Autologous Cellular Therapy

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➲ Instructions for Use

Table of Contents **Page**

Application 1
Coverage Rationale 1
Definitions 1
Applicable Codes 2
Description of Services 2
Clinical Evidence 3
U.S. Food and Drug Administration 13
References 13
Policy History/Revision Information 15
Instructions for Use 15

Related Commercial/Individual Exchange Policies

- Prolotherapy and Platelet Rich Plasma Therapies
- Spinal Fusion and Bone Healing Enhancement Products

Community Plan Policy

- Autologous Cellular Therapy

Application

UnitedHealthcare Commercial

This Medical Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit 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: Mesenchymal adult cells isolated from adipose tissue that can expand in vitro in an undifferentiated state and that 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 a targeted lesion in 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 production of artificial organs (Baryeh et al., 2021).

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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.

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
1095T	Harvesting and processing of autologous bone marrow aspirate concentrate (BMAC), with application onto scaffold or injection into anatomical recipient site (e.g., subchondral bone, joint space, chondral lesion), including imaging guidance, when performed, for therapeutic musculoskeletal treatment, excluding spinal procedures

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Description of Services

Over the past few decades, since the bioengineering revolution, Autologous Cellular Therapy 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

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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 transplant is the only stem cell therapy that is 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 have 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 that are needed for repair and regeneration, which could possibly lead to improvement in hand dysfunction.

ADRC 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 for 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. 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 peripheral arterial disease.

Clinical Evidence

The body of evidence in the published, peer-reviewed scientific literature that evaluated autologous cellular therapy (ACT) is mainly in the form of preliminary animal studies, case reports, case series, and a number of systematic reviews/meta-analyses 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. To assess the safety and efficacy of orthopedic, vascular, and rheumatologic applications of ACT, high-quality RCTs are required that compare patient-centered health outcomes between these and established therapeutic approaches. Additionally, RCTs that evaluate long-term outcomes are needed to firmly establish the safety and efficacy of ACTs.

Knee Osteoarthritis

The use of autologous adipose-derived regenerative cellular (ADRC) 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 in individuals with osteoarthritis (OA). Although some conclusions support improvement in pain and function in some individuals, limitations such as the heterogeneity of inclusion and exclusion criteria, lack of controls, type of cellular therapies that have been applied in different stages of OA, use of various quantities of these therapies, and lack of long-term outcomes prohibit strong, evidence-based conclusions regarding clinical safety and efficacy.

Kim et al. (2026) conducted a retrospective cohort study and reviewed the medical records of 151 consecutive patients with Kellgren-Lawrence grade II to IV KOA who were treated with intra-articular autologous adipose-derived stromal vascular fraction (SVF) injection and followed up for 1 year. After five patients were excluded due to dropout or loss to follow-up, 146 patients (217 knees) were analyzed, comprising 50 men and 96 women, with a mean age of 64.3 years and mean body mass index of 26.4 kg/m^2; inclusion required symptomatic KOA despite at least 3 months of nonsteroidal anti-inflammatory drug therapy. Each knee received a mean dose of 7.4×10^7 total SVF cells, including approximately 7.0×10^6 stromal cells, administered by a standardized intra-articular technique; pain was assessed using the visual analog scale (VAS) with Wilcoxon signed-rank and Spearman rank-order tests applied. The mean VAS score improved significantly from 6.5 ±1.2 at baseline to 3.1 ±1.6 at the final follow-up ($p < 0.01$), with perceived pain improvement occurring at a mean of 18.9 ±14.5 days after injection; higher SVF cell numbers were significantly correlated with greater pain improvement and lower final VAS scores (Spearman $p = -0.262$ and 0.370; both $p < 0.001$), while radiographic severity showed no significant correlation with pain outcomes. Radiographic Kellgren-Lawrence grades did not change significantly over 1 year ($p = 0.096$), and no clinically significant adverse events were observed; the prespecified secondary end points included radiographic severity and time to symptom improvement. The authors concluded that intra-articular SVF injection produced rapid and clinically meaningful pain relief within approximately 3 weeks, with higher SVF cell numbers associated with greater pain improvement and radiographic severity not significantly influencing outcomes;

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this supports high-dose SVF therapy as a broadly applicable treatment option for KOA. Key limitations include narrowly defined inclusion criteria that were restricted to KOA with Kellgren-Lawrence grade II to IV and persistent unilateral pain or functional limitation despite prior nonsteroidal anti-inflammatory therapy. The use of the VAS rather than multidimensional measures such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score may have limited the breadth of symptom assessment, although it enabled consistent evaluation of early pain changes. The optimal SVF cell dose remains undefined, and radiographic assessment based on conventional grading may not capture subtle structural or biological joint changes.

