Medical Coverage Policy

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Stem Cell Therapy for Orthopaedic Applications

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Related Coverage Resources

Autologous Platelet-Derived Growth Factors (Platelet Rish Plasma [PRP])
Bone Graft Substitutes

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Overview

This Coverage Policy addresses stem cell therapy to re-grow (also known as regenerate), damaged or missing cells and tissues in the muscles and skeleton. This type of stem cell therapy is known as regenerative therapy. Regenerative therapy is considered a field of medicine that is still under development.

Because they have the ability to grow rapidly the use of mesenchymal stem cells (MSCs) is being studied to restore the function of these cells and tissues. This is known as regenerative therapy. MSCs are found in several types of tissues, including the bone marrow, and are important for making and repairing skeletal tissues, such as cartilage, bone and the fat found in bone.

For the intent of this Coverage Policy "stem cell therapy" refers to mesenchymal stem cells that are taken from bone marrow, fat tissue, amniotic membrane, and blood and membrane in the joints.

Stem cell transplantation using stem cells for treatment of blood cancer, non-cancer conditions and solid tumors are not in scope of this policy.

Please review Cigna Medical Coverage Policy 0118 Bone, Cartilage and Ligament Graft Substitutes for uses other than those discussed in this Coverage Policy.

Coverage Policy

Stem cell therapy as treatment of orthopaedic and/or musculoskeletal conditions, is considered experimental, investigational or unproven for ALL indications, including the following:

- regeneration and/or repair of musculoskeletal tissue (e.g., ligament, tendon, and/or meniscus repair, muscle sprain, tendonitis, epicondylitis)
- treatment of joint disease (e.g., articular cartilage repair, joint capsular injury)
- degenerative disc disease (e.g., intervertebral disc repair)
- osteoarthritis (e.g., knee, hip, ankle, shoulder)
- fracture repair, including nonunion of long bone
- osteonecrosis repair

General Background

Stem cells are cells that have the ability to differentiate into a number of various cell types and are being used more frequently in the treatment of orthopaedic 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 well-established stem cell therapy in clinical practice (Gepstein, Skorecki, 2020).

According to the U.S. National Institute of Health (NIH), regenerative medicine is defined as " the process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage, or congenital defects" (NIH, 2010). In general, cellular therapies are purported to produce a regenerative effect by promoting growth and differentiation of local cells. In addition, stem cells possess paracrine and immune-modulating effects through growth factor and cytokine release. Theoretically, stem cells inhibit the release of pro-inflammatory cytokines and promote the survival of existing cells and the repair of damaged tissue.

Within orthopaedics, mesenchymal stem cells are derived mainly from bone marrow, however other sources include adipose tissue (i.e., lipoaspirate), umbilical cord tissue, amniotic fluid, and other extra-articular sources. Mesenchymal stem cells (MSCs) are adult-derived, undifferentiated, multipotent cells that express a variety of different cell surface proteins and can differentiate into a variety of lineages, such as adipogenic (fat cells), osteogenic (bone cells), and chondrogenic (cartilage cells). Adult MSCs do not reach pluripotency, pluripotency is the ability to differentiate into all cell types derived from three germ layers (i.e., ectoderm, mesoderm, endoderm) of the developing embryo (e.g., embryonic stem cell). If MSCs are placed within normal healthy bone, cartilage, or adipose tissue, the stem cells differentiate into that particular tissue. In theory, this property applies to all mesenchymal tissues, including muscle, tendon, and fibrous tissues. MSCs demonstrate little to no ability however to differentiate into nonmesenchymal tissue (e.g., neural or hepatic cells) (Cook, Young, 2022).

MSCs are immunosuppressive and as such do not result in host rejection. One of the proposed advantages of autologous MSCs is the ability to isolate them, expand them in vitro and deliver them as autologous therapy. Nevertheless both autologous and allogenic MSCs are being used as therapy to treat various orthopaedic conditions. Although processing techniques vary, and the optimal number of MSCs to be transplanted/seeded has yet to be established, MSCs can be concentrated for direct injection, or they be cultured and incubated. Once cultured MSCs can be mixed with other materials such as gels or pastes, or they can be seeded onto scaffolds and used as a support matrix for implantation. Seeded scaffolds have been investigated as a tissue-engineering method within the musculoskeletal system for bone and cartilage repair. However, stem cells may undergo malignant transformation (Wang, et al., 2012) and there is some concern that autologous MSCs may induce tumors by changing the action of cancer cells and accelerating tumor growth, and further that allogeneic MSCs may accelerate infectious risk (Wang, et al., 2018).

The steps involved in processing MSCs include harvesting the cells from bone marrow or lipoaspirate, isolation of the cells, followed by proliferation in a culture medium (i.e., culture expanded). Following proliferation the MSCs are stored using cryopreservation. Other manufacturing procedures can be done that avoid cellular isolation and proliferation (i.e., nonexpanded cells) although the resulting number of stem cells within these products are unknown. Authors are also investigating autologous stromal vascular fraction (SVF) as adipose-derived stem cells for regenerative treatment of osteoarthritis; SVF consists of nucleated stromal and vascular cells that are present in adipose tissue (progenitor and endothelial). SVF processing does not require cell expansion or culture (Garza, et al., 2020).

