage. However, the evidence is insufficient to prove the results due to high risk of bias and low-quality evidence of outcomes. According to the authors, further research of larger, randomized, double-blind, placebo-controlled, and multicenter trials are needed.

Rigato et al. (2017) conducted a systematic review of the literature and a meta-analysis of studies evaluating safety and efficacy of autologous bone marrow cell therapy for intractable peripheral arterial disease/critical limb ischemia. They assessed 19 randomized controlled trials (837 individuals), 7 nonrandomized trials (338 individuals), and 41 noncontrolled studies (1177 individuals). The cell therapy reduced the risk of amputation by 37%, improved amputation-free survival by 18%, and improved wound healing by 59%. Cellular therapy increased ankle brachial index increased transcutaneous oxygen tension, and reduced rest pain. The authors concluded that cellular therapy was found to be safe, being associated with mild and mostly transient adverse events related to local implantation/infusion. They also observed that higher quality studies were less likely to demonstrate an impact of the intervention, suggesting that “low-quality studies may have been biased in favor of cell therapy.” The authors therefore recommend high-quality RCTs to assess the benefit of the intervention. Some limitations of the review were low-moderate quality, high heterogeneity, and publication bias, and possible lack of statistical power.

Regeneration and/or Repair of Musculoskeletal Tissue

The use of autologous cell-based therapy or stem cell therapy to regenerate or repair musculoskeletal tissue including tendons and ligaments is an emerging field. There is a limited number of studies evaluating the efficacy of cell therapy for musculoskeletal tissue healing. Randomized controlled trials are needed to confirm the effectiveness of this therapy and the advantages of this therapy compared to other treatment options.

Centeno et al. (2024) performed a randomized controlled crossover trial comparing ultrasound-guided, percutaneous bone marrow concentrate (BMC) treatment (including autologous BMC and platelet products) with a home exercise therapy program for managing non-retracted supraspinatus tears. The primary objective was to compare patient-reported outcome measures (PROMs) over a short-term period of 3 months, hypothesizing that those receiving autologous orthobiologics would report significantly improved outcomes, sustained through the 2-year follow-up. Fifty-one patients were enrolled and randomly assigned to either the BMC treatment group (n = 34) or the exercise therapy group (n = 17). After three months, the BMC treatment group showed significantly greater improvements in median ΔDASH, ΔNPS, and SANE scores compared to the exercise therapy group (-11.7 vs -3.8, p = 0.01; -2.0 vs 0.5, p = 0.004; and 50.0 vs 0.0, p < 0.001, respectively). Patient-reported outcomes continued to improve throughout the study's two-year follow-up period without any serious adverse events. Among patients with both pre- and post-treatment MRIs, a majority (73%) demonstrated evidence of healing following BMC treatment. The study has several limitations, including a gender

discrepancy with more males enrolled, and the use of a self-directed home exercise program, which may not reflect outcomes from supervised rehabilitation. The control group design, using exercise therapy instead of a sham comparator, could affect results. Compliance might be improved with an exercise diary or formal supervision. Less rigorous post-BMC rehab protocols might impact outcomes. The combination of BMC, PRP, and PL used in the study may not represent results from BMC alone, and one patient required a second BMC treatment due to unknown reasons. Also, some of the data was missing. In conclusion, the study suggests that non-surgical treatments, like BMC with platelet injections, offer a promising alternative for treating rotator cuff tears. Additional RCTs are necessary to support these findings. Also, exploring other technological advancements in rotator cuff rehabilitation is also recommended.