Yanke et al. (2025) conducted an RCT to evaluate the effects of autologous bone marrow aspirate concentrate (BMAC) on the development and progression of OA in participants who were undergoing meniscectomy by comparing participant-reported outcomes, specifically International Knee Documentation Committee (IKDC) scores, between participants who received BMAC post meniscectomy and those who received a saline control injection. The study also compared physical examination, magnetic resonance imaging (MRI), radiographs, and synovial fluid analysis. There were 95 enrolled participants, with 83 (87.4%) included for the final analysis. No significant differences were found between the groups with regard to participant characteristics, intraoperative variables, concomitant procedures, preoperative patient-reported outcome measure (PROM) scores, or preoperative radiographic findings. At 1 year post operation, the BMAC group did not have significantly better IKDC scores ($p = 0.687$) or radiographic outcomes ($p > 0.05$ for all radiographic measures) compared with the control group. Secondary PROM scores also did not significantly differ between the groups ($p > 0.05$ for all PROMs). However, there were higher achievement rates of the minimal clinically important difference (MCID) for the Knee Injury and Osteoarthritis Outcome Score (KOOS) Sport (100.0% vs 80.0%, respectively; $p = 0.023$) and KOOS Symptoms (92.3% vs 68.0%, respectively; $p = 0.038$) at 1 year post operation in the BMAC group compared with the control group. All PROMs, excluding the Veterans RAND 12-Item Health Survey mental score, showed significant improvements compared with baseline at all postoperative time points in both the BMAC and control groups. The study's limitations include restrictive inclusion and exclusion criteria, which limit generalizability to broader populations, especially those outside the specified age range or with different comorbidities. Since this study was conducted at a single center, the findings may not apply to other health care 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; a sham incision at the anterior superior iliac spine was used in the control group. Lastly, the follow-up period may not have captured long-term outcomes, which is crucial for individuals post meniscectomy, 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 post operation, except the BMAC group achieved a 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 that evaluated the efficacy and safety of autologous-cultured adipose-derived mesenchymal stem cells (ADMSCs) and SVFs in treating KOA. By including a broad range of recent studies, it provided a comprehensive analysis of 31 studies that involved 1,406 individuals, 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 identified 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 hinder effective comparison, which highlights 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 individuals with KOA. 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 that includes larger RCTs is needed to refine application methods, clarify dose-response relationships, and establish standardized protocols to fully use the therapeutic potential of both therapies in treating KOA. (Kim et al., 2022, discussed below in the evidence, was included in this systematic review.)

Hayes published a Health Technology Assessment that evaluated the use of adipose-derived stem cell (ADSC) therapy for KOA. The focus of the Health Technology Assessment was the evaluation of the effectiveness and safety of ADSCs compared with those of 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 one study involved more than 1 year of follow-up. Benefits

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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 RCTs that include 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; updated 2026).

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

Wiggers et al. (2021) completed a systematic review of 14 RCTs to evaluate the use of autologous mesenchymal stem cell (MSC) therapy for the treatment of KOA and concluded that there was a positive effect with the use of MSC when compared with control treatments on PROMs and disease severity, although the certainty of the evidence was low to very low. The study populations ranged between 10 to 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 that of other treatments, observation, or no treatment on PROMs on knee function, knee pain, and knee-related quality of life at the 1-year follow-up. Bone marrow was the most frequently used source of stem cells (eight of 14 studies; 57%); adipose tissue was used in five trials (36%), and one trial (7%) used MSCs from activated peripheral blood. Most trials [n = 11 (79%)] performed one MSC injection, two trials (14%) did two MSC injections, and one trial (7%) did three MSC injections. In four trials (29%), MSC injections were given in addition to surgical interventions. Hyaluronic acid 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 hyaluronic acid 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 a high risk of bias (84%), with another 14% considered as some concerns and 2% as low risk. The sources of bias that were identified by the authors included the randomization procedures, adherence to the intervention, measurement tools used to assess outcomes, and risk of bias in selection of the reporting results. The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) summary findings by the authors for all combinations of MSC therapy and control interventions that were in the included RCTs were evaluated on clinical outcome measures [14 of 14 (100%)], pain score [10 of 14 (71%)], and an MRI scoring system [six of 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 of 43 (65%)] and radiological (MRI) outcome measures [five of six (83%)], with clinical outcome measures 1 year after MSC therapy showing improvement in 19 of 26 cases (73%). They noted that adverse events during the follow-up of the trials were mild, and no serious adverse events were reported in individuals who were treated with MSCs during a maximum follow-up of 4 years. Limitations of the systematic review include the inability of the authors to perform a meta-analysis due to the high clinical heterogeneity among the trials, inclusion of all grades of KOA, heterogeneity of the interventions in the studies, and variety of sources for the stem cells from bone marrow, adipose tissue, and activated peripheral blood. They recommended additional RCTs that include long-term follow-up to address these areas.

Gong et al. (2021) systematically reviewed the evidence for the efficacy of MSC injections in improving OA-related structural outcomes. Ovid MEDLINE and Embase were searched from their inceptions to April 2020 using MeSH (Medical Subject Headings) 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. Overall, 13 RCTs (phase 1 or 2) were identified: 10 in OA populations and three 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 (four bone marrow, one umbilical cord, one placenta, and one adipose tissue), and six studies used autologous MSCs (three adipose tissue, two bone marrow, and one peripheral blood). Among the 11 studies that examined cartilage outcomes, 10 found a benefit of MSCs on cartilage volume, morphology, quality, regeneration, and repair, which were assessed by MRI, arthroscopy, or histology. The evidence for subchondral bone was consistent in all three studies in populations that were 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 intra-articular 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.