Treatment modalities for orthopaedic and/or musculoskeletal conditions proven safe and effective in the peer-reviewed medical literature include the use of pharmaceutical agents, weight loss, physical therapy and exercise, acupuncture, chiropractic care, and surgical repair when all other treatment options have failed. Stem cell therapy is an emerging technology that authors assert

may be considered an alternative treatment modality and that may for some individuals avoid future surgical procedures (e.g., knee arthroplasty).

Please reference the Cigna Medical Coverage Policy 0118 Bone Graft Substitutes for information regarding demineralized bone matrix (DBM) and other products containing viable stem cells used to enhance healing of bone and 0507 Autologous Platelet-Derived Growth Factors (Platelet-Rich Plasma [PRP]) for use of PRP for orthopaedic indications.

Literature Review: Areas undergoing current investigation for the application of MSCs include but are not limited to regeneration and/or repair of musculoskeletal tissue, for example muscle, ligament, tendon, meniscus repair (Rinonapoli, et al., 2021**;** Centeno, et al., 2018a; Chew, et al., 2017; Lin, et al., 2017; Pas, et al., 2017b; Matsukura, et al., 2014; Centeno, et al., 2015; Vangsness, et al.,2014); treatment of joint disease, including, cartilage lesions, degenerative joint disease, and joint capsular injury (Ha, et al., 2019; Park, et al., 2017; Lee, Wang, 2017; Goldberg, et al., 2017; Filardo, et al., 2013; Ganjii, Hauzeur, 2009); osteoarthritis of the knee, hip, ankle, and shoulder (Wiggers, et al., 2021, Natali, et al., 2021; Garza, et al., 2020; Prodromos, et al., 2020; Simunec, et al., 2020**;** Lee, et al., 2019; Delanois, et al., 2019; Migliorini, et al., 2019; Emadedin, et al., 2018; Jevotovsky, et al., 2018; Centeno, et al., 2018b; Vannabouathong, et al., 2018; Pas, et al., 2017a; Cui, et al., 2016; Burke, et al., 2016; Vega, et al., 2015; Centeno, et al., 2014; Mobasheri, et al., 2014; Koh, et al., 2013; Pak, 2011); epicondylitis (Ahmad, et al., 2012); fracture (Yi, et al., 2022), including nonunion (Centeno, et al., 2011); and various spinal conditions such as spinal cord injury and intervertebral disc repair (Khan, et al., 2017).

The body of evidence in the published peer reviewed scientific literature evaluating MSCs for treatment of these conditions is mainly in the form of preliminary animal studies, case reports, case series, nonrandomized comparative trials, a number of systematic reviews/meta-analysis, and few randomized trials. The type/source of stem cell used and methods of extraction vary across studies, sample populations are small, reported outcomes are < two years in most studies, and injections include use of other components in some studies, such as hyaluronan or platelet rich plasma making it difficult to attribute the sole effect of MSCs as a treatment response. Regeneration and tissue remodeling has not been firmly established in well-designed, controlled studies and extraction and concentration methods, infusion procedures, indications for use are not standardized, and the optimal source of MSC including the quantity of cells to inject have not been firmly established. Additional RCTs evaluating long term outcomes are needed to firmly establish safety and efficacy of MSCs used for treatment of orthopaedic and /or musculoskeletal conditions. It is not yet proven that a clinical benefit outweighs potential harm that may be associated with MSC therapies.

Information available on the National Institutes of Health website regarding clinical trials indicates that several registered trials of MSCs for the treatment of osteoarthritis, tendon regeneration and other orthopaedic conditions are being conducted and few have been completed. The cells used within these trials include both expanded and nonexpanded MSCs for the treatment of a variety of orthopaedic and/or musculoskeletal conditions.

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

Meniscal Repair: The meniscus has poor intrinsic healing capacity. Use of stem cells for meniscal injuries has been performed in animals with few studies evaluating use in human meniscal injuries. A concern reported in the literature is the difference in mechanical properties in comparison with native meniscal tissue as well as differences in the extracellular matrix (Chew, et al., 2017). The presence of MSCs in synovial fluid following meniscal injury has been studied (Matsukura, et al., 2014). In comparison to normal knees MSCs were found to be present in

higher numbers in synovial fluid with meniscus injury than normal knees. The authors postulated the presence of MSCs in synovial fluid contributed to spontaneous healing of the meniscus, and that additional studies are needed to determine if interventions that increase quantity of MSCs further promote meniscus healing.

MSCs as treatment of meniscal injury involves either intraarticular injection or local delivery to the site using a seeded scaffold (tissue engineering technique), however clinical trials are very limited in number, involve a limited number of subjects and have short follow-up. Authors of a 2021 systmatic review evaluated stem ell applications for meniscal repair which included pre-clinical (n=13) and clinical studies (n=5; two case controls, one case report, one RCT and one case series (Rinonapoli, et al., 2021). They noted that based on the currently available evidence it is not possible to determine the best cell source or delivery method, although injection is the most studied and most promising. They further acknoweledged that additional research and higher quality studies are needed to establish any clinical benefit.