In a systematic review of 22 studies evaluating the use of cell-based therapy for the treatment of rotator cuff and epicondylar injuries, Baryeh et al. (2021) found there were mixed results with regards to clinical outcomes with some studies showing no significant difference between treatment and control groups. Of the 22 studies included, 16 evaluated cell therapy for rotator cuff pathology and the other 6 evaluated cell therapy for treatment of epicondylitis. There were 3 RCTs, 7 case series, 2 case-controlled studies, 7 cohort studies and 3 case reports included in their review. Three of these studies were found to have level 1 evidence, 3 had level 2 evidence and the remaining 16 had levels of evidence of 3 or below. Of the 16 studies involving rotator cuff injury, seven included cell therapy as an augment to repair surgery while 9 evaluated the use of intra-articular or intra-tendinous injections. The 6 studies pertaining to elbow epicondylitis consisted of one that used cell-based therapy to augment surgical treatment and the remaining 5 reported results following intra-tendinous injections of cell-based preparations into the lateral epicondyle. Of the studies that reported complications, only one complication was noted. The authors concluded that, within the limitations of their review, tenocytes showed the most promise in the management of epicondylar tendinopathy in that both clinical and imaging scores showed improvement that were maintained at up to 5-year follow-up. In the management of rotator cuff injury, BMC showed the most promising results when used in isolation or as an adjunct to surgical repair with improvements in functional scores and fewer complications. They also stated that, although there are many promising findings reported in the included studies, their review was limited by a lack of standardization methods, culture and cell type which made firm conclusions difficult to draw. They also found it was not possible to do a meta-analysis of the data due to the heterogeneity among the studies. The authors recommend future RCTs to establish whether cell-based therapies truly result in improved patient outcomes with focus on standardized techniques, cell types and treatment protocols.

Kon et al. (2021) systematically review the available literature on the use of biologic products, such as mesenchymal stem cells, to treat partial ruptures or to enhance ligamentization after anterior cruciate ligament (ACL) reconstruction. The aim of the review was to assess the available literature on this topic, to (i) describe the current state of the art in available biologic techniques; (ii) clarify the outcomes of their application; and (iii) identify areas needing further investigation and possible future development. A systematic review of the literature on the use of biologically active agents [platelet-rich plasma (PRP) or mesenchymal stem cells (MSCs)] to enhance outcomes of ACL surgery was performed: 31 studies were included. Based on the ACL injury pattern, 6 papers investigated biologic agents in ACL partial tears whereas 25 papers in ACL reconstruction. Sixteen of twenty-five studies dealing with ACL reconstruction were randomized controlled trials, whereas only case series are available for partial ACL tears. The authors concluded that current evidence is still lacking sound data to support the use of biological agents.

van den Boom et al. (2020) systematically reviewed the efficacy of stem cell therapy for individuals with tendon disorders. MEDLINE/PubMed, EMBASE, CINAHL, CENTRAL, PEDro, and SPORTDiscus; trial registers; and gray literature were searched to identify randomized controlled trials (RCTs) and non-RCTs, cohort studies, and case series with 5 or more cases. Studies investigating any type of stem cell therapy for individuals with tendon disorders were eligible if they included patient-reported outcome measures or assessed tendon healing. Risk of bias was assessed through use of the Cochrane risk of bias tools. Eight trials (289 individuals) were included in the review. All trials had moderate to high risk of bias (level 3 or 4 evidence). In Achilles tendon disorders, 1 trial found that allogenic-derived stem cells led to a faster recovery compared with platelet-rich plasma. Another study found no retears after bone marrow-derived stem cell therapy was used in addition to surgical treatment. There were 4 trials that studied the efficacy of bone marrow-derived stem cell therapy for rotator cuff tears. The controlled trials reported superior patient-reported outcomes and better tendon healing. A further 2 case series found that stem cell therapy improved patient-reported outcomes in individuals with patellar tendinopathy and elbow tendinopathy. The authors concluded that Level 3 evidence is available to support the efficacy of stem cell therapy for tendon disorders. According to the authors, the available studies are at considerable risk of bias and evidence-based recommendations for the use of stem cell therapy for tendon disorders in clinical practice cannot be made at this time. Stem cell injections should not be used in clinical practice given the lack of knowledge about potentially serious adverse effects.

Scleroderma

The available evidence published in the peer-reviewed literature is limited to case series without comparison groups and therefore inadequate to make conclusions about the safety, efficacy, and utilization of autologous adipose-derived

regenerative cellular (ADRC) therapy to treat scleroderma of the fingers and hands. Larger, randomized comparative studies are needed to assess health outcomes using this therapy.

