Stem Cell Therapy for Orthopedic Indications (Including Allograft Bone Products Used With Stem Cells)*

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DESCRIPTION

Note: This policy addresses stem cell therapy for orthopaedic applications, in particular mesenchymal stem cells (MSCs). MSCs have been proposed as a type of regenerative therapy. Regenerative therapy is considered an emerging field of medicine focusing on repair, replacement, or regeneration of cells and tissues. MSCs are found in a variety of tissues and have the ability to rapidly proliferate and differentiate to musculoskeletal tissue, including bone and cartilage.

Stem cell transplantation using hematopoietic stem cells for treatment of blood cancer, non-cancer conditions and solid tumors are not in scope of this policy. Refer* to *medical policy 07.03.11 Hematopoietic Stem Cell Transplantation (Bone Marrow Transplant) Autologous and Allogeneic*.

Mesenchymal stem cells (MSCs)

Mesenchymal stem cells (MSCs) are non-hematopoietic, multipotent stem cells that can differentiate into a variety of cell types. MSCs have immunomodulatory properties and secrete cytokines. MSCs can be derived from a variety of sources, including adipose tissue (adipose tissue-derived mesenchymal stem cells (AD-MSCs), bone marrow (bone marrow derived mesenchymal stem cells (BM-MSCs), peripheral blood and synovial tissue/Synovium-derived mesenchymal stem cells (S-MSCs), however, bone marrow is currently the primary source of mesenchymal stem cell procurement. MSC therapy has been proposed as a treatment option for orthopedic indications that include but are not limited to the following:

- Knee: Arthritis, meniscus tears, tendon and ligament tears, overuse injuries and other conditions
- Hip: Injuries, arthritis, bursitis, and other degenerative conditions
- Shoulder: Arthritis, rotator cuff tears, and other shoulder conditions
- Spine and cervical conditions: Back pain, pain from bulging or herniated discs, degenerated disc or pain from an extruded or torn disc
- Elbow: Injuries, overuse conditions and arthritis (tendon and ligament issues)
- Hand/Wrist: Arthritis and other conditions
- Foot/Ankle: Ligament tears, sprains, and instability of the ankle joint, an alternative to fusion or replacement surgery of the ankle
- Non-union fractures

Mesenchymal stem cells (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 can 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 and there is some concern that autologous MSCs may induce tumors by changing the action of cancer cells and accelerating tumor growth, and that allogeneic MSCs may accelerate infectious risk.

Optimal materials or grafts that promote bone growth and healing require the following properties:

- Osteogenic: contains osteoprogenitor cells that can lay down a new bone matrix

- Osteoinductive: provides signals required to induce differentiation of MSCs into mature osteoblasts
- Osteoconductive: passive scaffolding to promote vascular invasion and bone apposition on the surface for new bone formulation

The proposed benefits of MSC therapy are improved healing and possible avoidance of surgical procedures with protracted recovery times. MSCs are used as a stand-alone therapy in the form of an injection or in combination with scaffolds

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 results have not yet been published, according to Clinical Trials.gov a study is 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).

Regenexx Stem Cell Procedure
Regenexx "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.

Common Conditions Treated:
- Osteoarthritis of the knee, hip, ankle, shoulder, hands
- Patients with non-healing bone fractures
- Certain types of injuries to the meniscus, hip labrum, shoulder labrum, shoulder SLAP lesions
- Tendon injuries such a partial rotator cuff or other partial muscle-tendon tears

- Avascular necrosis of the hip, shoulder, knee, ankle

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.

Cartilage Defects

Clinical Context and Therapy Purpose
The purpose of stem cell therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with osteoarthritis (OA) or focal cartilage defects.

Osteoarthritis (OA) is a degenerative joint disease characterized by loss of cartilage, osteophyte formation, and periarticular bone change, resulting in disability. Mesenchymal stem cells (MSCs) are emerging as an attractive option for osteoarthritis (OA) of the knee joint, due to their marked disease-modifying ability and chondrogenic potential.

Populations
The relevant population of interest is individuals with osteoarthritis (OA) or focal cartilage defects.

Interventions
The therapy being considered is treatment with mesenchymal stem cells (MSCs).

Comparators
Comparators of interest include conservative management with medication or hyaluronic acid (HA) injection, microfracture, and autologous chondrocyte implantation.

Outcomes
The general outcomes of interest are symptoms, morbid events, functional outcomes, QOL, and treatment-related morbidity (TRM). Specific scales may include the:

- Knee Injury and Osteoarthritis Outcome Score (KOOS; 5 subscales with 0-100 scale),
- Lysolm Knee Scale (LKS) score (0-100 scale),
- Tegner Activity Score (TAS); a visual analog scale (VAS) for pain (0-100 mm or 0-10 cm scale),
- Western Ontario and McMaster Universities Arthritis Index (WOMAC) which has 3 subscores: pain, which includes 5 items; stiffness, with 2 items; and physical function, with 17 items.

- WOMAC response criteria is an improvement of 20% in at least 2 items together with an improvement of 10 points in the overall scale.
- Cartilage is evaluated with the Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART, 0-100 points, where higher scores indicate better cartilage repair).
- Follow-up over months to years is of interest for relevant outcomes.