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Dai et al. (2021) assessed a systematic review and meta-analysis of RCTs, which evaluated the efficacy and safety of intra-articular mesenchymal stromal cell injections for KOA treatment. A systematic literature search in PubMed, Embase, Scopus, and the Cochrane Library through April 2020 was performed to identify level I RCTs that evaluated the clinical efficacy of mesenchymal stromal cells vs that of control treatments for KOA. Outcomes were analyzed on an intention-to-treat basis with random-effects models. Overall, 13 RCTs were included in the meta-analysis. Compared with placebo, there was no significant difference in VAS for pain [mean difference (MD), 1.62; 95% 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 mesenchymal stromal cells. Moreover, the smallest treatment effect of VAS for pain, WOMAC pain score, WOMAC function score, and WOMAC stiffness score did not exceed the MCID. Additionally, there was no significant difference in the percentage of individuals crossing the MCID threshold between mesenchymal stromal cells and placebo groups for VAS for pain [relative risk (RR), 0.93; 95% CI, 0.55-1.57] or WOMAC total score (RR, 0.40; 95% CI, 0.13-1.21). Compared with hyaluronic acid, mesenchymal stromal cell injection was associated with significantly better improvement in VAS for pain (MD, 2.00; 95% CI, 0.94-3.07), WOMAC pain score (MD, 4.58; 95% CI, 0.49-8.67), WOMAC total score (MD, 14.86; 95% CI, 10.59-19.13), and WOMAC stiffness score (MD, 1.85; 95% CI, 0.02-3.69). 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 the percentage of individuals crossing the MCID threshold between the mesenchymal stromal cells and hyaluronic acid groups for WOMAC total score (RR, 0.57; 95% CI, 0.21-1.55). The authors also found that mesenchymal stromal cells did not increase adverse events compared with hyaluronic acid and placebo. The authors concluded that intra-articular mesenchymal stromal cell injection was not found to be superior to placebo in pain relief and functional improvement in individuals with symptomatic KOA. 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 KOA.

Prodromos et al. (2020) evaluated a systematic review related to autologous MSC therapy as a treatment for KOA. The authors conducted a PubMed search for human clinical studies that used autologous MSC injections (AMSCIs) for the treatment of OA and a second search for the placebo arms of injectate OA treatment. The review included 34 studies, which were entered into three subgroups of studies; group I included WOMAC and VAS score outcomes (n = 29), group 2 included studies that measured outcomes using variables other than WOMAC or VAS scores (n = 5), and group 3 included randomized trials that used one to three injections of saline as a placebo arm (n = 18). All AMSCI cohorts showed improvement at a mean of 15.3 months post treatment. Mean WOMAC and VAS scores improved at 6 months and at the final follow-up ($p < 0.0001$ for all). Scores > 2 years were also significant (WOMAC $p = 0.001$/VAS $p = 0.004$). The results exceeded the MCID at each time point. AMSCI improvement also substantially exceeded the previously published 6-month placebo treatment improvement. No dose-response relationship was seen. The AMSCI cohorts had continuing improvement ≥ 6 months and continued upward at 1 year. Placebo scores were already trending downward by 6 months. The authors concluded that AMSCI is a consistently significantly effective treatment for OA and that it should no longer be stated that data are 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 that were available for analysis. The heterogeneity of the studies also limited the ability to compare treatment types.

Garza et al. (2020) completed a multisite, prospective, double-blinded, randomized, placebo-controlled clinical trial, which evaluated if participants who were receiving intra-articular SVF would have greater improvement than participants who were receiving placebo injections. Adult participants with symptomatic KOA were eligible. Overall, 39 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. WOMAC scores and MRIs were obtained prior to the operation and at 6 and 12 months after injection. The Wilcoxon rank sum nonparametric test was used 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 in 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 compared with the placebo group (high dose, $p = 0.04$; low dose, $p = 0.02$). The improvements were dose dependent. The median percentage change in WOMAC score from baseline to 1 year after injection in the high-dose, low-dose, and placebo groups was 89.5%, 68.2%, and 0%, respectively. The high- and low-dose groups had a greater percentage change at 12 months compared with the placebo group (high dose, $p = 0.006$; low dose, $p = 0.009$). An MRI 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 KOA symptoms and pain for at least 12 months. The authors indicated that the efficacy and safety that were demonstrated in this placebo-controlled trial support its implementation as a treatment option for symptomatic KOA. According to the authors, the trial had limitations, including that participants were unblinded after 6 months, which potentially biased 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

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assess the (1) efficacy of SVF treatment in individuals with other comorbidities, (2) long-term outcomes, and (3) delay or elimination of progression to total knee arthroplasty after SVF treatment.

