Autologous Cellular Therapy for Certain Indications (for Indiana Only)

Policy Number: CS176IN.01
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Instructions for Use

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Related Policies

- Bone or Soft Tissue Healing and Fusion Enhancement Products
- Prolotherapy and Platelet Rich Plasma Therapies

Application

This Medical Policy only applies to the state of Indiana.

Coverage Rationale

Autologous cellular therapy is unproven and not medically for all indications, including but not limited to:

- Osteoarthritis of the knee
- Peripheral arterial disease
- Regeneration and/or repair of musculoskeletal tissue
- Scleroderma of the hands

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 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.

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.

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" (NIH, 2010).

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
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 orthopaedic 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.

A 2019 Hayes published an evidence analysis research brief evaluating the use of autologous micro-fragmented adipose tissue (MFAT) injection for treatment of degenerative joint disease (DJD). The review included nine abstracts, including 1 randomized controlled trial (RCT), 3 prospective uncontrolled studies, 3 reports of 2 retrospective uncontrolled studies, and 2 commentaries. The Lipogems system was used in one study, others did not report the source of MFAT. Hayes concluded that overall the findings are conflicting for improvement of health outcomes, and until reviewed further conclusions regarding the safety and effectiveness could not be made. Additional studies are underway, however at present there is insufficient evidence in the peer reviewed scientific literature to support safety and efficacy of Lipogems for treatment of knee osteoarthritis or other orthopedic /musculoskeletal conditions.

Schiavone et al. (2019) reported the preliminary clinical and functional results of a series of patients with early knee osteoarthritis (KOA) treated with the intra-articular injection of autologous adipose-derived stem cells (aASCs) plus arthroscopic debridement. The hypothesis was that protocol would significantly improve the clinical and functional outcomes in patients with early KOA. Fifty-two patients with early KOA, who received arthroscopic debridement followed by percutaneous injection of aASCs, were enrolled into the study and retrospectively analyzed with an average follow-up of 15.3 months. Patients were assessed through the IKS knee and function scores and VAS pain scale. The results showed the mean IKS knee score improved from 37.4 points pre-operatively to 62.6 points at the latest follow-up, and the mean IKS function score improved from 57.2 points pre-operatively to 83.0 points at the latest follow-up. The mean VAS score decreased from 8.5 pre-operatively to 5.1 at the latest follow-up. Additionally, patients with a pre-operative VAS score greater than 8 were found to show greater clinical

and functional benefits compared with patients with VAS score lower than 8. The authors concluded that the knee injection of aASCs associated to arthroscopic debridement increased significantly the clinical and functional scores in patients with early KOA at a mid-term follow-up, especially those with higher pre-operative VAS scores. The study was limited by lack of comparison group. These results should be confirmed by randomized controlled studies.

Panchal et al. (2018) conducted a study to evaluate the safety and efficacy of using autologous, micro-fractured, minimally manipulated adipose tissue in patients with refractory knee osteoarthritis (OA). A total of 17 subjects (26 knees) with a median age of 72 years (range: 54-78 years) and a history of knee OA (Kellgren-Lawrence, grade of 3 or 4) underwent treatment with ultrasound-guided injection of micro-fractured adipose tissue. Micro-fractured fat was obtained using a minimal manipulation technique in a closed system (Lipogems), without the addition of enzymes or any other additives. The study subjects were clinically evaluated using the numerical pain rating scale (NPRS), the 100-point Knee Society Score (KSS) with its functional component (FXN), and the lower extremity activity scale (LEAS) at 6 weeks, 6 months, and 12 months following this procedure. When compared with baseline, significant improvements were noted in the mean values of NPRS, FXN, and LEAS at 6 weeks, 6 months, and 12 months. The mean KSS significantly improved at 6 weeks and 12 months. In particular, the average KSS score improved from 74 to 82, the FXN score improved from 65 to 76, and the LEAS score improved from 36 to 47. These values were significantly greater than the previously published minimal clinically important difference described for KSS and FXN in patients who underwent total knee arthroplasty for primary OA. No serious adverse events were reported. The injection of autologous, micro-fractured, minimally manipulated adipose tissue appears to be a safe and effective treatment option for patients with refractory, severe (grade 3 or 4) knee OA. According to the authors, this study demonstrated significant improvements in pain, quality of life, and function for at least 12 months in this study population. This intervention may represent a nonsurgical treatment option to avoid knee joint replacement in this population; however, further investigation is needed. The study was limited by lack of comparison group receiving established treatment for osteoarthritis.

