Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)

Policy # 00258
Original Effective Date: 06/16/2010
Current Effective Date: 05/17/2017

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of mesenchymal stem cell therapy (MSCs) for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue to be investigational.*

Based on review of available data, the Company considers allograft bone products containing viable stem cells, including but not limited to demineralized bone matrix (DBM) with stem cells, for all orthopedic applications to be investigational.*

Based on review of available data, the Company considers allograft or synthetic bone graft substitutes that must be combined with autologous blood or bone marrow for all orthopedic applications to be investigational.*

Background/Overview
Mesenchymal stem cells are multipotent cells (also called stromal multipotent cells) that possess the ability to differentiate into various tissues including organs, trabecular bone, tendon, articular cartilage, ligaments, muscle, and fat. MSCs are associated with the blood vessels within bone marrow, synovium, fat, and muscle, where they can be mobilized for endogenous repair as occurs with healing of bone fractures. Bone marrow aspirate is considered the most accessible source and, thus, the most common place to isolate MSCs for treatment of musculoskeletal disease. However, harvesting MSCs from bone marrow requires an additional procedure that may result in donor-site morbidity. In addition, the number of MSCs in bone marrow is low, and the number and differentiation capacity of bone marrow–derived MSCs decreases with age, limiting their efficiency when isolated from older patients.

Tissues such as muscle, cartilage, tendon, ligaments, and vertebral discs show limited capacity for endogenous repair. Therefore, tissue engineering techniques are being developed to improve the efficiency of repair or regeneration of damaged musculoskeletal tissues. Tissue engineering focuses on the integration of biomaterials with MSCs and/or bioactive molecules such as growth factors. In vivo, the fate of stem cells is regulated by signals in the local 3-dimensional microenvironment from the extracellular matrix and neighboring cells. It is believed that the success of tissue engineering with MSCs will also require an appropriate 3-dimensional scaffold or matrix, culture conditions for tissue-specific induction, and implantation techniques that provide appropriate biomechanical forces and mechanical stimulation. The
ability to induce cell division and differentiation without adverse effects, such as the formation of neoplasms, remains a significant concern. Given that each tissue type requires different culture conditions, induction factors (signaling proteins, cytokines, growth factors), and implantation techniques, each preparation must be individually examined.

The U.S. Food and Drug Administration (FDA) has stated:
“A major challenge posed by SC [stem cell] therapy is the need to ensure their efficacy and safety. Cells manufactured in large quantities outside their natural environment in the human body can become ineffective or dangerous and produce significant adverse effects, such as tumors, severe immune reactions, or growth of unwanted tissue.”

**FDA or Other Governmental Regulatory Approval**
U.S. Food and Drug Administration
Concentrated autologous MSCs do not require approval by the U.S. FDA.

Demineralized bone matrix, which is processed allograft bone, is considered minimally processed tissue and does not require FDA approval. At least 4 commercially available DBM products are reported to contain viable stem cells:

- AlloStem®‡ (AlloSource) is 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) is 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.

Whether these products can be considered minimally manipulated tissue is debated. A product would not meet the criteria for FDA regulation part 1271.10 if it is dependent on the metabolic activity of living cells for its primary function. Otherwise, a product would be considered a biologic product and would need to demonstrate safety and efficacy for the product’s intended use with an investigational new drug and biologics license application (BLA).

Other products contain DBM and are designed to be mixed with bone marrow aspirate. Some products currently available are:

- Fusion Flex™‡ (Wright Medical): a dehydrated moldable DBM scaffold that will absorb autologous bone marrow aspirate.
- Ignite®‡ (Wright Medical): an injectable graft with DBM that can be combined with autologous bone marrow aspirate.

Other commercially available products are intended to be mixed with bone marrow aspirate and have been cleared by FDA through the 510(k) process, such as:
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- CopiOs sponge or paste (Zimmer): synthetic bone graft material consisting of mineralized, lyophilized collagen.
- Collage™‡ Putty (Orthofix): composed of type-1 bovine collagen and beta tricalcium phosphate.
- Vitoss®‡ (Stryker, developed by Orthovita): composed of beta tricalcium phosphate.
- nanOss®‡ Bioactive (rti surgical, developed by Pioneer Surgical): nanostructured hydroxyapatite and an open structured engineered collagen carrier.

FDA product code: MQV.