A randomized controlled trial published by Vangsness, et al. (2014) involved 55 subjects who underwent partial medial meniscectomy (across seven facilities) and were randomized to one of three treatment groups: Group A, in which patients received an injection of 50×10^6 allogeneic mesenchymal stem cells; Group B, 150×10^6 allogeneic mesenchymal stem cells; and the control group, a sodium hyaluronate (hyaluronic acid/hyaluronan) vehicle control. Injection was given seven to 10 days following surgery, MSCs were cultured ex vivo and not human leukocyte antigen matched. Clinical outcomes were followed for two years and included safety, meniscal regeneration, and the overall condition of the knee joint. Knee pain was reported using VAS and Lysholm knee scales. Using VAS subjects who received MSC injections had a significant reduction in pain compared with the controls. MRI demonstrated a significant increase in meniscal volume, defined as a >15% threshold, in 24% (3 subjects) of subjects in Group A at two years indicating tissue regeneration according to the authors. A total of 427 adverse events were reported, 272 were mild, 126 were moderate, 28 were severe, and one was life threatening (heart attack one year post procedure). The most common adverse events were arthralgia, joint swelling, joint stiffness, injection-site joint pain, joint effusion, headache, and peripheral edema. Serious adverse events were deemed unlikely to be related to the treatment. The study is limited by small sample population, differences in MRI scans across facilities, and lack of control for osteoarthritis across groups as noted by the authors.

Osteonecrosis: Osteonecrosis is a progressive disease involving the death of bone tissue due to an impaired vascular supply. Osteonecrosis of the femoral head leads to femoral head collapse and need for subsequent hip arthroplasty. The implantation of stem cells into the necrotic lesion of the hip, resulting from osteonecrosis, has been studied in the medical literature as a method of preserving the femoral head. However, studies are in early stages and bone repair originating from the injected cell therapy has not been firmly established.

Li and colleagues published the results of a systematic review and meta analysis evaluating stem cell therapy combined with core decompression versus single biomechanical support as treatment of osteonecrosis of the femoral head. The analysis included 10 randomized controlled trials involving 498 subjects, 719 hips. A majority of the RCTs were not high quality, involved small sample size (n=18-125), and had short term followup (2-3 yrs on average). Stem cell counts and source varied among studies. Clinical outcomes were assessed using Harris hip score, VAS, and adverse events. Publication bias was not able to be assessed and there was heterogeneity in outcome indicators. Based on the review the Harris hip score and VAS both differed when compared with the control group, favoring stem cell therapy for relief of pain and were statistically significant (MD=8.87, 95% CI,[P<0.00001]; MD=-14.07, 05% CI, [P<0.00001], respectively). The was no significant difference in adverse events among groups. According to the authors stem cell combined with core decompression was effective with few complciations, however further high

quality, large sample, multicenter long term RCTS are needed to establish safety and efficacy (Li, et al., 2021). Andronic et al. (2021) published the results of a systematic review comparing biologic augmentation combined with core decompression to core decompression alone as treatment of osteonecrosis of the femoral head. This review included 10 studies reporting on 560 hips (484 subjects), using bone marrow stem cells, platelet rich plasma or bone morphogenetic protein as the biological augmentation. It was noted only four studies reported improvement in all clinical scores in the augmentation group, seven studies observed a reduction in the rate of radiographic progression, and only 5 found reduced rates of conversion to total hip arthroplasty. The authors acknowledged the current evidence remains inconclusive to support a benefit of biologic augmentation to core decompression as treatment of osteonecrosis**.** In 2011 Pak reported a series of case reports evaluating the potential of adipose derived MSCs to regenerate bones in human osteonecrosis. Within this study adipose MSCs were combined with additives such as hyaluronic acid, platelet rich plasma and calcium chloride and injected into the osteonecrotic hip of two subjects and knees of two subjects with OA of the knee. MRI results revealed bone formation and cartilage formation three months post treatment however additional studies are needed to support regeneration was attributed to the MSCs.

Knee Osteoarthritis: The bulk of evidence surrounding stem cell use for orthopaedic conditions has focused on regenerating cartilage for individuals with knee osteoarthritis. Stem cells can be either injected directly into the defect or seeded onto a scaffold providing mechanical support and can be administered with or without adjuvant treatment. Authors contend implantation of subchondral bone marrow MSCs and scaffolds loaded with bone marrow MSCs may improve pain and survivorship of the joint, and potentially reduce the need for surgery (Hernigou, et al., 2021).

Kim et al. (2022) published the results of an RCT assessing intra-articular injection of adipose-derived mesenchymal stem cell (ADMSC) after medial open-wedge high tibial osteotomy (MOWHTO) (n=13) compared to medial open-wedge high tibial osteotomy (MOWHTO) (n=13). Subjects were followed for 24 months. The primary outcome was the serial changes of cartilage defect on periodic magnetic resonance imaging (MRI) evaluation using valid measurements until postoperative 24 months. Secondary outcomes included two stage arthroscopic evaluation for macroscopic articular cartilage status and postoperative functional improvements reported by the patients. At 24 month followup both serial MRIs and arthroscopic evaluation (69.2%, 23.1% respectively) demonstrated that the experimental group had significantly better cartilage regeneration compared with the high-tibial osteotomy group. At 18 months post treatment, functional improvements were also greater in the stem cell group, although not statistically significant. The authors concluded that injection of adipose-derived mesenchymal stem cells is a potential disease modifying treatment for the treatment of knee osteoarthritis without any safety issue. Limitations include small sample population and short term outcomes.