Review of Evidence
In January 2022, ECRI completed a clinical evidence assessment regarding allogeneic mesenchymal stem cell therapy for chronic knee pain. This report focuses on intra-articular allogeneic mesenchymal stem cell (MSC) injection's safety and effectiveness for relieving pain from knee osteoarthritis (OA) compared with other nonsurgical approaches to treating chronic joint pain. We selected the best available evidence and included studies reporting on patients with chronic joint pain of nonmalignant musculoskeletal etiology, originating in a synovial joint and treated with intra-articular or arthroscopic injection of allogeneic MSCs. We included several systematic reviews (SRs) on MSC use for knee OA because they had different purposes and different inclusion and analysis methods. The SRs assessed cell therapy for OA, which included allogeneic MSC therapy, MSC injections for improving OA-related structural outcomes, and the effect different MSC sources (allogenic versus autologous) have on knee OA. Our searches identified studies examining only chronic knee pain. Two SRs used network meta-analysis to make broad treatment comparisons. Evidence limitations: Substantial heterogeneity across studies greatly hampers the ability to make conclusions about MSC therapy's efficacy for knee OA. In knee studies included in the SRs, differences in dosage, source, processing methods, number of injections, OA severity, and the countries and health systems in which studies were conducted contribute to the heterogeneity and limit the evidence base's reliability. Small sample sizes and lack of blinding in most studies also contribute to moderate to high risk of bias. An SR (Ding et al. 2021) noted the "study is not suitable for making conclusions about which strategy is more advanced in the clinic but is more suitable for making recommendations for the design of further RCTs." All SRs cited the need for more high-quality RCTs to determine the proper methods for using autologous or allogeneic MSCs to treat knee OA. The RCTs examining allogeneic MSC therapy had too few patients to produce reliable results or to add to the SRs' findings.

Evidence is inconclusive: mixed results

Conclusions:
Available evidence from three systematic reviews (SRs) with meta-analyses and three additional randomized controlled trials (RCTs) suggests that intra-articular allogeneic MSC injections may reduce chronic pain in knee OA, but substantial heterogeneity across studies limits the reliability of SR results and the ability to make conclusions about how it compares with other noninvasive treatments for OA knee or ankle joint pain.

Rationale
Differences across studies in MSC dose, source, processing methods, number of injections, and OA severity among patients prevent drawing conclusions about comparative effectiveness. Also, where studies were conducted (i.e., different clinical practices in various countries and health systems) contributes to data heterogeneity, limiting the evidence base's reliability. The uncertainty within the evidence base about how best to use allogeneic MSCs has led to uncertainty about MSC therapy's value compared with other nonsurgical treatments for chronic OA joint pain.

Evidence gaps:
Large multicenter RCTs that use standardized methods of allogeneic MSC preparation, dose, and administration are needed to determine how best to use allogeneic MSCs to treat joint OA.

In January 2022, ECRI completed a clinical evidence assessment regarding autologous mesenchymal stem cell therapy for chronic knee or ankle pain from osteoarthritis. This report focuses on intra-articular autologous MSC injection's safety and effectiveness for relieving pain from knee or ankle joint OA compared with other nonsurgical approaches to treating chronic joint pain. Due to the many studies and systematic reviews (SRs) published on mesenchymal stem cells (MSC) use in joint pain, we focused our selection criteria to SRs with meta-analyses published within the past two years, which also are more likely to reflect current clinical practices. We included several SRs on MSC use for knee OA that have some overlapping studies because each SR had a different purpose and different inclusion and analysis methods. The SRs assessed MSC dosage, compared adipose tissue- derived MSC and stromal vascular fraction, made comparisons with hyaluronic acid injections and platelet rich plasma, compared bone marrow (BM)-derived MSC and adipose-derived (AD) MSC, or assessed only autologous MSCs (some SRs combined autologous and allogeneic MSC). Some SRs used network meta-analysis to make broad treatment comparisons.

We reviewed full text of the 10 SRs we selected, which provided data to address the ability of intra-articular autologous MSC injection to treat chronic OA joint pain in the knee or ankle. We assessed nice SRs that evaluated MSC use for chronic OA knee pain and one SR that assessed MSC for chronic OA ankle pain. The SR on ankle pain was unable to draw any conclusions due to very low strength of evidence. Evidence limitations: Substantial heterogeneity across studies greatly hampers the ability to make conclusions about MSC therapy's efficacy for knee OA. The SR on MSC for ankle OA pain was inconclusive due to very-low-strength evidence. In knee studies, differences in dosage, source, processing methods, number of injections, OA severity, and the countries and health systems in which studies were conducted contribute to the heterogeneity and limit the evidence base's reliability. Small sample sizes and lack of blinding in most studies also contribute to moderate to high risk of bias. An SR with network meta-analysis (Zhao et al. 2021) noted "the heterogeneity between studies may limit the reliability of our results." Autologous MSC was the most often studied preparation, but some SRs included studies using allogeneic preparations. Dai et al. 2021 questioned

whether the response to MSC exceeded the minimum clinically important difference. The uncertainty within the evidence base about how best to make and administer MSCs has led to uncertainty about MSC therapy's value compared with other nonsurgical treatment options. All SRs cited the need for more high-quality RCTs to determine the proper methods for using MSC to treat knee OA.

Evidence is inconclusive: mixed results

Conclusions
Available evidence from several systematic reviews (SRs) with meta-analyses suggests that intra-articular autologous MSC injections may reduce chronic pain in knee OA, but substantial heterogeneity across studies limits the reliability of SR results and the ability to make conclusions about how it compares with other noninvasive treatments for OA knee or ankle joint pain. The strength of evidence on ankle OA was too low to permit conclusions.

Rationale
Differences across studies in MSC dose, source, processing methods, number of injections, and OA severity among patients prevent drawing conclusions about comparative effectiveness. Also, where studies were conducted (i.e., different clinical practices in various countries and health systems) contributes to data heterogeneity, limiting the evidence base's reliability. The uncertainty within the evidence base about how best to use MSC has led to uncertainty about MSC therapy's value compared with other nonsurgical treatments for chronic OA joint pain.

Evidence Gaps
Large multicenter randomized controlled trials (RCTs) that use standardized methods of MSC preparation, dose, and administration are needed to determine how best to use MSC to treat joint OA.