Almadori et al. (2024) conducted a systematic review to evaluate the current literature on fat grafting and other ASC-based therapies for treating facial systemic sclerosis. The aim of the review was to assess their efficacy and safety, as well as to explore the current practices for optimizing treatment. There were 12 studies that matched the inclusion criteria, 174 individuals were treated. Of these, 87.3% (n = 152) were considered to have improved. The complications, graded with the Clavien-Dindo grading system, were Grade 1 (no treatment required) or Grade 2 (antibiotic required). Individuals received a mean (standard deviation) of 2.5 (3.68) (median, 1.35; range, 1-14) lipotransfer procedures. Overall, an average volume of 14.60 (6.24) mL was injected in the facial area (median, 16 mL; range, 3-27 mL). The average interval between procedures was 5.30 [2.04] months (median, 6 months; range 3-6.91 months). At the time of inclusion, individuals were diagnosed with scleroderma disease on average after 14.7 (7.35) years. There were limitations to these studies, including small sample sizes, inconsistent outcome assessments and short follow-up periods. The long-term strength of the effects remains uncertain, and the optimal number of treatments needed to establish a clear evidence-based protocol has yet to be determined. The current evidence is low, and the risk of bias is high. RCTs are necessary to eliminate the potential placebo effect, which is frequently higher in cohort studies that mainly depend on patient-reported outcome measures for evaluation.

Khanna et al. (2023) conducted the Scleroderma Treatment with Celution Processed Adipose Derived Regenerative Cells (STAR) randomized, double-blind, placebo-controlled clinical trial. A total of 105 individuals were screened, and 88 individuals were enrolled in the trial. Forty individuals were randomized to receive placebo [19 individuals with diffuse cutaneous SSc (dcSSc)] and 21 with limited cutaneous SSc (lcSSc), and 48 individuals were randomized to receive ADRCs (32 individuals with dcSSc and 16 with lcSSc). Change in hand function according to CHFS score was numerically higher for the ADRC group compared to the placebo group but did not achieve statistical significance (mean ±SD improvement in the CHFS score at 48 weeks 11.0 ±12.5 versus 8.9 ±10.5; p = 0.299). For individuals with dcSSc, the between-group difference in the CHFS at 48 weeks was 6.3 points (nominal p = 0.069). For the secondary end point, the dcSSc group exhibited a between-group difference of 0.17 points in the HAQ DI (nominal p = 0.044) at 48 weeks. Of the ADRC-treated individuals with dcSSc, 52% reported improvement greater than the minimum clinically important difference for both CHFS and HAQ DI compared to 16% in the placebo group (nominal p = 0.016). Small-volume adipose tissue harvest and ADRC treatment were well tolerated. The study confirmed the feasibility and tolerability of small-volume adipose tissue harvest and cell injection into each finger for SSc individuals with hand dysfunction. While the ADRC group showed greater improvement in CHFS scores, the differences were not statistically significant for the full cohort or the dcSSc and lcSSc subgroups. The most notable differences were in the dcSSc group. Some endpoints exceeded established MCIDs, indicating promising but not complete results. The STAR trial data will help design and select endpoints for a more robust follow-up trial.

Escobar-Soto et al. (2021) evaluated the efficacy and safety of human MSC (hMSC) in individuals with systemic sclerosis (SSc) through a systematic literature review (SLR). A systematic search was done of the literature in the following databases: Medline/OVID, Lilacs, Embase, and Cochrane/OVID. Exclusion criteria included animal models, autologous/allogenic hematopoietic stem cell transplants, narrative reviews, and letters to the editor. The level of evidence and the quality rating were rated [Joanna Briggs Institute (JBI) lists]. A total of 508 articles were identified, of which 11 were included (8 case series and 3 case reports). The 11 articles included 101 individuals (85 female, age range 18-75 years). The level of evidence was mostly 4 (JBI); the quality of evidence was met (≥ 50% of JBI items). Synthesis without meta-analysis (SWiM) showed that vascular skin involvement (digital ulcers, necrosis, and gangrene) and associated pain were the predominant outcomes, while improvements were found in almost all cases. One patient died in the first month, and the frequency of complications was low. Expanded hMSCs were used in 24 individuals and other cell sources in the remaining individuals. The authors concluded that there is too little reported data to reach definite conclusions about the use of hMSC in SSc. Further studies with better epidemiological designs are needed to evaluate the benefit of hMSCs in SSc individuals. Authors Del Papa et al. (2015) which were previously cited in this policy, are included in the Escobar-Soto et al. (2021) systematic review.