Zhang and colleagues (2022) reported the results of a RCT evaluating the use of stromal vascular fraction injection (n=56) for treatment of knee osteoarthritis compared with hyaluronic acid injection (n=70). Inclusion criteria were meeting the diagnostic criteria in the American Rheumatism Association Revised Classification Criteria for Knee Osteoarthritis; Kellgren–Lawrence (KL) grade 2–3; age 20–85 years; and no history of significant trauma. Subjects were randomly assigned to either the SVF group or a group that received hyaluronic acid (control). Injections were administered monthly for three months. Subjects were followed for one, two, three, and five years to assess pain and function using VAS and WOMAC scores. Using MRI cartilage structure and volume and bone marrow lesions were assessed over the medial tibia, medial femur, medial patella, lateral tibia, lateral femur, and lateral patella. Clinical failure was defined as surgery related to knee osteoarthritis. A total of 51 subjects in the treatment group and 64 in the control were evaluated at five year followup. The VAS and WOMAC scores in the treatment group were lowest after one year and then increased annually but remained lower than pretreatment scores at five years. The VAS and WOMAC scores in the control group did not change much from

pretreatment at 1 year, then increased annually and were significantly higher than pretreatment at 5 years. Kaplan–Meier responsive curves of all patients in the two groups were plotted and compared. The SVF group showed a responsive rate of 62.5% (35/56) at the 5-year follow-up, and the rate in the HA group was 20% (14/70). At the five year followup the total cartilage volume was significantly reduced in both groups from baseline to 5 years, and was higher in the treatment group and small proportion of patients who received stromal vascular fraction had signs of repair of the full-thickness cartilage defect. There was no significant difference in bone marrow lesion size, severity, patella-femoral pathology or mechanical axis from baseline to 5 years and no difference between the two groups. A total of nine subjects underwent surgery during the follow-up period (3 in the SVF group and 6 in the HA group) and were included in the Kaplan-Meier analysis but not thecompariosn analysis. Limitations of the trial include lack of a targeted injection to a specific lesion site as noted by the authors which precludes knowing the exact destination of the cells, and exclusion of KL Grade 4 subjects which precludes knowing efficacy in this group.

Wong and colleagues (2021) published the results of an RCT evaluating results of intra-articular cultured autologous bone-marrow derived MSC injections in conjunction with microfracture and medial opening-wedge high-tibital osteotomy as treatment of unicompartmental arthritis. A total of 56 subjects were randomly allocated to either a cell-recipient group (n=28) or control group (n=28). The cell recipient group received MSCs and hyaluronic acd three weeks post surgery while the control group received only hyaluronic acid. Inclusion criteria were medial-compartment OA with genu varum in patients aged younger than 55 years diagnosed either arthroscopically and/or radiologically, normal lateral joint space, no fixed flexion deformity of the knee, and no collateral ligament instability. Subjects with a joint line congruity angle of more than 2, malalignment of the knee from femoral causes, a fixed flexion deformity, or age older than 55 years were excluded. Outcomes were measured at 6 months, one year and two years following the procedure using Tegner and Lysholm scores, IKDC scores, and at one year MRI was used to look for cartilage regeneration based on the Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) scoring system. The authors noted that they will continue to follow subjects for five and ten year outcomes. Results of the trial demonstrate that the cell recipient group showed significantly better Tegner, Lysholm and IKDC scores. In addition, MRI scans showed significantly better MOCART scores for the cell recipient group. Limitations of the trial include short-term follow-up and lack of blinding.

Several authors have published systematic reviews with meta meta-analysis evaluating treatment of knee osteoarthritis using only MSCs (Tan, et al, 2021**;** Ma, et al., 2020; Prodromos, et al., 2020 **)**, MSCs / stromal vascular fractions (Kim, et al., 2021**)**, or MSCs and other biologic agents (Wiggers, et al., 2021; Zhao, et al., 2021; Anil, et al., 2021; Cao, et al., 2021). Within these publications some overlap of studies is noted, however authors tend to report an improvement in pain and function following the intervention (i.e., intra-articular injection of MSCs). Kim and associates (2021) published the results of a systematic review involving five RCTs evaluating the efficacy and safety of intra-articular injections of autologous adipose-derived mesenchymal stem cels (ASCs) or adipose-derived stromal vascular fractions (ADSVFs) without adjuvant treatments, compared with placebo or hyaluronic acid in patients with knee osteoarthritis. VAS scale and WOMAC scores were used to determine pain relief and functional improvement, respectively. Cartilage status was analyzed using MRI. A total of 5 RCTs were included in the review, follow-up occurred at 6 months in one study and 12 months in the remaining four. Based on the meta-analysis, subjects who received ASCs or ADSVFs showed significantly better pain relief at 6 months (Z = 7.62; P\.0001) and 12 months (Z = 7.21; P\.0001) and functional improvement at 6 months (Z = 4.13; P\.0001) and 12 months (Z = 3.79; P = .0002), without a difference in procedure-related knee pain or swelling compared with controls. A total of three studies reported significantly improved cartilage status after the injection however a meta-analysis was not able to be done due to heterogenous MRI assessment. Limitations of the review include a small number of studies, small sample sizes, use of variable cell concentrations, and short term follow-up.

Tan et al. (2021) reviewed 19 total studies (Level 1 and 2) evaluating intra-articular injection of MSCs without adjuvant therapy, with a mean duration of followup of 11.9 months, and reported that only the source of MSCs and whether the MSCs were cultured or noncultured were clinically important and statistically significant moderators of the treatment outcome. Bone marrow MSCs reduced VAS for pain by 1.50 and WOMAC by 23.2 compared with adipose MSCs. In addition, the use of cultured MSCs resulted in reduced VAS scores and WOMAC scores compared to non cultured MSCs. Limitations noted by the authors include the level of evidence reviewed (1 and 2) and adequately powered trials, duration of follow-up (range 3-48 months, average 11.9 months) and pooling of studies which could have introduced confounders not controlled for in the original studies.