In 2020, Maheshwer et. al. identified 25 studies with 439 participants that used MSCs for treatment of OA.[4,] Although 13 studies were considered level I RCTs by the authors (range of 7 to 40 participants), low quality RCTs would normally be downgraded to level II. Meta-analysis suggested improvement in self-reported function, but only in patients who underwent concomitant surgery, and there was no significant improvement in pain. Few studies reported on cartilage quality. Most of the studies were rated as poor or fair quality. Conclusions are limited due to substantial variability in MSC source, preparation, and concentration in the current literature.

Kim et. al. (2020) in a more focused systematic review and meta-analysis of 6 randomized controlled trials (203 patients) that evaluated cultured MSCs for OA was reported by Kim et al (2020). Four of the studies used bone-marrow derived MSCs, 1 used adipose-derived cells and the other cultured placental cells. Only 2 of the 6 studies were rated as low risk of bias. Pain outcomes measured with VAS and WOMAC pain scales were improved at 6 to 12 months, but there was no significant improvement in measures of WOMAC function or cartilage measured by magnetic resonance imaging.

One randomized controlled trial by Centeno, et al. (2018) evaluated Regenexx therapy for knee osteoarthritis (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 included 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.

Borakati et al (2017), completed a systematic review and meta-analysis which included 15 comparative studies (n=582) on the use of MSCs to treat OA or focal osteochondral lesions. The studies (13 published and 2 unpublished data) included 5 RCTs, 1 case-control, and 9 cohort studies. A majority of the studies were conducted in Asia, and the source of the MSCs varied (bone marrow, blood, amniotic fluid, adipose tissue). The largest trial had only 56 participants, giving low statistical power for the individual studies. The overall quality of the evidence was considered low, with 3 studies rated as "satisfactory" and the rest rated "poor" on the Jadad scale. Pain assessment results were noted for each of the controlled studies, resulting in a pooled standardized mean difference of -1.27 (95% confidence interval, -1.95 to -0.58) in favor of the group treated with MSCs. Reviewers reported a Z-statistic effect size of 3.62, again in favor of the groups treated with MSCs ($p<0.001$); although there was high heterogeneity across controlled studies (I^2=92%). There was also suggestion of publication bias; the investigators found 79 trials on clinicaltrials.gov, of which only 3 were listed as ‘complete with results,’ many trials had been inactive for several years, and 9 had ‘unknown’ status.

The source of MSCs may have an impact on outcomes, but this is not well-understood, and the available literature uses multiple sources of MSCs. Because of the uncertainty over whether these products are equivalent, the evidence is grouped by the source of MSC.

Summary of Evidence

Clinical Issues for Application of Mesenchymal Stem Cells

- There is no consensus on the optimal dose or cell number to achieve the utmost effect of stem cells. The optimal dose of MSC implantation for cartilage regeneration has not yet been established.
- Treatment strategies for clinical application may also be one of the issues faced by clinicians. Injective treatment is relatively efficient because it is easy to apply and does not require hospitalization, but precise delivery to target site may be difficult.
- Potential risks of MSCs in clinical use, such as tumorigenesis, immune response, and heterotrophic calcification are also considerable issues. Therefore, it should be recognized that such risk of MSC-mediated abnormal reactions might occur in some cases and mandating a careful assessment of the patient's condition. Further research is also needed to guarantee the safety of MSCs.

The use of mesenchymal stem cells (MSCs) for orthopedic conditions is an active area of research. Despite continued research into the methods of harvesting and delivering treatment, there are uncertainties regarding the optimal source of cells and the delivery method and safety. Mesenchymal stem cells (MSCs) may be derived from a variety of sources, including adipose tissue [adipose tissue-derived mesenchymal stem cells (AD-MSCs)] bone marrow [bone marrow derived mesenchymal stem cells (BM-MSCs)], peripheral blood and synovial tissue/synovium-derived mesenchymal stem cells [S-MSC]). The evidence includes systematic reviews-meta-analysis, randomized controlled trials (RCTs) and nonrandomized comparative trials. The quality of evidence is low and there is a possibility of publication bias. Overall, there is a lack of evidence that clinical outcomes are improved with the use of mesenchymal stem cells (MSCs) for orthopedic conditions. A recent evidence review completed by ECRI January 2022, states that differences across studies in MSC dose, source, processing methods, number of injections, and OA severity among patients prevent drawing conclusions about comparative effectiveness. Also, where studies were conducted (i.e., different clinical practices in various countries and health systems) contributes to data heterogeneity, limiting the evidence base's reliability. The uncertainty within the evidence base about how best to use MSC has led to uncertainty about MSC therapy's value compared with other nonsurgical treatments for stem cell therapy for orthopedic indications. The evidence is insufficient to determine the effects of the technology on health outcomes. ***Note:*** *Current society guidelines do not recommend the use of stem cell therapy for orthopaedic indications their current positions include the following information:*

- *"There is little data to suggest stem cell therapy will benefit patients with advanced osteoarthritis. Furthermore, there is no data to support the idea that stem cell can sense the environment into which they are injected and repair damaged tissue. The claims that stem cells regenerate severely damaged or lost cartilage is not supported by scientific evidence. The available evidence is troubling and does not allow an assessment as to whether the potential clinical benefits of such therapies outweigh any potential harms. While the efficacy of this*

treatment has yet to be established, the potential harm clearly exits and is likely underappreciated."

Meniscal Defects

Clinical Content and Therapy Purpose
The purpose of stem cell therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with meniscal defects.

Populations
The relevant population of interest is individuals with meniscal defects.

Interventions
The therapy being considered is stem cell therapy.

Comparators
Comparators of interest include conservative management.