An updated ECRI report on autologous MSC therapy for chronic knee or ankle pain from OA indicated that meta-analyses suggest that intra-articular autologous MSC infusions are safe and may reduce chronic pain in KOA but that 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 that of other nonsurgical treatments for chronic KOA 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. ECRI also recommended additional studies to assess MSC therapies in specific groups of individuals and to compare MSCs with other pharmacological or biological therapies, such as hyaluronic acid, growth factors, and non-stem cells (ECRI, 2019; updated January 2022).

Hayes published an updated Health Technology Assessment that evaluated the use of autologous microfragmented adipose tissue (MFAT) injection for the treatment of OA. The evidence base for the 2020 Hayes assessment included four observational small studies (n = 17, 17, 20, and 35) without experimentally designed non-MFAT comparison groups. The Lipogems system was the only device that was 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 2024).

Peripheral Arterial Disease

Autologous intra-arterial or intramuscular bone marrow cell transplant for peripheral arterial disease (PAD) and other occlusive conditions is an emerging technology. While the existing evidence to date shows some potential benefit of ACT for PAD, this evidence is from predominately small, uncontrolled, nonblinded, nonrandomized studies. Furthermore, the data from available RCTs are 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 is needed to answer these questions before definitive conclusions can be made regarding the safety and efficacy of this treatment.

Oliveira Filho et al. (2025) conducted a phase 1/2, single-center, randomized clinical trial using a PROBE (Prospective Randomized Open Blinded End-Point) design to evaluate the safety and efficacy of autologous ADSC therapy for ulcers in participants with critical limb ischemia. Overall, 40 participants with advanced PAD and no option for revascularization were randomized 1:1 to receive either expanded autologous ADSCs applied via perilesional subcutaneous injections and biodressings or conventional hydrogel dressings. Eligible adults were aged 18 to 90 years and had Fontaine IV or Rutherford 5 to 6 critical limb ischemia, one to three ulcers between 1 and 20 cm^2, and no improvement after at least 3 weeks of conventional treatment; exclusions included pregnancy, active infection, necrosis, cancer, immunomodulator use, major amputation, or recent COVID-19. The primary efficacy outcomes were total ulcer epithelialization and limb salvage rate, defined as nonoccurrence of major amputation, with safety end points that included absence of major amputation, infection, gangrene, and death. Analyses were planned using an intention-to-treat approach, with t tests, Wilcoxon, chi-square, or Fisher exact tests at a 5% significance level. The prespecified secondary end points included limb perfusion improvement, quality of life [SF-36 (36-Item Short Form Survey Instrument) and EQ-5D], pain reduction (VAS), and laboratory and physiological parameters. The authors concluded that the study aims to develop an advanced cell therapy protocol to help prevent limb amputation and improve quality of life in individuals with PAD, which offers an alternative treatment for those with critical limb ischemia and arterial ulcers who have exhausted other options. There are limitations, including the inability to perform biopsies and track the administered stem cells. Another limitation is that although the study's strength lies in being an RCT for a disease stage with virtually no effective treatment, this context may limit generalizability. The methodology supports the evaluation of the safety and efficacy of cell therapy for PAD with critical ischemia and ulcers, but further confirmation is required.

Sojakova et al. (2025) conducted a longitudinal prospective study that analyzed 129 autologous stem cell treatments that were administered to 118 limbs in 107 participants with diabetes and no-option, chronic, limb-threatening ischemia during a 16-year period. Eligible participants were aged 18 to 90 years and had ulcers or gangrene, transcutaneous oxygen pressure below 30 mm Hg, or ischemic pain that lasted at least 2 weeks; participants were excluded for systemic or deep infections, severe edema, hematologic abnormalities, recent myocardial infarction or stroke, untreated retinopathy, malignancy, or inability to undergo anesthesia. Bone marrow (250 mL) was harvested, processed by either harvest or