Anil et al. (2021) evaluated injectable nonoperative treatments for osteoarthritis of the knee using a network meta-analysis of RCTs that included intra-articular injections of various injectates (e.g., autologous conditioned serum, bone marrow aspirate, botulinum toxin, corticosteroids, hyaluronic acid, MSCs, ozone, saline, PRP, plasma rich growth factor, and SVF). A total of 79 RCTS with 8761 subjects were included in the review. VAS scores, and WOMAC scores, when available were analyzed at 1, 3, 6, and 12 months. Clinical outcomes were compared using a frequentist approach and treatments were ranked using the P-score. Follow-up ranged from four weeks to 24 months. At all post-injection time points, the treatment with the highest P-score for VAS score was SVF([P-score Range = 0.8922–99230). Additionally, the authors noted that SVF had the highest
WOMAC score at 12-months post-injection, (P-score = 0.9034), indicating that these patients also had the highest functional outcome scores following treatment. However, worth noting is that according to the authors, the harvest method of SVF in the majority of studies involved the use of collagenase to separate the adipose and in the United States collagenase digestion cannot be used due to FDA regulations. Therefore, for SVF to be used in the United States, it requires mechanical fractioning to separate the SVF from the adipose tissue. Limitations noted by the authors include lack of available data between the studies and reported outcome measures that were obtained at various points during the post-operative period. Additionally, variation in harvest- ing and separating SVF may lead to different therapeutic effects.

Ma et al. (2020) reviewed 10 RCTs and concluded that compared to the control groups intra-articular injected MSCs also resulted in decreased VAS scores and improved WOMAC scores in the short term. Reported follow-up in the studies reviewed was 6-12 months. An increase in cartilage volume occurred in the MSC group compared with the control group, although it was not significant, and although unable to conclude MSCs repair defects, the authors suggest it supports a delay in the degeneration of the cartilage. Limitations of the review include the use of various types of MSCs in the studies, control group heterogeneity, (hyaluronic acid was used in the control group in five of the studies, a placebo in four of the studies, and conservative management in one study), some subjects having advanced OA of Kellgren–Lawrence Grade 4 OA, and lack of complete data in some studies leading to attrition bias.

Prodromos et al. (2020) published the results of a systematic review evaluating autologous mesenchymal stem cell therapy as treatment of knee osteoarthritis. The review included 34 studies entered into three subgroups of studies: Group I included WOMAC and VAS score outcomes (n=29), Group 2 included studies that measured outcomes using other than WOMAC or VAS scores (n=5), and Group 3 included randomized using 1-3 injections of saline as a placebo arm (n=18). Various sources of stem cells were used in the studies including adipose derived stem cells, stromal vascular fraction, bone marrow aspirate, culture expanded bone marrow, and minimally manipulated fat grafts. Follow-up after treatment ranged from six months to 5 years, with a mean of 14.4 months for final followup. All studies in Group I reported significant improvement after treatment at all time points; WOMAC scores and VAS scores improved at six

months and final followup, and exceeded the minimal clinically significant difference at all time points. In Group 2 the reported scores improved significantly from baseline to final followup. No dose-response relationship was found between cell dose and outcome. In the author's opinion, stem cell injections for osteoarthritic knee pain results in relief that is longer lasting (at mean of 15.3 months) in comparison to conventional treatments (i.e., corticosteroids, hyaluronan, nonsteroidal anti-inflammatory, and oral analgesics.

Garza and colleagues (2020) evaluated intra-articular stromal vascular fraction (SVF) compared with placebo for reduction of symptoms associated with knee osteoarthritis in a randomized, controlled, double blind trial. Subjects received either high dose SVF (n=13), low dose SVF (n=13) or placebo (no SVF, n=13) injected into the knee joint. Outcomes were measured using WOMAC scores at 3, 6 and 12 months post injection and MRI at 6 months and one year post treatment. The primary efficacy followup point was six months, as such subjects were unblinded at this point in the trial. The median percent change in WOMAC for high dose, low dose and placebo group was 83.8%, 51.5%, and 25%, respectively at 6 month followup; at one year WOMAC scores were 76.9%, 76.9% and 46.2%, respectively. However, only 26 subjects were available for followup at one year versus 37 at six months. MRI at one year follow-up was available for 23 subjects, there was no evidence of disease progression or change in cartilage thickness. The authors concluded the SVF injections decreased osteoarthritic symptoms for at least 12 months. Limitations of the study include unblinding at 6 months, imputed scores for missing values, small sample size and short term followup. Additional long term evaluation is needed to determine impact to disease progression.

Lee et al. (2019) reported the results of a randomized, double blind placebo controlled trial evaluating high dose autologous adipose derived mesenchymal stem cell (MSC) injection for treatment of knee osteoarthritis. Patient selection criteria included Kellgren-Lawrence grade 2 to 4 osteoarthritis of the knee, pain of at least four or more on the VAS, for at least 12 weeks, and at least one focal or localized grade 3 or 4 lesion on MRI scan. Subjects received either intra-articular injection of normal saline (n=12) or adipose MSC injection (n=12) with followup at one, three and six months post injection. Results demonstrate that at six months followup injection of MSC was associated with improvement in WOMAC score, as compared to baseline (55% reduction), as well as VAS for knee pain, and range of motion. Outcomes for subjects within the control group were not significantly improved. MRI demonstrated no change of cartilage defect at six months in the treatment group, however MRI demonstrated an increased defect in the control group. In the authors opinion there was satisfactory improvement in function and pain relief at six months followup however additional studies are needed with larger sample size to firmly establish clinical efficacy.