Outcomes
The general outcomes of interest are symptoms, morbid events, functional outcomes, quality of life (QOL), and treatment-related morbidity (TRM).

Review of Evidence
Damage to the meniscal cartilage in the knee is a very common orthopedic injury and predisposes to the development of OA. The tissue is relatively avascular and does not spontaneously heal well.

In 2017, Whitehouse et. al. published a report on techniques of in vitro expansion of autologous-derived MSCs and a case series of the first-in-human implantation to treat meniscal defects in 5 patients. The regulatory framework in the United Kingdom allows cell manipulation and requires immunohistochemical documentation of the presence and volume of mesenchymal cells. Over the first 12 months post procedure, 3 of the 5 patients were reported to have clinical symptom relief, which persisted through 24 months. MRI scans showing lack of meniscal displacement were the only other postoperative assessment. The 2 patients who failed to obtain symptom relief at 6 and 12 months had to repeat arthroscopic procedures with meniscectomy.

Vangsness et. al. (2014) reported on an industry-sponsored phase 1/2 randomized, double-blind, multicenter Study of Chondrogen - Adult Universal Cell Delivered by Intra-Articular Injection Following Meniscectomy in Patients 18-60 Years (NCT00225095, NCT00702741) of cultured allogeneic MSCs (Chondrogen; Osiris Therapeutics) injected into the knee after partial meniscectomy. The 55 patients in this United States study were randomized to intra-articular injection of either $50´10^6$ allogeneic MSCs, $150´10^6$ allogeneic MSCs in HA, or an HA vehicle control at 7 to 10 days after meniscectomy. The cultured MSCs were derived from BMAC of

unrelated donors. At 2-year follow-up, 3 patients in the low-dose MSC group had significantly increased meniscal volume measured by MRI (with an a priori determined threshold of at least 15%) compared with none in the control group or the high-dose MSC group. There was no significant difference between the groups in LKS scores. On subgroup analysis, patients with OA who received MSCs had a significantly greater reduction in pain at 2 years than patients who received HA alone. This trial appears to have been a post hoc analysis and, hence, should be considered preliminary. No serious adverse events were reported as related to the investigational treatment.

Summary of Evidence
The evidence on the use of MSCs to repair or regenerate damaged meniscal tissue consists of preclinical animal studies, first-in-human uncontrolled implantation of expanded autologous MSCs into meniscal tears, and an early-phase randomized trial of cultured allogeneic MSCs injected into the site of partial meniscectomy. Results are preliminary. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Joint Fusion Procedures

Clinical Context and Therapy Purpose
The purpose of stem cell therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with joint fusion procedures.

Populations
The relevant population of interest is individuals with joint fusion procedures.

Interventions
The therapy being considered is stem cell therapy.

Comparators
Comparators of interest include iliac crest bone graft.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, quality of life (QOL) and treatment related morbidity (TRM).

Demineralized bone matrix (DBM) is a type of allograft. It is produced through a process that involves the decalcification of cortical bone; substantially decreasing the structural strength. However, it is more osteoinductive than ordinary allograft. Although the reason for this is not completely understood, it has been speculated that the osteoinductive growth factors contained in the extracellular bone matrix are easily accessed once the mineral phase of the bone has been removed.

Cell Based

Bone graft substitutes that are cell-based use cells to generate new tissue either alone or seeded onto a support matrix (e.g., in combination with allograft material). Support matrix may include xenograft (i.e., bovine) or human type I collagen. Cell based substitutes that are available include mesenchymal and other cell-based products.

- Mesenchymal stem cells (MSCs) may also be administered by combining the cells with demineralized bone matrix (DBM). DBM is considered minimally processed tissue and does not require FDA approval. MSCs are multipotent stem cells that express a variety of different cell surface proteins and can differentiate into a variety of cell types. Obtained from bone marrow they have shown to differentiate into osteoblasts, chondrocytes, myocytes, adipocytes, and neuronal cells.
- The use of demineralized bone matrix (DBM) with MSCs has been and continues to be investigated for various procedures, including spinal fusion and for intervertebral disc regeneration. Although currently under investigation, data published in the medical literature evaluating cell-based substitutes is in preliminary stages and mainly in the form of nonhuman trials or case reports; data supporting safety and efficacy are lacking. Therefore, the use of allograft bone products containing viable stem cells, including but not limited to demineralized bone matrix (DBM) with stem cells, is considered investigational for all orthopedic applications, due to the lack of evidence supporting safety and efficacy.

There is limited evidence on the use of allografts with stem cells for bone fusion of the extremities of spine or the treatment of nonunion. The results of several industry sponsored early phase trials are available.

In 2017, Peppers et. al. reported on a prospective, radiographic evaluation, multicenter study of allogeneic bone matrix containing stem cells (Trinity Evolution) in patients undergoing two-level anterior cervical discectomy and fusion. This study involved 40 patients that presented with symptomatic cervical degeneration at two adjacent vertebral levels and underwent instrumented anterior cervical discectomy and fusion (ACDF) using Trinity Evolution (TE) autograft substitute in a polyetheretherketone (PEEK) cage. At 12 months, radiographic fusion status was evaluated by dynamic motion plain radiographs and thin cut CT with multi-planar reconstruction by a panel that was blinded to clinical outcome. Fusion success was defined by angular motion ($\leq 4°$) and the presence of bridging bone across the adjacent vertebral endplates. Clinical pain and function assessments included the Neck Disability Index (NDI), neck and arm pain as evaluated by visual analog scales (VAS), and SF-36 at both 6 and 12 months. At both 6 and 12 months, all clinical outcome scores (SF-36, NDI, and VAS pain) improved significantly ($p < 0.05$) compared to baseline values. There were no adverse events or infections that were attributed to the graft material, no subjects that required revisions, and no significant decreases to mean neurological evaluations at any time as compared to baseline. At 12 months, the per subject and per level fusion rate was 89.4 and 93.4%, respectively. Subgroup analysis of subjects with risk factors for pseudoarthrosis (current or former smokers, diabetic, or obese/extremely obese) compared to those without risk factors demonstrated no significant differences in fusion rates. Limitations to this study