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Gelofusine centrifugation, and injected intramuscularly into the calf on the same day. The primary end points were limb salvage (time without major amputation) and amputation-free survival (time without major amputation or death), which were analyzed using Cox proportional hazards regression. Major amputation occurred in 41 of 118 limbs (31.8%), mostly within the first year, and mortality reached 35.5% at 5 years. Immunosuppression [hazard ratio (HR), 2.48; 95% CI, 1.30-4.73; p = 0.006], clinical infection (HR, 3.21; 95% CI, 1.66-6.21; p < 0.001), higher Global Limb Anatomic Staging System femoropopliteal score (HR, 1.58; 95% CI, 1.31-1.90; p < 0.001), and higher WIfI (Wound, Ischemia, Foot Infection) score (HR, 1.69; 95% CI, 1.20-2.38; p = 0.003) were associated with poorer limb salvage, while direct oral anticoagulant use (HR, 0.16; 95% CI, 0.03-0.90; p = 0.038) was protective. For amputation-free survival, significant predictors included immunosuppression (HR, 2.32; 95% CI, 1.09-4.95; p = 0.030), lower transcutaneous pressure of oxygen ($TcPO_2$; HR, 1.03; 95% CI, 1.00-1.05; p = 0.026), higher WIfI composite score (HR, 1.25; 95% CI, 1.02-1.54; p = 0.033), chronic kidney disease (HR, 1.25; 95% CI, 1.08-1.43; p = 0.002), and hypoalbuminemia (HR, 0.93; 95% CI, 0.89-0.98; p = 0.002). The prespecified secondary end points included ulcer healing classifications [Wagner, TEXAS, WIfI, and SINBAD (Site, Ischemia, Neuropathy, Bacterial Infection, Depth)] and cell product parameters. The authors concluded that ACT was a prospective revascularization method for no-option, chronic, limb-threatening ischemia, with the best outcomes in participants without infection and femoropopliteal stenosis, and that the first year after therapy was critical for both clinical effect and amputation risk. The authors emphasized close follow-up and infection management and stated that therapy should be carefully considered in individuals with severe chronic kidney disease, hemodialysis, or immunosuppressive treatment. Key limitations include the absence of a control group, focus on ACT outcomes during a 16-year follow-up, and inclusion of dialysis and immunosuppressed participants who are often excluded from similar studies. Interpretation is further limited by variability among published studies on responder parameters, differences in cell types and methods, and the confirmed influence of chronic kidney disease and inflammatory state. Future placebo-controlled designs should minimize bias while ensuring individuals' safety through low-risk sham procedures, close monitoring, predefined stopping rules, and careful ethical oversight; consideration of allogeneic cells, optimal administration routes, and less invasive harvesting such as adipose-derived MSCs may also improve therapeutic outcomes.

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

Pu et al. (2022) reviewed a meta-analysis of 12 RCTs on the therapeutic efficacy and safety of ACT for atherosclerosis obliterans, which included 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 stimulation, with individuals in one study receiving ACT repeatedly and individuals in the other 11 studies receiving cell products only once. Follow-up ranged from 1 month up to 12 months. The authors used the Cochrane Collaboration's tool to measure the risk of bias of each study and found that most studies were considered to be at a 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 of individuals and providers or outcome assessment and that some studies had issues with selective reporting of partial outcomes at the end points. The authors determined that ACT therapy may provide benefit in some individuals regarding limb salvage, limb blood perfusion, and rest pain alleviation. The RCTs that they reviewed included intervention groups that received autologous cell implantation and control groups that 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 (ABI), 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 is limited by the number of included studies and individuals; inclusion of some studies that were deemed to be relatively low quality; number of studies included in subgroup analyses being too small; inherent heterogeneity of the included trials due to the diversity of source and dosage of the cell products, route of administration, follow-up duration, and treatments in the control groups; and broad spectrum of the severity of limb ischemia. They recommended larger RCTs that include long-term follow-up to confirm the efficacy and safety of ACT for the treatment of atherosclerosis obliterans.

Sharma et al. (2021) evaluated the safety and efficacy of angiogenesis induced by intra-arterial autologous bone marrow–derived stem cell (BMSC) injection in individuals with severe PAD. Overall, 81 individuals with severe PAD (77 men), including 56 with critical limb ischemia and 25 with severe claudication, were randomized to receive sham injection (group

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A) or intra-arterial BMSC injection at the site of occlusion (group B). The primary end points included improvement in the ABI of > 0.1 and $TcPO_2$ of > 15% at the mid- and lower foot at 6 months. The secondary end points included relief from rest pain, > 30% reduction in ulcer size, and reduction in major amputation in individuals with critical limb ischemia 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 had more improvements in the ABI of > 0.1 [35 of 41 (85.37%) vs 13 of 40 (32.50%); $p < 0.0001$] and $TcPO_2$ of > 15% at the midfoot [35 of 41 (85.37%) vs 17 of 40 (42.50%); $p = 0.0001$] and lower foot [37 of 41 (90.24%) vs 19 of 40 (47.50%); $p < 0.0001$]. No individuals with critical limb ischemia underwent major amputation in group B compared with four in group A ($p = 0.0390$). No significant difference was observed in relief from rest pain or > 30% reduction in ulcer size among individuals with critical limb ischemia or in > 50% improvement in pain-free walking distance among individuals with severe claudication. The authors concluded that intra-arterial administration of autologous BMSCs results in significantly greater improvement in hemodynamic parameters such as the ABI and $TcPO_2$ in individuals with severe PAD. Issues related to inadequate numbers and function of progenitor cells in older individuals and individuals with comorbidities and the occurrence of cytokine and angiogenic factors need to be addressed. The authors indicated that large-scale RCTs that address these issues would help in the institution of an evidence-based stem cell therapy protocol in the management of individuals with severe PAD.