A 2017 ECRI custom product brief concluded that the available evidence for the LIPOGEMS® System has major limitations. The included studies are at high risk of bias due to a lack of randomization, blinding, reporting on subjective outcomes, and single-center patient recruiting. Outcomes from the case report study, reporting on patients with degenerative chondral lesions, are not generalizable because of a small patient population. Moreover, studies do not report on important patient-oriented outcomes. Additional studies comparing the effectiveness of Lipogems-processed autologous adipose tissue reinjections with that of other processing methods, with that of no adipose tissue grafting (placebo), and with that of unprocessed autologous adipose tissue grafting are necessary for determining the comparative effectiveness of Lipogems-processed adipose tissue.

Russo et al. (2017, included in the ECRI report cited above) conducted a retrospective study on the 1-year safety and outcome of a single intra-articular injection of autologous and micro-fragmented adipose tissue in 30 patients affected by diffuse degenerative chondral lesions. The safety of the procedure was evaluated by recording type and incidence of any adverse event. The clinical outcomes were determined using the KOOS, IKDC-subjective, Tegner Lysholm Knee, and VAS pain scales taken pre-operatively and at 12 months follow-up. A level of at least 10 points of improvement in the scores was selected as the cut-off representing a clinically significant difference. The results showed no relevant complications or clinical worsening was recorded. A total median improvement of 20 points was observed in IKDC-subjective and total KOOS, and a higher percentage of success was found in VAS pain and Tegner Lysholm Knee, where the total median improvement was 24 and 31 points, respectively. The authors concluded that the results of this study show the safety and feasibility of using autologous and micro-fragmented adipose tissue in patients affected by diffuse degenerative chondral lesions, and that the technique is safe, minimally invasive, simple, one-step, with low percentage of complications. Although it is not possible to draw a clear conclusion about the efficacy because 80% of the patients had an associated surgery, the authors concluded that the results of this study were satisfactory, with the majority of patients significantly improved in terms of clinical outcomes with respect to baseline. This study is limited by a small patient population and lack of comparison group or randomization. Further high-quality studies with larger populations are needed before clinical usefulness of this procedure is proven.

Jo et al., (2014) reported a phase 1/2 trial of intra-articular injection of adipose-derived MSCs for the treatment of osteoarthritis of the knee. Phase 1 was a dose-escalation study of nine patients and phase 2 assessed efficacy of the highest dose in another nine patients. The case series of 18 patients was approved by the Korean Food and Drug Administration. Intention-to-treat analysis showed a 39% improvement in Western Ontario and McMaster Universities Arthritis Index score and a 45% improvement in VAS score at 6 months post injection. The knee section of the Knee Society clinical rating system showed significant increases in the low-dose group (91%) and in the high-dose group (50%), compared with baseline. There was also an increase in the volume of cartilage in the medial femoral condyle for both high- and low-dose groups, although this change was only significant in the low-dose patients, who showed a 27% increase. For the high-dose group and other domains, changes in

cartilage volume were insignificant over six months. Histology showed thick, hyaline-like cartilage regeneration. The results of two-year follow-up are reported below, as are the limitations of both phases of the trial.

Jo et al. (2017, included in the Hayes report described above), reported a 2-year follow-up of this phase ½ trial. Functional outcomes were assessed by Western Ontario and McMaster Universities Osteoarthritis Index, Knee Society clinical rating System, KOOS, and VAS. The high-dose group showed significantly improved scores at 2 years compared with baseline and 1-year follow-up, while the medium- and low-dose groups showed insignificant changes or deterioration from 1-year to 2-year follow-up. In the high-dose group, the Western Ontario and McMaster Universities Osteoarthritis Index score decreased from baseline 54.2 to 16.0 at 1-year follow-up; after 2 years, the score was 19.0, which reflected the tendency of high-dose patients to improve early in treatment and remain at a stable level of improvement. Those in the medium- and low-dose groups, on the other hand, were more likely to show signs of deterioration after two years, a finding supported by structural measures (e.g., no significant changes in cartilage defects were reported for these patients, as assessed by MRI). In the high-dose group, measurement of the medial femoral defect showed a 49.4% decrease after 2 years), and measurement of lateral tibial condyles defect showed a 64.4% decrease (p=0.037); additionally, no adverse events were reported, prompting investigators to call for more randomized trials of the treatment. Among the trial's limitations were a lack of a control group and the absence of data at one year for both MRI results and patients receiving a medium stem cell dose.

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.

In a double-blinded randomized placebo-controlled phase 3 trial, Lindeman et al. (2018) try and resolved a controversy regarding 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), 7 nonrandomized trials (338 patients), and 41 noncontrolled studies (1177 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.