include a lack of a control group and thus TE treatment was not directly compared to autograft or non-cellular autograft treatments. Additionally, since the surgeons were not restricted with their use of operative approaches or fixation, either or both may have impacted outcomes. The impact of these factors on the outcome was not evaluated. Lastly there was no sample size estimation in the protocol because there were no formal statistical hypotheses. The authors concluded, subjects who received Trinity Evolution in combination with PEEK interbody device during a two-level ACDF procedure had a high rate of fusion success both overall and when stratified into high-risk groups, while having no serious adverse events related to the graft material.

A prospective, clinical, and radiographic 12-month outcomes study (2016 Vanichkachorn et.al) of patients undergoing single level anterior cervical discectomy and fusion (ACDF) for symptomatic cervical degenerative disc disease utilizing a novel viable allogeneic stem cell and cancellous bone matrix (Trinity Evolution) was reported using historical controls as the comparator. The ACDF procedure was performed using the polyetheretherketone interbody spacer and bone graft substitute (Trinity Evolution) in 31 patients at multiple clinical sites. At 6 and 12 months, radiographic fusion was evaluated as determined by independent radiographic review of angular motion (≤4°) from flexion/extension X-rays combined with presence of bridging bone across the adjacent endplates on thin cut CT scans. In addition, other metrics were measured including function as assessed by the Neck Disability Index (NDI), and neck and arm pain as assessed by individual Visual Analog Scales (VAS). The fusion rate for patients using a PEEK interbody spacer in combination with TE was 78.6 % at 6 months and 93.5 % at 12 months. When considering high risk factors, 6-month fusion rates for patients that were current or former smokers, diabetic, overweight or obese/extremely obese were 70 % (7/10), 100 % (1/1), 70 % (7/10), and 82 % (9/11), respectively. At 12 months, the fusion rates were 100 % (12/12), 100 % (2/2), 100 % (11/11) and 85 % (11/13), respectively. Neck function, and neck/arm pain were found to significantly improve at both time points. Reported adverse events included carpal tunnel syndrome, minor pain, numbness, permanent and/or unresolved pain and swelling. Independent medical adjudication of the 26 adverse events occurring in 31 patients found that no adverse events were definitely or probably related to Trinity Evolution, However, 5 adverse events were found to be possibly related to Trinity Evolution with 3 events of mild severity and 2 of moderate severity.

In 2015, Jones et. al. reported on a prospective, multicenter, open-label clinical trial using allogeneic bone matrix containing viable osteogenic cells (Trinity Evolution) in foot and/or ankle arthrodesis. A total of 103 subjects were prospectively enrolled at 10 participating sites. No restrictions were placed on the diagnosis, which included arthritis (primary osteoarthritis, post-traumatic osteoarthritis, and rheumatoid), deformity, neuropathy (Charcot and diabetic), revision surgery and degenerative joint disease, and arthrodesis was performed on 171 joints. The per protocol population consisted of 92 patients at 6 months and 76 patients at 12 months, with 153 and 129 total arthrodesis, respectively. At 6 weeks and at 3, 6, and 12 months, imaging was performed and the subject's pain, function, and quality of life (QOL) status (Visual Analog Scale, American

Orthopaedic Foot & Ankle Society Hindfoot Scale, and the Short Form 36) were recorded. At 6 months, fusion rates were 68.5% for all patients and 81.1% for all joints; at 12 months, rates were 71.1% and 86.8%, respectively. Certain high-risk subjects (eg, with diabetes or obesity) had fusion rates comparable to those of normal patients. Statistically significant improvements in pain, function, and QOL were observed, and fusion correlated with both function and QOL outcomes at 6 and 12 months. There were no adverse events attributable to CBA. The authors concluded fusion rates using CBA were higher than or comparable to fusion rates with autograft that have been reported in the recent literature, and CBA fusion rates were not adversely affected by several high-risk patient factors. CBA was a safe and effective graft material to achieve fusion in patients with compromised bone healing and may provide an effectively autograft replacement for foot and/or ankle arthrodesis.

In 2014, Eastlack et. al. reported on outcomes from a prospective multicenter study of 182 patients treated with anterior cervical discectomy and fusion using Osteocel Plus in a polyetheretherketone cage and anterior plating at 1 or 2 consecutive levels. Clinical outcomes included visual analogue scale for neck and arm pain, neck disability index, and SF-12 physical and mental component scores. Computed tomography and plain film radiographic measures included assessment of bridging bone, disc height, disc angle, and segmental range of motion. At 24 months, 74% of patients (180/249 levels treated) were available for follow-up. These patients had significant improvements in clinical outcomes, with 87% of levels achieved solid bridging, and 92% of levels had a range of motion less than 3 degrees. With 26% loss to follow up at 24 months and lack of standard care control group, interpretation of these results is limited.

Summary of Evidence
They use of mesenchymal stem cell (MSCSs) based bone graft substitutes has been and continues to be investigated for various procedures, including spinal fusion, intervertebral disc regeneration and other orthopedic procedures. The evidence on the use of MSCs as a component of joint fusion procedures primarily comes from industry-sponsored, prospective, open-label procedures. Although currently under investigation data supporting safety and efficacy of these indications is lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

The International Society of Stem Cell Research (ISSCR)
In 2019, 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. 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.