A systematic review published by Pas et al. (2017a) evaluated stem cell injections for treatment of knee osteoarthritis. A total of five randomized controlled trials (RCT) and one non RCT met inclusion criteria and were included as part of the review. Inclusion criteria were published and unpublished trials, subjects with any degree of osteoarthritis of the knee, stem cells of any origin compared with any other intervention, a minimal proof of stem cell count/typing, and patient reported outcomes for pain, a validated imaging scoring system and/or adverse events. There was no restriction of time, language or content. In all studies bone-marrow-derived stem cells, adipose-derived mesenchymal stem cells and/or peripheral blood stem cells were used. The number of subjects injected with stem cells ranged from 15 to 36 ; 155 in total were treated with stem cells and 155 served as controls across all studies. In one trial subjects received a total of eight injections, in five trials subjects received only one injection of MSCs. Subjects in five RCTs received injections of platelet rich plasma (PRP) and/or hyaluronic acid (HA) at the same time as MSCs; HA and PRP were also used as monotherapy for the control groups. In two trials uncultured MSCs were used. The authors noted all trials were at high risk of bias, resulting in level-3 evidence. All five RCTs reported superior efficacy for patient-reported outcomes (Visual Analogue

Scale, Western Ontario and McMaster Universities Arthritis Index, Tegner, Lysholm, International Knee Documentation Committee, Knee Injury and Osteoarthritis Outcome Score, Lequesne) compared with controls at final follow-up which ranged from 24–48 months. No serious adverse events were reported. Superior radiological outcomes were found favoring stem cell injection. The authors concluded however in the absence of high level evidence stem cell injections for treatment of knee OA is not recommended.

Cui and colleagues (2016) published the results of a meta-analysis evaluating the efficacy of stem cell therapy in treating patients with osteoarthritis. A total of 18 clinical trials met the inclusion criteria, 10 single-arm prospective studies (sample range of 5-41), four quasi-experimental studies (sample range of 18-56), and four RCTs (sample range 50-56). The MSCs utilized were bone marrow-derived, adipose derived and/or peripheral blood stem cells, some in addition to an activation agent (e.g., collagen matrix, adipose tissue, platelet rich plasma). Follow-up within these trials ranged from three to 24 months. Various outcome measurements included International Knee Documentation Committee (IKDC) scores, Visual Analog Scores (VAS), Tegner and Lysholm scores, and Western Ontario and McMaster Universities OA Index (WOMAC) scores. Compared with pretreatment a pooled effect size was reported as 1.81 at 24 months, with all prior follow-up trending upward, favoring MSC treatment for reducing pain and improving function. A dose related response was unclear regarding the number of MSCs used in treatment. Using only the data from the RCTs MSC treatment was not found to be superior. Transient regional pain and local swelling were the predominant adverse vents reported (7 trials) and none of the patients were diagnosed with cancer associated with MSC use. Limitations of the study include small sample size, lack of long term follow-up, varying doses of MSCs, and the addition of activation agents, which also varied among trials.

Vega et al. (2015) reported the results of a RCT evaluating bone marrow-derived MSCs as treatment for osteoarthritis of the knee. All subjects had chronic knee pain and failure of other conservative measures. The control group (n=15) received intra-articular hyaluronic acid while the experimental group (n=15) received intra-articular injections of allogenic bone marrow-derived MSCs. Clinical outcomes were followed for one year and included assessment of pain, disability and quality of life and MRI for assessing cartilage quality. At one year follow-up the treatment group demonstrated decreases in poor cartilage areas, improved quality of cartilage and pain relief. The effects were significant at both 6 and 12 months for MSC treated subjects. The authors noted their results in comparison with other results for autologous bone marrow-derived MSCs was smaller, and for autologous adipose- derived MSCs was similar. The study is limited by short term follow-up and small sample size.

While there is a growing body of evidence, including systematic reviews and meta-analyses, the evidence assessing the safety and effectiveness of MSC therapy remains limited by short term outcomes, lack of controls, use of different sources and quanities of MSCs, inclusion of adjuvant therapy in some trials, and inconsistencies in reporting methods. Although some conclusions support improvement in pain and function for some individuals in the short term, limitations such as heterogeneity of inclusion and exclusion criteria, MSC therapies which have been applied in different stages of osteoarthritis, and lack of long term outcomes prohibit strong evidence based conclusions regarding clinical safety and efficacy.

