Autologous Cellular Therapy (For Ohio Only)

Policy Number: CS176OH.B – P
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Instructions for Use

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Related Policies

- Spinal Fusion Enhancement Products (For Ohio Only)
- Prolotherapy and Platelet Rich Plasma Therapies (For Ohio Only)

Application

This Medical Policy only applies to the state of Ohio.

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 (ACSs): 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.

Autologous Adipose-Derived Regenerative Cell 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.

Autologous Cell 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.

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.

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.

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
27599	Unlisted procedure, femur or knee (when used to report LIPOGEMS)

Description of Services

Over the past few decades, since the bioengineering revolution, Autologous Cell 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 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 Cell 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 cell 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 autologous cellular therapy (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

The use of autologous adipose-derived regenerative cell therapy, also referred to as autologous cellular implant derived from adipose tissue, has been proposed for a knee osteoarthritis. The bulk of evidence surrounding cellular therapy for orthopedic conditions has focused on regenerating cartilage for individuals with osteoarthritis. 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 osteoarthritis, the use of various quantities of these therapies, and lack of long-term outcomes prohibit strong evidence-based conclusions regarding clinical safety and efficacy.

Gong et al. (2021) systematically review the evidence for the efficacy of mesenchymal stem cell (MSC) injections in improving osteoarthritis (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 (four bone marrow, one umbilical cord, one placenta, one adipose tissue) and six studies used autologous MSCs (three adipose tissue, two bone marrow, one 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 three 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 randomized controlled trials, Dai et al. (2021) evaluated the efficacy and safety of intra-articular mesenchymal stromal cells (MSCs) injections for knee osteoarthritis (OA) 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 patients 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 patients 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 patients with symptomatic knee OA. According to the authors, additional direct testing, and combination trials of different type 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 knee osteoarthritis. The authors conducted a PubMed search for human clinical studies using autologous mesenchymal stem cell injections (AMSCI) for the treatment of osteoarthritis (OA) and a second search for placebo arms of injectate OA treatment. The review included 34 studies entered 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 one to three 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 greatly exceeded the minimal clinically important difference (MCID) at each time point. AMSCI improvement also substantially exceeded 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 osteoarthritis, 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 osteoarthritis. 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 patients 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 patients 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: patients 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 patients 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 ECRI report for autologous stem cell therapy for chronic joint pain indicated that meta-analyses show that autologous mesenchymal stem cells (MSC) infusions are safe and may reduce chronic joint pain, 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, more studies are needed to assess MSC therapies in specific patient groups and compare MSCs with other pharmacologic or biologic therapies, such as hyaluronic acid, growth factors, and non-stem cells (ECRI, 2019).

Hayes published a health technology assessment evaluating the use of autologous micro fragmented adipose tissue (MFAT) injection for treatment of osteoarthritis. The evidence base for the 2020 Hayes assessment included four observational studies 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 knee osteoarthritis is 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, autologous micro fragmented adipose tissue injection for treatment of osteoarthritis, 2020; Updated April 2021).

Hayes completed a 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 2018 Hayes review indicated that there is low-quality evidence that suggests some benefits of stem cell therapy compared with alternative therapies for pain and other outcomes in three of six 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 three 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 2020 update indicated that based on the new evidence there was an unlikely change from the 2018 Hayes review findings (Hayes, comparative effectiveness review of stem cell therapy for joint pain, 2018; Updated October 2020).

Peripheral Arterial Disease

Autologous intra-arterial or intra-muscular bone marrow cell transplantation for peripheral arterial disease and other occlusive conditions is an emerging technology. While the existing evidence to-date shows some potential benefit of autologous therapy 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.

Sharma et al. (2021) evaluated the safety and efficacy of angiogenesis induced by intraarterial autologous bone marrow-derived stem cell (BMSC) injection in patients with severe peripheral arterial disease (PAD). Eighty-one patients 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 months. Secondary endpoints included relief from rest pain, > 30% reduction in ulcer size, and reduction in major amputation in patients with CLI and > 50% improvement in pain-free walking distance in patients with severe claudication. Technical success was achieved in all patients, 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 patients 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 patients with CLI or in > 50% improvement in pain-free walking distance among patients 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 patients with severe PAD. Issues related to inadequate numbers and function of progenitor cells in elderly patients and patients 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 patients 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 patients 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 outcomes 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, 1,186 patients and 1,280 extremities were included, and many 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” patients 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.

In a double-blinded randomized placebo-controlled phase 3 trial, Lindeman et al. (2018) evaluated cell therapy for peripheral artery disease (PAD). Inclusion criteria for participants included stable or progressive disabling PAD, no imminent need for amputation, absent accepted options for revascularization; diabetic disease was an exclusion criteria. Bone marrow (500-700mL) was harvested, and bone marrow-derived mononuclear cells were concentrated to 40 mL. Concentrated cells or placebo (diluted blood) were intramuscularly injected at 40 locations of the calf muscle. Fifty-four patients were randomized; twenty-eight of these patients received bone marrow -derived mononuclear cells and 26 received a placebo. No significant differences were observed for the primary (number of amputations, (pain free) walking distance) and secondary outcome parameters (ankle brachial index, pain scores, quality of life (SF-36)). The authors concluded this trial failed to confirm that bone marrow-derived mononuclear cell therapy was beneficial for patients with PAD and therefore should not be offered as a clinical treatment.