American College of Rheumatology/Arthritis Foundation
In 2019, the American College of Rheumatology/Arthritis Foundation updated the 2012 ACR guideline for the management of osteoarthritis for the management of osteoarthritis of the hand, hip and knee which included the following recommendation:

- Stem cell injections are strongly recommended *against* in patients with knee and/or hip OA.
- There is concern regarding the heterogeneity and lack of standardization in available preparations of stem cell injections, as well as techniques used. This treatment has not been evaluated in hand OA and, therefore, no recommendation is made with regard to OA of the hand.

American Academy of Orthopaedic Surgeons (AAOS)
In 2020, the American Academy of Orthopaedic Surgeons (AAOS) updated their position statement on the use of emerging biologic therapies. This updated position statement applies to the use of stem cell and other biologic treatments for musculoskeletal joint conditions. The position statement states the following:

The increasing use of biologics to try to improve outcomes for orthopaedic patients presents new questions of safety and effectiveness for those products. As noted in the statement "Innovation and New Technologies in Orthopaedic Surgery," 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 regard to the requirements for evidence of safety and effectiveness needed for clearance by regulatory bodies, including the 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 believes that surgeons should be cognizant of the risks, benefits, regulatory status, and labeled indications of the products they use.

For all products, but particularly those for which the FDA does not critically evaluate effectiveness data, clinicians bear a greater responsibility to independently weigh that evidence. This responsibility also extends to off-label use of FDA-regulated products and cases where the devices used to create or deliver the biologic product, rather than the product itself, are what has been approved by the FDA. It also applies to cases where a manufacturer believes they are exempt from certain FDA regulations without formal review of exemption, such as the so-called 361 exemption for human cell and tissue products. In all of these examples, the clinicians using these biologic products need to be particularly careful to weigh the available evidence and conduct shared decision making with the patient in the informed consent process.

The AAOS Standards of Professionalism state, "An orthopaedic surgeon, or his or her qualified designee, shall present pertinent medical facts and recommendations to, and obtain informed consent from, the patient or the person responsible for the patient." The mandatory standard obligates surgeons to disclose any products that may be used during the episode of care and engage in frank discussion regarding the risks and benefits of biologics when they are part of that episode of care.

For any product, but in particular for biologic products where information on efficacy may be limited, orthopaedic surgeons and their organizations/facilities should support and participate in orthopaedic randomized, controlled trials; registries; and other data collection systems. Through voluntary reporting of key patient and orthopaedic treatment information to local, state, and national repositories, patient outcomes will be improved. Documentation and reporting are critical to establishing the body of evidence needed to demonstrate the safety and effectiveness of emerging biologics.

AAOS champions the interests of patients by improving treatment options through education and research and by fostering a culture of safety and evidence-based treatment.

In 2020, the American Academy of Orthopaedic Surgeons (AAOS) updated their position statement on the management of glenohumeral joint osteoarthritis that included the following recommendation:

- Injectable Biologics: In the absence of reliable evidence, it is the opinion of the work group that injectable biologics, such as stem cells or platelet-rich plasma, cannot be recommended in the treatment of glenohumeral osteoarthritis.

American Association of Hip and Knee Surgeons (AAHKS)
In 2019, the American Association of Hip and Knee Surgeons, Hip Society, and Knee Society issued a position statement on biologics for advanced hip and knee arthritis which included the following:

An increasing number of facilities and physicians have begun to offer intraarticular injections of stem cells and platelet rich plasma (PRP) as a therapeutic intervention to patients with advanced hip and knee arthritis.

It is our position that biologic therapies, including stem cell and PRP injections, cannot currently be recommended for the treatment of advanced hip or knee arthritis.

This position statement has been endorsed by The Hip Society and The Knee Society. An increasing number of facilities and physicians have begun to offer intraarticular injections of stem cells and platelet rich plasma (PRP) as a therapeutic intervention to patients with advanced hip and knee arthritis. These injections are often marketed directly to the public based on the promise of pain relief and healing of damaged cartilage. Improvements in joint function, reduction in pain, and an increase in cartilage in the affected joint are often touted as potential benefits. Patient testimonials or expert opinions

are often used to demonstrate that these "natural" alternatives to major surgery are effective. However, these claims are not based on scientific evidence. Furthermore, these treatments have not been standardized, are often administered without approval from the Food and Drug Administration (FDA) and are typically very costly to the patient as they are not covered by insurance companies. In the absence of regulatory oversight, the formulations for the biologic injections may vary dramatically between manufacturers, preparation, processing, host biology, anatomic location, and disease type.

Biologic treatments such as stem cell and PRP injections have some promising applications in many different areas of health and medical research. There is potential for these treatments to repair damaged tissues and augment the body's reparative process following injury. With regards to orthopaedics, stem cells may have the potential of regenerating damaged cells and developing into bone and cartilage. PRP contains growth factors that may reduce inflammation and promote healing. Unfortunately, highly preliminary basic science research has prematurely led to the rapid promotion of these technologies for clinical use in a number of diseases including osteoarthritis. Osteoarthritis is a slowly progressive degenerative disorder that involves damage to joint cartilage, structural changes in bone, and inflammation of the soft tissues around the joint. Advanced arthritis involves complete loss of cartilage and exposure of damaged bone (so-called "bone-on-bone arthritis"). Unfortunately, there is currently no curative treatment for advanced hip and knee arthritis**.** For many patients with advanced hip and knee arthritis, nonsurgical management results in continued pain and loss of function that negatively impacts quality of life. Total hip and knee arthroplasty is evidence-based and remains the mainstay of treatments for those with advanced degenerative disease who fail nonsurgical management. While joint replacement has been shown to be very effective at improving quality of life for most patients, surgery is not without risks and associated fears for some patients.