Muscle/Tendon/Ligament Repair: Stem cell therapy as treatment of tendon and ligament disorders is also an emerging field. Similar to other musculoskeletal tissues tendons and ligaments possess poor regenerative capability. There is a paucity of studies evaluating the efficacy of stem cell therapy for tendon/ligament healing. A systematic review evaluating the evidence for the use of stem cell therapy for tendon disorders was published by Pas, et al., 2017(b). A total of four published trials and three unpublished/pending trials were included in the review (n=79). Two of the trials evaluated bone marrow stem cells injected for treatment of rotator cuff repair, one trial

used allogenic adipose derived stem cells for treatment of epicondylar tendinopathy and one trial evaluated bone marrow derived stem cells for treatment patellar tendinopathy. According to the authors all trials were high risk of bias and level four evidence. Absence of controls limited interpretation regarding any benefit. With the exception of the trial using adipose derived stem cells none of the trials using bone marrow MSCs performed cell culturing or cell typing. In epicondylar tendinopathy, patellar tendinopathy and rotator cuff repairs improved healing, functional outcomes and pain scores were reported compared with baseline. Re-rupture of repaired rotator cuffs treated with stem cells preoperatively were reduced in comparison with historical controls or other literature. Only one trial reported adverse events, safety concerns remain. Reporting of cell analysis was inconsistent among trials and it is unknown what if any effect cell dose had. The authors concluded the evidence was insufficient to support the use of stem cell therapy for treatment of tendon disorders.

Because of their multipotent potential and ability to exert paracrine effects and potential to improve blood flow mesenchymal stem cells have been studied as a treatment of rotator cuff disease (Lin, et al, 2017). Rotator cuff repairs occur most commonly at the tendon-bone interface. During repair, reattaching the tendon to the bone is challenging due to various physiological reasons, often resulting in frequent failure. Nevertheless, there is a paucity of evidence evaluating the effect of MSC therapy for rotator cuff disease and outcomes demonstrating improved healing are inconsistent.

U.S. Food and Drug Administration (FDA)
Medical and surgical procedures do not require FDA approval. In addition, 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, under Code of Federal Regulation, title 21, parts 1270 and 1271. Currently there are no allogenic MSC materials using engineered or expanded MSCs approved by the FDA for orthopaedic applications (Cook, Young, 2022). According to the FDA, "the only stem cell-based products that are FDA-approved for use in the United States consist of blood-forming stem cells (hematopoietic progenitor cells) derived from cord blood". Safety concerns of the FDA regarding the use of unproven stem cells include administration site reactions, failure of cells to work as expected, the growth of tumors, and the ability of cells to move from placement sites and change into inappropriate cell types and multiply.

Regenexx®: Regenexx ® (Des Moines, Iowa, [previously known as Regenerative Sciences]) "regenerative" procedures (e.g., RegenexxSD® [Same Day Stem Cell Procedure], RegenexxAD® [Adipose Derived Stem Cell Procedure]), have been recommended for treatment of musculoskeletal trauma, overuse injuries, and degenerative issues. During Regenexx® procedures, cells of various derivatives, often from bone, are injected to locally diseased joint areas with the expectation that they will seek out and repair diseased cartilage bone, ligaments and tendons. According to the manufacturer, the Regenexx- Same Day (SD)/Regenexx-SD Plus procedure involves the injection of a highly concentrated stem cell mixture combined with autologous platelet-derived growth factors, referred to as SCP (Super Concentrated Platelets). It has been proposed for a variety of orthopaedic applications including but not limited to repair or regeneration of musculoskeletal tissue, spinal fusion, and bone repair.

In addition, Regenexx describes a licensed culture-expansion site, Regenexx Cayman that provides Regenexx-C (cultured stem cell treatment) and Regenexx Cryopreservation (stem cell storage). The manufacturer asserts these techniques are reported to yield up to 1,000 times more stem cells. Regenexx-C is stated to be ideal for patients with more severe orthopaedic injuries or conditions, patients who want to treat multiple joints, or patients who want to store their stem cells for future treatment. This procedure is not FDA approved.

One randomized controlled (RCT) was located (Centeno, et al., 2018b) in the peer reviewed scientific literature evaluating Regenexx therapy for knee OA. This study included patients with symptomatic knee osteoarthritis (n=48) who were assigned to either an exercise therapy control group (n=22) or treatment group with image-guided injection of autologous bone marrow concentrate (BMC) and platelet products (n=26). At three months subjects were allowed to crossover to the bone marrow treatment group. Measured outcomes included the Knee Society Score (KSS), Pain Visual Analogue Scale, Short Form-12 Scales (SF-12), and Lower Extremity Activity Scale (LEAS). Follow-up for clinical outcomes occurred at 6-weeks, 3, 6, 12 and 24 months. A total of 14 patients were lost to follow-up. All 22 patients in the control group crossed over to BMC treatment after three months. Patients who received a specific protocol of BMC and platelet products improved significantly in activity levels, as well as pain, range of motion and stability, compared to patients who underwent a home exercise therapy program for 3 months. Pain decreased for both the exercise therapy and the BMC groups, and function increased for the BMC group, although did not differ significantly between the 2 groups. Exercise therapy provided significant improvements in ROM and activity levels at 3-months compared to baseline. No serious adverse events were reported. Limitations of this RCT include the small sample size and the allowance of those in the exercise group to crossover at three months and receive BMC. Additional controlled studies with larger sample sizes evaluating Regenexx processes/procedures/products are needed to support safety and effectiveness.

In 2020 Centeno et al. published mid-term results of a randomized controlled trial evaluating the use of bone marrow concentrate and platelet rich plasma versus exercise therapy as treatment for rotator cuff tears (n=25, 14 subjects in the bone marrow group, 11 subjects in the exercise therapy group) .The study is ongoing and the authors note enrolment continues however the midterm review includes the reported outcomes of subjects who reached 12 month followup (n=24). The preliminary outcomes suggest a size decrease in most tears post bone marrow treatment, and improvements in DASH and NPS scores at three and six months compared to exercise. However, final outcomes are pending completion of the study.