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 patients), seven nonrandomized trials (338 patients), and 41 noncontrolled studies (1,177 patients). The cell therapy reduced the risk of amputation by 37%, improved amputation-free survival by 18%, and improved wound healing by 59%. Cell therapy increased ankle brachial index increased transcutaneous oxygen tension, and reduced rest pain. The authors concluded that cell 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.

Moazzami et al. (2014) conducted a Cochrane systematic review to evaluate the effectiveness and safety of local intramuscular autologous mononuclear cells to treat lower limb ischemia. Study results of two randomized controlled trials indicated positive treatment effects in terms of significantly reduced number of amputations and significantly increased in pain-free walking distance when compared with controls. However, study authors concluded that the evidence base is currently insufficient to support the use of this treatment and larger randomized controlled trials with enough power are needed to assess the role of intramuscular mononuclear cell implantation in patients with lower limb ischemia.

Fadini et al. (2010) conducted a meta-analysis to determine whether autologous cell therapy is effective in the treatment of peripheral arterial disease (PAD). The authors included 37 controlled and non-controlled, randomized, and non-randomized trials using autologous bone marrow or granulocyte colony stimulating factor (G-CSF) mobilized peripheral blood cells to treat PAD. Autologous cell therapy was effective in improving surrogate indexes of ischemia, subjective symptoms, and hard endpoints (ulcer healing and amputation). G-CSF monotherapy was not associated with significant improvement in the same endpoints. Patients with thromboangiitis obliterans showed some larger benefits than patients with atherosclerotic PAD. The intramuscular route of administration and the use of bone marrow cells seemed somehow more effective than intraarterial administration and the use of mobilized peripheral blood cells. The authors concluded that intramuscular autologous bone

marrow cell therapy is a feasible, relatively safe, and potentially effective therapeutic strategy for PAD patients, who are not candidates for traditional revascularization. This review did not include some of the more recent RCTs included in the Rigato meta-analysis (Rigato 2017) discussed above. Larger, placebo-controlled, randomized multicenter trials are needed to confirm these findings.

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.

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, six 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 patients 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 five or more cases. Studies investigating any type of stem cell therapy for patients 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 patients) were included in the review. All trials had moderate to high risk of bias (level 3 or 4 evidence). In Achilles tendon disorders, one 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 four 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 two case series found that stem cell therapy improved patient-reported outcomes in patients 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 cell (ADRC) therapy to treat scleroderma of the fingers and hands. Larger, randomized comparative studies are needed to assess health outcomes using this therapy.

Escobar-Soto et al. (2021) evaluated the efficacy and safety of human MSC (hMSC) in patients 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 (eight case series and three case reports). The 11 articles included 101 patients (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 patients and other cell sources in the remaining patients. 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 patients. 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 patients 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.

Guillaume-Jugnot et al. (2016) reported on the 12-month outcome of patients from an open-label clinical trial assessing injection of autologous adipose-derived stromal vascular fraction (ADSVF) for treatment of systemic sclerosis involving the hands. In this case series, twelve females, mean age 54.5 years, were assessed one year after ADSVF injection. ADSVF was obtained from lipoaspirate using an automated processing system and subsequently injected into the subcutaneous tissue of each finger in a one-time procedure. Endpoints were changes in hand disability and skin fibrosis, vascular manifestations, pain and QOL at the 12- month follow-up. During the visit, patients estimated the benefit of the procedure with a specific self-completed questionnaire. A significant decrease from baseline of 51.3% for Cochin Hand Function Scale score, 63.2% for Raynaud's phenomenon (RP) severity and 46.8% for QOL (Scleroderma Health Assessment Questionnaire) was observed. A significant improvement of finger edema, skin sclerosis, and motion and strength of the hands was also noted. The reduction in hand pain approached statistical significance. The questionnaire revealed a benefit in daily activities. The authors concluded that ADSVF injection is a promising therapy and may have benefits that extend for at least 1 year. According to the authors, these results should be confirmed by a randomized placebo-controlled trial in a larger population.

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 cell 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 patients, 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 AAOA 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 AHA and the ACC on the management of patients 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) and the 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 patients 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 patients with chronic limb-threatening ischemia (Aboyans et al., 2018).

The 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, 2019).

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
02/01/2023	• Created state-specific policy version
04/01/2022	**Related Policies** • Updated reference link to reflect title change for the Medical Policy titled *Spinal Fusion Enhancement Products* (previously titled *Bone or Soft Tissue Healing and Fusion Enhancement Products*)
11/01/2021	**Title Change** • Previously titled *Autologous Cellular Therapy for Certain Indications* **Coverage Rationale** • Replaced language indicating "Autologous Cellular Therapy is unproven and not medically necessary for all indications, *including but not limited to [list of examples]*" with "Autologous Cellular Therapy is unproven and not medically necessary for all indications *due to insufficient evidence of efficacy*" • Removed list of examples of unproven and not medically necessary indications **Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version CS176.A

Instructions for Use

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

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