The published literature studying the use of biologics for the treatment of osteoarthritis is evolving. Some evidence suggests that PRP may temporarily improve the symptoms of mild to moderate osteoarthritis of the knee. However, there is little data to suggest it will benefit patients with advanced osteoarthritis. Furthermore, there is no data to support the idea that stem cells can sense the environment into which they are injected and repair damaged tissue. The claim that either PRP or stem cells regenerate severely damaged or lost cartilage is not supported by scientific evidence. The limited amount of available scientific evidence is troubling and does not allow an assessment as to whether the potential clinical benefits of such therapies outweigh any potential harms, or if these biologic therapies are more cost-effective than standard treatments such as acetaminophen, oral anti-inflammatory agents or corticosteroid injections.

While the efficacy of these treatments has yet to be established, the potential for harm clearly exists and is likely underappreciated. While PRP is generally considered safe, the injection of any substance in the knee carries the potential for complications including intraarticular infection. Multiple cases of serious harm have been documented following stem cell treatments, and these adverse events are likely underreported given the current

regulatory environment. It is paramount that the safety of these treatments be fully established before they can be supported for routine use.
It is therefore our position that biologic therapies, including stem cell and PRP injections, cannot currently be recommended for the treatment of advanced hip or knee arthritis. With unproven benefits, high out-of-pocket costs for patients, and clear safety concerns, we do not support the routine clinical use of these therapies. While we do recognize the potential benefit of biologic therapies, we encourage rigorous, well-designed clinical trials to establish the safety, efficacy, and cost-effectiveness of these potential treatments prior to widespread adoption.

American Association of Neurological Surgeons
In 2014, the American Association of Neurological Surgeons (AANS) issued a guideline on fusion procedures for degenerative disease of the lumbar spine that states "The use of demineralized bone matrix (DBM) as a bone graft extender is an option for 1 and 2 level instrumented posterolateral fusions. Demineralized Bone Matrix: Grade C (poor level of evidence)."

Regulatory Status
The U.S. Food and Drug Administration (FDA) regulates 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. MSCs are included in these regulations.

Concentrated autologous mesenchymal stem cells (MSCs) do not require approval by the U.S. Food and Drug Administration (FDA). No products using engineered or expanded MSCs have been approved by the FDA for orthopedic applications.

The following products are examples of commercialized demineralized bone matrix (DBM) products. They are marketed as containing viable stem cells (MSCs). In some instances, manufacturers have received communications and inquiries from the FDA related to the appropriateness of their marketing products that are dependent on living cells for their function.

- Allostem (AlloSource): partially demineralized allograft bone seeded with adipose-derived MSCs.
- Map3 (RTI Surgical) contains cortical cancellous bone chips, DBM, and multipotent adult progenitor cells.
- Osteocel Plus (NuVasive): DBM combined with viable MSCs that have been isolated from allogeneic bone marrow.
- Trinity Evolution Matrix (Orthofix) DBM combined with viable MSCs that have been isolated from allogeneic bone marrow.
- Vitoss Bioactive Foam Bone Graft Substitute (Stryker): Type I bovine collagen mixed with autologous mesenchymal stem cells (MSCs).
- Copios Bone void filler (sponge and powder disc) (Kensey Nash): Type I bovine dermal collagen mixed with autologous mesenchymal stem cells (MSCs).

- DBX demineralized bone matrix putty, paste and mix (Musculoskeletal Transplant Foundation): processed human bone and sodium hyaluronate mixed with autologous mesenchymal stem cells (MSCs).
- Integra MOZIAK Osteoconductive Scaffold-Putty (IsoTis OrthoBiologics): Human cancellous bone mixed with autologous mesenchymal stem cells (MSCs).
- Formagraft Collagen Bone Graft Matrix (R and L Medical): Bovine fibrillary collagen mixed with autologous mesenchymal stem cells (MSCs).

Lipogems received FDA 5109k) 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).

In 2020, the FDA updated their guidance on "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use."

Human cells, tissues, and cellular and tissue-based products (HCT/P) are defined as human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. If an HCT/P does not meet the criteria below and does not qualify for any of the stated exceptions, the HCT/P will be regulated as a drug, device, and/or biological product and applicable regulations and premarket review will be required.

An HCT/P is regulated solely under section 361 of the PHS Act and 21 CFR Part 1271 if it meets all of the following criteria:

"1) The HCT/P is minimally manipulated.

2) The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent.

3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and

4) Either:

i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or

ii) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and: a) Is for autologous use; b) Is for allogeneic use in a first-degree or second-degree blood relative; or c) Is for reproductive use."

The FDA does not consider the use of stem cells for orthopedic procedures to be homologous use.

PRIOR APPROVAL

Prior approval is recommended.

POLICY

See Related Medical Policies

- 02.01.32 Platelet-Rich Plasma and Autologous Protein Solution for Orthopedic Applications
- 02.01.18 Prolotherapy
- 08.01.28 Stem Cell Therapy for Peripheral Arterial Disease

Note: *This policy addresses stem cell therapy for orthopaedic applications, in particular mesenchymal stem cells (MSCs). MSCs have been proposed as a type of regenerative therapy. Regenerative therapy is considered an emerging field of medicine focusing on repair, replacement, or regeneration of cells and tissues. MSCs are found in a variety of tissues and have the ability to rapidly proliferate and differentiate to musculoskeletal tissue, including bone and cartilage.*

Stem cell transplantation using hematopoietic stem cells for treatment of blood cancer, non-cancer conditions and solid tumors are not in scope of this policy. Refer medical policy 07.03.11 Hematopoietic Stem Cell Transplantation (Bone Marrow Transplant) Autologous and Allogeneic.*