A prospective case series with interventions occurring between December 2007 and September 2012 and a 3-month minimum follow-up was conducted by Franz et al. (2015) to determine if intramuscular and intra-arterial stem cell injections delay or prevent major limb amputations. Forty-nine patients with severe limb-threatening peripheral arterial disease, without other options for revascularization enrolled. Dual intramuscular and intra-arterial injection of bone marrow mononuclear cells harvested from the iliac crest was performed. Major limb amputation at 3 months was the primary outcome measure. No complications related to the procedure were reported. Of 49 patients enrolled, two patients died, but had not undergone major amputation, and five patients underwent major amputation within the first 3 months. Three-month follow-up evaluations were

conducted on the remaining 42 patients. After 3 months, seven patients died but had not undergone major amputation, and seven underwent major amputation. At a mean follow-up of 18.2 months, the remaining 29 patients had not undergone a major amputation. Freedom from major adverse limb events was 91.1% at 3 months and 75.6% at 12 months. The authors concluded that the results of this analysis indicate that autologous bone marrow mononuclear cell implantation therapy it is an effective strategy for limb salvage for patients with severe peripheral arterial disease. These findings are however limited by lack of a comparison group. Further research with randomized controlled trials is needed to validate these findings.

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.

Matoba et al. (2008, included in the Rigato 2017, Moazzami 2014, and the Fadini 2010 systematic reviews) reported 3-year follow-up results for the TACT trial. The case series assessed the 3-year safety and clinical outcomes of angiogenic cell therapy by investigating the mortality and leg amputation-free interval as primary end points. The median follow-up time for surviving patients was 25.3 months (range, 0.8-69.0 months), and 3-year overall survival rates were 80% in patients with atherosclerotic peripheral arterial disease and 100% in 41 patients with thromboangiitis obliterans (TAO). Three-year amputation-free rate was 60% in PAD and 91% in patients with TAO. The multivariate analysis revealed that the severity of rest pain and repeated experience of bypass surgery were the prognostic factors negatively affecting amputation-free interval. The significant improvement in the leg pain scale, ulcer size and pain-free walking distance was maintained during at least 2 years after the therapy, although the ankle brachial index and transcutaneous oxygen pressure value did not significantly change. The authors concluded that angiogenic cell therapy using bone marrow mononuclear cells can induce a long-term improvement in limb ischemia, leading to extension of amputation-free interval. The findings were however limited by lack of comparison group. Larger, placebo-controlled, randomized multicenter trials are needed to confirm these findings.

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.

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 1 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.

Del Papa et al. (2015) treated systemic sclerosis (SSc)-related digital ulcers (DUs) by implantation of autologous adipose tissue-derived cell (ATDC) fractions as part of a pilot study. Fifteen patients with SSc having a long-lasting DU in one fingertip who were unresponsive to intensive systemic and local treatment were enrolled in this case series. The grafting procedure consisted of the injection, at the base of the corresponding finger, of 0.5-1 ml of autologous ATDC fractions, separated by centrifugation of adipose tissue collected through liposuction from subcutaneous abdominal fat. Time to heal after the procedure was the primary end point of the study, while reduction of pain intensity and of analgesic use represented a secondary end point. Healing of the DUs was reached in all the enrolled patients (mean time to healing 4.23 weeks; range 2-7 weeks). A significant reduction of pain intensity was observed after a few weeks, while the number of capillaries was significantly increased at the 3- and 6-month nailfold video capillaroscopy (NVC) assessment. Finally, a significant after-treatment reduction of digit artery resistivity was also observed. Even with the limitations related to the small number of patients included and to the open-label design of the study, the authors concluded that observed strongly favorable outcome suggests that local grafting with ATDCs could represent a promising option for the treatment of SSc-related DUs. According to the authors, the positive outcome reported in this trial requires confirmation in larger, controlled studies. The study is limited by the lack of comparison group.

Professional Societies

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 orthopaedic 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 offered to their patients, including benefits and risks. The varying regulatory pathways by which biologic therapies come to market require the additional burden for surgeons to become familiar with the Food and Drug Administration's current thinking with respect to the source, retrieval and/or manufacturing methods, processing, storage, and use of these products, whether alone or as part of combination products. AAOS believes that surgeons should be cognizant of the risks, benefit, regulatory status and labeled indications of the products they use. Unlike devices, the effects of these products may not be limited to the duration of their implantation. Autogenous products may be subject to regulatory review" (AAOS, 2017).

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

The most recent recommendations from the American Heart Association and the American College of Cardiology on the management of 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).

European Society of Cardiology (ESC)

This guideline addresses novel therapies to stimulate neovascularization, known as therapeutic angiogenesis. These therapies promote revascularization and remodeling of collateral vessels to reduce the symptoms of peripheral vascular disease and prevent amputation. At present angiogenic gene and stem cell therapy are still being investigated, and it is too early to give firm recommendations, the guideline therefore recommends that "stem cell/gene therapy is not indicated" for patients with intermittent claudication (Tendera et al., 2011).

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 (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
04/01/2021	• New Medical Policy

Instructions for Use

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

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