Daumas et al. (2017) reported on open-label phase-1 clinical trial 6- and 12-month outcomes from the same cohort of individuals in the below trial conducted by Guillaume-Jugnot et al., 2016. In this case series, twelve females who were initially enrolled in the clinical trial were assessed during a scheduled medical care, which took place between 22 and 30 months after ADSVF treatment. Multiple patient-reported outcomes showed sustained improvement, in comparison with the assessment performed just before surgery: 62.5% in the Cochin Hand Function Scale, 51.1% in the Scleroderma Health Assessment Questionnaire, 33.1% in hand pain, and 88.3% in the Raynaud Condition Score. A decrease in the number of digital ulcers number was noted. Mobility, strength, and fibrosis of the hand also showed improvement. The authors concluded that despite the limits of an open label study, the results are in favor of the long-term safety of the

adipose-derived stromal vascular fraction injection. The lack of a control group limits the conclusions that can be drawn from this study.

Clinical Practice Guidelines

American Academy of Orthopaedic Surgeons (AAOS)

The American Academy of Orthopaedic Surgeons (AAOS) does not take a position for or against the use of autologous cellular therapy for orthopedic applications, however within a position statement regarding the use of emerging biologic therapies the AAOS states the following: “surgeons must be aware of the scientific basis for the different treatment options available to their individuals, including the benefits and risks. Biologic therapies vary widely with regards to the requirements for evidence of safety and effectiveness needed for clearance by regulatory bodies, including the US Food and Drug Administration (FDA). Not all biologic products require extensive FDA regulation, and in some cases, the FDA has primarily focused on safety concerns and has ceded responsibility for determining the efficacy of these products to the clinician” (AAOS, 2017, Updated September 2020).

A 2020 guideline from the AAOS on the management of glenohumeral joint osteoarthritis states that injectable biologics such as stem cells cannot be recommended in the treatment glenohumeral joint OA. There was consensus from the panel that better standardization and high-quality evidence from clinical trials is needed to provide definitive evidence on the efficacy of biologics in glenohumeral OA (AAOS, 2020).

American College of Cardiology (ACC)/American Heart Association (AHA)

The most recent recommendations from the American Heart Association and the American College of Cardiology on the management of individuals with lower extremity peripheral artery disease do not have any reference to the use of stem cell therapy for PVD (Bailey, 2019; Gerhard-Herman, 2017).

Department of Veterans Affairs (VA)/Department of Defense (DoD)

The VA/DoD’s evidence-based clinical practice guideline on the non-surgical management of hip and knee osteoarthritis (2020) does not recommend the use of stem cell injections (e.g., mesenchymal, adipose-derived, and bone marrow-derived) for the treatment of osteoarthritis (OA) of the hip or knee. The guideline indicates that there is limited research on stem cell therapy for the treatment of knee and hip OA. While there appear to be some promising areas, much is still unknown. Researchers will need to further evaluate efficacy over the current standard of care and the comparative efficacy of the various stem cell derivations. Analysis of interval timing of injections, concentrations, and type of cells utilized, as well as post-procedure rehabilitation protocols, also need investigation (VA/DoD clinical practice guideline for the non-surgical management of hip and knee osteoarthritis, 2020).

European Society of Cardiology (ESC)

The ESC published a guideline that addresses diagnosis and management of individuals with peripheral arterial diseases. The guideline indicates that angiogenic gene and stem cell therapy are still being investigated with insufficient evidence in favor of these treatments. The guideline therefore recommends that stem cell/gene therapy is not indicated for individuals with chronic limb-threatening ischemia (Aboyans et al., 2018).

International Society of Stem Cell Research (ISSCR)

The International Society of Stem Cell Research (ISSCR) published information regarding stem cell types and uses and asserts there is little evidence they are beneficial. MSC therapy remains in early experimental stages (International Society for Stem Cell Research, 2024).

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.

The use of concentrated, autologous mesenchymal stem cells (MSCs) do not require FDA approval. The FDA does regulate human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research.

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Policy History/Revision Information

Date	Summary of Changes
06/01/2026	**Applicable Codes** • Added CPT codes 0999T, 1000T, and 1001T • Added notation to indicate CPT codes 0263T, 0264T, 0265T, 0489T, 0490T, 0565T, 0566T, 0717T, 0718T, 0999T, 1000T, and 1001T are not on the State of Idaho Medicaid Fee Schedule and therefore may not be covered by the State of Idaho Medicaid Program; for additional information on non-covered and excluded services, refer to the *Idaho Medicaid Provider Handbook, General Information, General Information and Requirements for Providers: Non-Covered and Excluded Services* **Supporting Information** • Updated *References* section to reflect the most current information • Archived previous policy version CS176ID.B

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state, or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state, or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state, or contractual requirements for benefit plan coverage govern. Before using this policy, check the federal, state, or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.