Mesenchymal Stem Cell (MSC) Therapy

Mesenchymal stem cell (MSC) therapy from bone marrow (bone marrow derived mesenchymal stem cells [BM-MSCs]), adipose tissue (adipose tissue-derived mesenchymal stem cells [AD-MSCs]), peripheral blood or synovial tissue/synovium-derived mesenchymal stem cells (S-MSC) alone or in combination with platelet-derived products (e.g. platelet-rich plasma, lysate) as treatment of orthopaedic and/or musculoskeletal conditions is considered **investigational** for all indications including but not limited to 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

The use of mesenchymal stem cells (MSCs) for orthopedic conditions is an active area of research. Despite continued research into the methods of harvesting and delivering treatment, there are uncertainties regarding the optimal source of cells and the delivery method and safety. Studies have included mesenchymal stem cells (MSCs) from bone marrow, adipose tissue, peripheral blood. Overall, the quality of evidence is low and there is a possibility of publication bias. Additional studies in a larger sample of patients with longer follow-up would be needed to evaluate the long-term efficacy and safety to include avoidance of surgical procedures. Also, current society guidelines do not support the use of mesenchymal stem cells for orthopaedic conditions and includes the following: *"There is little data to suggest stem cell therapy will benefit patients with advanced osteoarthritis. Furthermore, there is no data to support the idea that stem cell can sense the environment into which they are injected and repair damaged tissue. The claims that stem cells regenerate severely damaged or lost cartilage is not supported by scientific evidence. The available evidence is troubling and does not allow an assessment as to whether the potential clinical benefits of such therapies outweigh any potential harms"* The evidence is insufficient to determine the effects of the technology on health outcomes.

Regenexx

Mesenchymal stem cell (MSC) therapy, alone or in combination with platelet-derived products (e.g., platelet-rich plasma, lysate) as treatment of orthopaedic and/or musculoskeletal conditions including but not limited to the following:

- Regenexx
- Regenexx Stem Cell Same Day Procedure (RegenexxSD)
- Regenexx Super Concentrated Platelet Rich Plasma (Regenexx-SD Plus)
- Regenexx Adipose Derived Stem Cell Procedure (RegenexxAD;

is considered **investigational** for all indications including but not limited to 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

The use of mesenchymal stem cells (MSCs) for orthopaedic conditions is an active area of research. Despite continued research into the methods of harvesting and delivering treatment, there are uncertainties regarding the optimal source of cells and the delivery method and safety. The quality of evidence is low and there is a possibility of publication bias. Overall, there is a lack of evidence that clinical outcomes are improved with Regenexx procedures. Additional studies in a larger sample of patients with longer follow-up would be needed to evaluate the long-term efficacy and safety to include avoidance of surgical procedures. Also, current society guidelines do not support the use of mesenchymal stem cells for orthopaedic conditions and includes the following: *"There*

is little data to suggest stem cell therapy will benefit patients with advanced osteoarthritis. Furthermore, there is no data to support the idea that stem cell can sense the environment into which they are injected and repair damaged tissue. The claims that stem cells regenerate severely damaged or lost cartilage is not supported by scientific evidence. The available evidence is troubling and does not allow an assessment as to whether the potential clinical benefits of such therapies outweigh any potential harms" The evidence is insufficient to determine the effects of the technology on health outcomes.

Allograft Bone Products with Viable Stem Cells
Allograft bone products containing viable stem cells, including but not limited to demineralized bone matrix (DMB) with stem cells used alone, added to their biomaterials for grafting or seeded onto scaffolds is considered **investigational** for all orthopedic applications. There is insufficient evidence to support a conclusion concerning the net health outcomes or benefits associated with this procedure:

- Allostem (Allosource)
- CopiOs Bone voice filler (sponge and powder disc) (Kensey Nash)
- DBX demineralized bone matrix putty, paste and mix (Musculoskeletal Transplant Foundation)
- Formagraft Collagen Bone Graft Matrix (R and L Medical)
- Integra MOZIAK Osteoconductive Scaffold-Putty (IsoTis OrthoBiologics)
- Map3 (RTI Surgical)
- Osteocel Plus (NuVasive)
- Trinity Evolution Matrix (Orthofix)
- Vitoss Bioactive Foam Bone Graft Substitute (Stryker)

Note: *See regulatory information above for additional information regarding demineralized bone matrix (DBM) product(s) containing viable stem cells.*

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 20999 unlisted musculoskeletal procedure
- 38205 blood derived hematopoietic progenitor cell harvesting for transplantation, per collection allogeneic
- 38206 blood derived hematopoietic progenitor cell harvesting for transplantation, autologous
- 38212 Transplant preparation of hematopoietic progenitor cells; red blood cell removal

- 38215 Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear or buffy coat layer
- 38230 bone marrow harvesting for transplantation allogeneic
- 38232 bone marrow harvesting for transplantation autologous
- 38240 Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
- 38241 Hematopoietic progenitor cell (HPC) Autologous transplantation
- 0232T injection(s), platelet-rich plasma, any tissue, including image guidance, harvesting and preparation when performed
- 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 bone marrow harvest
- 0264T Complete procedure excluding bone marrow harvest
- 0265T Unilateral or bilateral bone marrow harvest only for intramuscular autologous bone marrow cell therapy
- 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

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POLICY HISTORY

Date	Reason	Action
February 2022	Annual Review	Policy Revised
February 2021	Annual Review	Policy Revised
February 2020	Annual Review	Policy Revised
February 2019	Annual Review	Policy Renewed
August 2018	Interim Review	Policy Revised
February 2018	Annual Review	Policy Revised
April 2017	Annual Review	Policy Revised
April 2016	Annual Review	Policy Renewed
May 2015	Annual Review	Policy Revised
March 2015	Interim Review	Policy Revised
June 2014		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
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