Gao et al. (2019) completed a systematic review and meta-analysis that 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, CENTRAL (Cochrane Central Register of Controlled Trials), Chinese Biomedical Literature Database, CNKI (China National Knowledge Infrastructure), and ClinicalTrials.gov, were searched from the 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 the GRADE evidence profile. The primary outcomes consisted of amputation rate, major amputation rate, ulcer healing rate, and side effects. The second outcome included the ABI, transcutaneous oxygen tension, pain-free walking distance, and rest pain score. Statistical analysis was conducted via RevMan 5.3 and Stata 12.0. According to the 27 RCTs, 1,186 individuals and 1,280 extremities were included, and the majority of studies showed a high risk of bias. A meta-analysis indicated that autologous stem cell therapy was more effective than conventional therapy in the healing rate of ulcers [odds ratio (OR), 4.31 (2.94, 6.30)]. There was also significant improvement in the ABI [MD, 0.13 (0.10, 0.17)], transcutaneous oxygen tension [MD, 0.13 (0.10, 0.17)], and pain-free walking distance [MD, 178.25 (128.18, 228.31)], while a significant reduction was seen in amputation rate [OR, 0.50 (0.36, 0.69)] and rest pain scores [MD, -1.61 (-2.01, -1.21)]. However, the result presented no significant improvement in major limb salvage [0.66 (0.42, 1.03)]. Additionally, 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 the diabetes mellitus subgroup. Eight trials reported the side effects of autologous stem cell therapy, and no serious side effects related to stem cells were reported. The GRADE evidence profile showed that all the quality evidence of outcomes was low. Based on the review, the authors concluded that autologous stem cell therapy may have a positive effect in no-option individuals with PAD but that it presented no significant improvement in major limb salvage. However, the evidence is insufficient to prove the results due to a high risk of bias and low-quality evidence of outcomes. According to the authors, further research in larger, randomized, double-blinded, placebo-controlled, multicenter trials is needed.

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 that evaluate the efficacy of cell therapy for musculoskeletal tissue healing. RCTs are needed to confirm the effectiveness of this therapy and advantages of this therapy compared with those of other treatment options.

Dias et al. (2026) conducted a review that evaluated preclinical and emerging clinical evidence on MSC secretome derivatives, including conditioned media and extracellular vesicles, for tendon healing. Studies were selected based on relevance to tendon biology and regenerative mechanisms, encompassing animal models such as horse, rat, rabbit, and mouse with a tendon or ligament injury. Secretome sources included MSCs from amniotic membrane, adipose tissue, bone marrow, tendon stem cells, umbilical cord, and induced pluripotent stem cells, delivered via local injection or scaffold-based systems. The preclinical findings consistently showed improved tendon structure, collagen organization, angiogenesis, reduced inflammation, and enhanced biomechanical properties following MSC secretome treatment, and in horses with spontaneous tendon or ligament injury, local injection of amniotic membrane MSC secretome reduced the reinjury rate to 15.38% and improved clinical and ultrasound outcomes. No standardized analysis approach or end point measurement instrument was reported, and no CIs or p values were provided. The prespecified secondary end points included inflammation, extracellular matrix remodeling, histology, biomechanics, cellular responses, molecular signaling, and clinical or imaging outcomes. The authors concluded that MSC secretome represents a promising cell-free therapeutic alternative to stem cell–based approaches for tendon repair; it offers advantages in safety, scalability, and regulatory feasibility, with both conditioned media and extracellular vesicles demonstrating immunomodulatory and

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regenerative properties that promote tendon functional healing. There are limitations, including an incomplete understanding of the relative roles of MSC condition media and extracellular vesicles in tendon healing, substantial variability in secretome composition, and lack of standardized protocols for production, characterization, and dosing. Exosome manufacturing remains constrained by low-yield, time-consuming isolation methods that require specialized equipment and the need for large quantities for clinical trials, leading to batch-to-batch inconsistency and limited reproducibility. Additional limitations include the finite proliferative capacity of MSCs, variability in culture and delivery parameters, scarcity of large animal studies with objective functional outcomes, and absence of advanced clinical trials, all of which underscore the need for rigorous standardization to achieve reliable and scalable therapeutic translation.

Salamanna et al. (2026) conducted a systematic review and indirect meta-analysis following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and the PICOS framework to compare PRP and MSC-based therapies for lumbar degenerative disc disease. Adult individuals with discogenic low back pain or intervertebral disc degeneration that was confirmed by clinical or imaging evaluation were included and received intradiscal, transforaminal, or ganglionic injections of PRP or MSCs vs placebo or conservative treatment. The review synthesized 21 studies (nine RCTs and 12 prospective studies), totaling 1,124 individuals, with analyses performed using random-effects models and indirect comparisons via the Bucher method. The primary outcomes were pain intensity, which was measured by the VAS or numeric rating scale, and functional disability, which was assessed by the Oswestry Disability Index or Roland-Morris Disability Questionnaire. Quantitative pooling of five randomized trials showed that PRP significantly reduced pain at 6 months (MD, -16.4 mm; 95% CI, -22.3 to -10.5 mm) and disability (Oswestry Disability Index, -12.7; 95% CI, -17.4 to -8.1), with effects persisting at 12 months, while MSCs produced smaller pain improvements (MD, -4.3 mm; 95% CI, -5.4 to -3.1 mm) and negligible disability change. The secondary end points included quality of life [SF-36, SF-12 (12-Item Short Form Survey), and EQ-5D], imaging parameters (disc height, Pfirrmann grade, and Modic changes), and adverse events. The authors concluded that both PRP and MSC therapies demonstrate potential in managing discogenic low back pain, with PRP offering more robust and consistent short-term clinical benefits in pain reduction and functional improvement, while MSCs showed less pronounced effects. There are limitations, including the lack of direct comparisons between PRP and MSC therapies regarding clinical indications, disease severity, and selection of individuals as well as the unexamined potential of combined or sequential use of these treatments. The analysis was restricted to RCTs to preserve internal validity, yet it was constrained by incomplete data reporting, limited trial numbers, and variability in study quality, outcome measures, and follow-up duration. Substantial heterogeneity in biological sources, preparation methods, cell concentrations, delivery protocols, and immunologic factors complicate direct efficacy comparisons and underscores the need for standardized, long-term trials to clarify optimal protocols and the durability of effect.