The overall body of evidence indicates that safety and efficacy of Regenexx procedures, including BMC with platelet rich plasma and other lysate preparations, are currently unproven. Although the body of evidence is emerging, concerns regarding quality and oversight, preparation, application/procedure, safety, clinical utility, and durability have been reported among authors.

Cartistem®: Cartistem® is a combination of human umbilical cord blood-derived mesenchymal stem cells and sodium hyaluronate, and is intended to be used as a single-dose therapeutic agent for cartilage regeneration in
humans with cartilage defects of the knee as a result of aging, trauma, or degenerative diseases (National Institute of Health, Clinicaltrials.gov NCT01733186). Although published results are not found in peer-reveiwed at this time according to Clinical Trials.gov studies are underway evaluating the efficacy and safety of Cartistem®.

Lipogem®: Lipogem® Microfragmented Adipose Tissue Transplant System (Lipogem, Norcross, GA) is an adipose-derived regenerative cell therapy described by the manufacturer as closed circuit processing system used to remove adipose tissue from the body and transfer it via injection into a patients injured joint or diseases soft tissue. It is asserted Lipogems preserves the structural properties and microarchitecture of the original tissue: the scaffold (the adipose tissue and the stromal structure), the cells (endothelium, pericytes / MSCs), and the growth factors (cytokines and chemokines. Lipogems received FDA 510(k) approval in 2016 as a suction lipoplasty system. It is noted with the 510(k) approval the device is intended for use in the following surgical specialties when the transfer of harvested adipose tissue is desired: orthopaedic surgery, arthroscopic surgery, neurosurgery, gastrointestinal and affiliated organ surgery, urological surgery, general surgery, gynecological surgery, thoracic surgery, laparoscopic surgery,

and plastic and reconstructive surgery when aesthetic body contouring is desired (FDA, K161636). Panchal et al (2017) reported on 17 subjects with osteoarthritis of the knee who underwent Lipogem injection intra-articularly under ultrasound guidance. Pre and post treatment outcomes were collected at six weeks, six months and 12 months following therapy using NPRS (numerical pain rating scale), the 100-point Knee Society Score (KSS) and lower extremity activity scale (LEAS). Although the authors reported significant improvements in MPRS, mean KSS at 12 months the study is limited by small sample population, lack of control, and short term outcomes. Additional research is required to support clinical efficacy.

Professional Societies/Organizations
The American Association of Orthopaedic Surgeons published an evidence based clinical practice guideline, endorsed by several other societies, on the management of glenohumeral joint OA (AAOS, 2020). Within this guideline the AAOS states that injectable biologics, such as stem cells, are not recommended in the treatment of glenohumeral joint osteoarthritis. There is 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 osteoarthritis. The strength of evidence was graded as "No reliable evidence" to determine benefits and harms.The 2021 updated guideline on management of osteoarthritis of the knee does not address stem cell injection (AAOS, 2021) nor does the guideline for osteoarthritis of the hip (AAOS, 2017).

The American College of Rheumatology and Arthritis Foundation published guidelines on osteoarthritis of the hand, hip, and knee and provide a strong recommendation against stem cell injections in patients with knee and/or hip osteoarthritis noting the "heterogeneity in preparations and lack of standardization of techniques". A recommendation was not made for hand osteoarthritis within the guideline because the use of stem cells has not been evaluated for this condition (ACRA, 2019).

The International Society of Stem Cell Research (ISSCR) published information regarding stem cell types and uses (ISSCR, 2019) and asserts there is little evidence they are beneficial. MSC therapy remains in early experimental stages. According to ISSCR, mesenchymal stem cells are cells that originate from stroma, the connective tissue surrounding tissues and organs. Although various MSCs are thought to have stem cell and immunomodulatory properties as treatment for various disorders. Scientists do not fully understand whether these cells are actually stem cells or what types of cells they are capable of generating. They do agree that not all MSCs are the same, and that their characteristics depend on where in the body they come from and how they are isolated and grown. Some types of stem cells are capable of migration after transplantation, meaning there is a risk of off-target effects and inappropriate integration.

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	No NCD found	
LCD	Local	No LCD found	

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare and Medicaid Services (CMS) code updates may occur more frequently than policy updates
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Experimental/Investigational/Unproven:

CPT®* Codes	**Description**
20999	Unlisted procedure, musculoskeletal system, general
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
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
0627T	Percutaneous injection of allogeneic cellular and/or tissue-based product, intervertebral disc, unilateral or bilateral injection, with fluoroscopic guidance, lumbar; first level
0628T	Percutaneous injection of allogeneic cellular and/or tissue-based product, intervertebral disc, unilateral or bilateral injection, with fluoroscopic guidance, lumbar; each additional level (List separately in addition to code for primary procedure)
0629T	Percutaneous injection of allogeneic cellular and/or tissue-based product, intervertebral disc, unilateral or bilateral injection, with CT guidance, lumbar; first level
0630T	Percutaneous injection of allogeneic cellular and/or tissue-based product, intervertebral disc, unilateral or bilateral injection, with CT guidance, lumbar; each additional level (List separately in addition to code for primary procedure)
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

Considered Experimental/Investigational/Unproven when used to report stem cells used as treatment of orthopaedic and/or musculoskeletal conditions:

HCPCS Codes	**Description**
P9099	Blood component or product not otherwise classified

***Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.**

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Revision Details

Type of Revision	Summary of Changes	Date
Annual	No clinical policy statement changes.	3/15/2024

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