Centeno et al. (2024) performed a randomized controlled crossover trial that compared ultrasound-guided, percutaneous bone marrow concentrate (BMC) treatment (including autologous BMC and platelet products) with a home exercise therapy program for managing nonretracted supraspinatus tears. The primary objective was to compare PROMs during a short-term period of 3 months; they hypothesized that those who were receiving autologous orthobiologics would report significantly improved outcomes, which would be sustained through the 2-year follow-up. Overall, 51 participants were enrolled and randomly assigned to either the BMC treatment group (n = 34) or the exercise therapy group (n = 17). After 3 months, the BMC treatment group had significantly greater improvements in median ΔDASH (Disabilities of the Arm, Shoulder, and Hand), ΔNPS (numeric pain scale), and SANE (Single Assessment Numeric Evaluation) scores compared with 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). Participant-reported outcomes continued to improve throughout the study's 2-year follow-up period, without any serious adverse events. Among participants with both pre- and posttreatment MRIs, a majority (73%) had evidence of healing following BMC treatment. The study has several limitations, including a gender discrepancy, with more male participants 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. Adherence might be improved with an exercise diary or formal supervision. Less rigorous post-BMC rehabilitation protocols might impact outcomes. The combination of BMC, PRP, and platelet lysate used in the study may not represent results from BMC alone, and one participant required a second BMC treatment due to unknown reasons. Also, some of the data were missing. In conclusion, the study suggests that nonsurgical treatments like BMC with platelet injections offer a promising alternative for treating rotator cuff tears. Additional RCTs are necessary to support these findings. Exploring other technological advancements in rotator cuff rehabilitation is also recommended.

Baryeh et al. (2021) found that there were mixed results when completing a systematic review of 22 studies, which evaluated the use of cell-based therapy for the treatment of rotator cuff and epicondylar injuries: regarding clinical outcomes, some studies showed no significant difference between the treatment and control groups. Of the 22 studies that were included, 16 evaluated cell therapy for rotator cuff pathology, and the other six evaluated cell therapy for treatment of epicondylitis. There were three RCTs, seven case series, two case-controlled studies, seven cohort studies, and three case reports included in their review. Three of these studies were found to have level 1 evidence, three had

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level 2 evidence, and the remaining 16 had levels of evidence of 3 or below. Of the 16 studies that involved rotator cuff injury, seven included cell therapy as an augment to repair surgery, while nine evaluated the use of intra-articular or intratendinous injections. The six studies that pertained to elbow epicondylitis consisted of one that used cell-based therapy to augment surgical treatment, and the remaining five reported results following intratendinous 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; both clinical and imaging scores showed improvement that was maintained at up to the 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 that were 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 that it was not possible to do a meta-analysis of the data due to the heterogeneity among the studies. The authors recommended future RCTs to establish whether cell-based therapies truly result in improved outcomes in individuals, with focus on standardized techniques, cell types, and treatment protocols.

Kon et al. (2021) systematically reviewed the available literature on the use of biological products, such as MSCs, 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 and describe the current state of the art in available biological techniques; clarify the outcomes of their application; and identify areas that need further investigation and possible future development. A systematic review of the literature on the use of biologically active agents (PRP or MSCs) to enhance outcomes of ACL surgery was performed; 31 studies were included. Based on the ACL injury pattern, six papers investigated biological agents in ACL partial tears, whereas 25 papers discussed ACL reconstruction. Overall, 16 of 25 studies about ACL reconstruction were RCTs, whereas only case series were 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 in individuals with tendon disorders. MEDLINE/PubMed, Embase, CINAHL (Cumulative Index to Nursing and Allied Health Literature), CENTRAL, PEDro, SPORTDiscus, trial registers, and gray literature were searched to identify RCTs and non-RCTs, cohort studies, and case series with five or more cases. Studies that investigated any type of stem cell therapy in individuals with tendon disorders were eligible if they included PROMs 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 a moderate to high risk of bias (level 3 or 4 evidence). In Achilles tendon disorders, one trial found that allogeneic-derived stem cells led to a faster recovery than PRP. Another study found no retears after BMSC therapy was used in addition to surgical treatment. There were four trials that studied the efficacy of BMSC therapy for rotator cuff tears. The controlled trials reported superior patient-reported outcomes and better tendon healing. Two 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 a 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 that do not have comparison groups; therefore, they are inadequate to make conclusions about the safety, efficacy, and use of autologous 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 ADSC-based therapies for treating facial systemic sclerosis (SSc). The aim of the review was to assess the therapies' efficacy and safety and explore the current practices for optimizing treatment. There were 12 studies that matched the inclusion criteria, and 174 individuals were treated. Of them, 87.3% (n = 152) were considered to have improved. The complications, which were graded with the Clavien-Dindo grading system, were grade 1 (no treatment required) or grade 2 (antibiotic required). Individuals received a mean (SD) 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 that are 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

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necessary to eliminate the potential placebo effect, which is frequently higher in cohort studies that mainly depend on PROMs for evaluation.

Khanna et al. (2023) conducted the STAR (Scleroderma Treatment With Celution Processed Adipose Derived Regenerative Cells) randomized, double-blinded, placebo-controlled clinical trial. Overall, 105 participants were screened, and 88 participants were enrolled in the trial. In total, 40 participants were randomized to receive placebo [19 participants with diffuse cutaneous SSc (dcSSc) and 21 with limited cutaneous SSc (lcSSc)], and 48 participants were randomized to receive ADRCs (32 participants with dcSSc and 16 with lcSSc). Change in hand function according to CHFS (Cochin Hand Function Scale) score was numerically higher in the ADRC group than the placebo group but did not achieve statistical significance (mean ±SD improvement in CHFS score at 48 weeks: 11.0 ±12.5 vs 8.9 ±10.5; p = 0.299). In participants 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 had a between-group difference of 0.17 points in the HAQ-DI (Health Assessment Questionnaire - Disability Index; nominal p = 0.044) at 48 weeks. Of the ADRC-treated participants with dcSSc, 52% reported improvement greater than the MCID for both the CHFS and HAQ-DI compared with 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 in participants with SSc and hand dysfunction. While the ADRC group had 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 end points exceeded established MCIDs, which indicated promising but not complete results. The STAR trial data will help design and select end points for a more robust follow-up trial.

Escobar-Soto et al. (2021) evaluated the efficacy and safety of human MSC (hMSC) in individuals with SSc through a systematic literature review. A systematic search was done of the literature in the following databases: MEDLINE/Ovid, LILACS (Latin American and Caribbean Health Sciences Literature), Embase, and Cochrane/Ovid. The exclusion criteria included animal models, autologous/allogeneic 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]. Overall, 508 articles were identified, of which 11 were included (eight case series and three 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 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 individual died in the first month, and the frequency of complications was low. Expanded hMSCs were used in 24 individuals, and other cell sources were used 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 that use better epidemiological designs are needed to evaluate the benefit of hMSCs in individuals with SSc. Del Papa et al. (2015), previously cited in this policy, is included in the Escobar-Soto et al. (2021) systematic review.

Daumas et al. (2017) reported on an open-label phase 1 clinical trials 6- and 12-month outcomes from the same cohort of participants in the below trial that was conducted by Guillaume-Jugnot et al. (2016). In this case series, 12 female participants who were initially enrolled in the clinical trial were assessed during scheduled medical care, which took place between 22 and 30 months after adipose tissue-derived SVF treatment. Multiple participant-reported outcomes showed sustained improvement compared with the assessment performed just before surgery: 62.5% in the CHFS, 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 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 SVF 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 AAOS does not take a position for or against the use of ACT for orthopedic applications; however, in a position statement regarding the use of emerging biological therapies, the AAOS states, “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 U.S. 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 OA states that injectable biologics such as stem cells cannot be recommended in the treatment of glenohumeral joint OA. There was consensus from the panel that

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better standardization and high-quality evidence from clinical trials are 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 AHA and the ACC on the management of patients with lower extremity PAD do not have any reference to the use of stem cell therapy for peripheral vascular disease (Gornik et al., 2025)

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

The VA/DOD's evidence-based clinical practice guideline on the nonsurgical management of hip OA and KOA (2020) does not recommend the use of stem cell injections (e.g., mesenchymal, adipose derived, bone marrow derived) for the treatment of 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 used as well as postprocedure rehabilitation protocols also need investigation.

European Society of Cardiology (ESC)

The most recent recommendations from the ESC on the management of patients with lower extremity PAD do not have any reference to the use of stem cell therapy for peripheral vascular disease (Mazzolai et al., 2024).

International Society for Stem Cell Research (ISSCR)

The ISSCR published information regarding stem cell types and uses and asserts that there is little evidence that these are beneficial. MSC therapy remains in early experimental stages (ISSCR, 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 does not require FDA approval. The FDA does regulate human cells and tissues intended for implantation, transplant, or infusion through the Center for Biologics Evaluation and Research.

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Policy History/Revision Information

Date	Summary of Changes
10/01/2026	**Applicable Codes** • Updated list of applicable CPT codes to reflect quarterly edits; added 1095T **Supporting Information** • Archived previous policy version 2026T0612M

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.

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