No products using engineered or expanded MSCs have been approved by FDA for orthopedic applications. In 2008, FDA determined that the MSCs sold by Regenerative Sciences for use in the Regenexx™‡ procedure would be considered drugs or biological products and thus require submission of a new drug application (NDA) or BLA to FDA. In 2014, a federal appellate court upheld FDA’s power to regulate adult stem cells as drugs and biologics and ruled that the Regenexx cell product fell within FDA’s authority to regulate human cells, tissues, and cellular and tissue-based products. To date, no NDA or BLA has been approved by FDA for this product. As of 2015, the expanded stem cell procedure is only offered in the Cayman Islands. Regenexx network facilities in the United States provide same-day stem cell and blood platelet procedures, which do not require FDA approval (available at: http://www.regenexx.com/common-questions/regenexx-fda-clarification).

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source
At the time this evidence review was created, the literature consisted almost entirely of review articles describing the potential of stem cell therapy for orthopedic applications in humans, along with basic science experiments on sources of MSCs, regulation of cell growth and differentiation, and development of scaffolds. Authors of these reviews indicated that the technology was in an early stage of development. In literature searches of the MEDLINE database, use of cultured MSCs in humans was identified in only a few centers in the United States, Europe, and Asia. Since this review was created, the evidence base has been steadily increasing, although there is a lack of high-quality randomized controlled trials (RCTs), and nearly all studies to date have been performed outside of the United States.

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

One systematic review was published in 2013 that included multiple sources of MSC. In 2013, Filardo et al conducted a systematic review of MSCs for the treatment of cartilage lesions. They identified 72 preclinical and 18 clinical reports. Of the 18 clinical reports, none was randomized, 5 were comparative, 6 were case
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series, and 7 were case reports. The source of MSCs was adipose tissue in 2 clinical studies, bone marrow concentrate in 5, and in 11 studies, the source was bone marrow-derived. Many of these trials had been performed by the same research group in Asia. Following is a summary of the key literature to date, focusing on comparative studies.

MSCs Expanded From Bone Marrow

**Autologous Bone Marrow**

In 2013 (after the systematic review by Filardo was published), Wong et al reported an RCT of cultured MSCs in 56 patients with osteoarthritis who underwent medial opening-wedge high tibial osteotomy and microfracture of a cartilage lesion. Bone marrow was harvested at the time of microfracture and the MSCs were isolated and cultured. After 3 weeks, the cells were assessed for viability and delivered to the clinic, where patients received an intra-articular injection of MSCs suspended in hyaluronic acid (HA), or for controls, intra-articular injection of HA alone. The primary outcome was the International Knee Documentation Committee (IKDC) score at 6 months, 1 year, and 2 years. Secondary outcomes were the Tegner Activity Scale and Lysholm Knee Scale scores through 2 years and the Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) scoring system by magnetic resonance imaging (MRI) at 1 year. All patients completed the 2-year follow-up. After adjusting for age, baseline scores, and time of evaluation, the group treated with MSCs showed significantly better scores on the IKDC (mean difference [MD], 7.65 on 0-100 scale; \( p=0.001 \)), Lysholm (MD=7.61 on 0-100 scale; \( p=0.02 \)), and Tegner (MD=0.64 on a 0-10 scale; \( p=0.02 \)). Blinded analysis of MRI results found higher MOCART scores in the MSC group. The group treated with MSCs had a higher proportion of patients who had complete cartilage coverage of their lesions (32% vs 0%), greater than 50% cartilage cover (36% vs 14%), and complete integration of the regenerated cartilage (61% vs 14%). This study is ongoing and recruiting additional patients.

Wakitani et al first reported use of expanded MSCs for repair of cartilage defects in 2002. Cells from bone marrow aspirate of 12 patients with osteoarthritic knees were culture expanded, embedded in collagen gel, transplanted into the articular cartilage defect, and covered with autologous periosteum at the time of high tibial osteotomy. Clinical improvement was not found to differ between the experimental group and a group of 12 control patients who underwent high tibial ostetomy alone. Wakitani et al have since published several cases of patients treated for isolated cartilage defects, with clinical improvement reported at up to 27 months. However, most of the defects appear to have been filled with fibrocartilage. A 2011 report from Wakitani et al was a follow-up safety study of 31 of the 41 patients (3 patients had died, 5 had undergone total knee arthroplasty) who had received MSCs for articular cartilage repair in their clinics between 1998 and 2008. At a mean of 75 months (range, 5-137 months) since the index procedure, no tumors or infections were identified. Function was not reported.

Another study from Asia evaluated the efficacy of bone marrow–derived MSCs compared with autologous chondrocyte implantation (ACI) in 36 matched patient pairs. Thirty-six consecutive patients with at least 1 symptomatic chondral lesion on the femoral condyle, trochlea, or patella were matched with 36 cases of ACI performed earlier, based on lesion sites and 10-year age intervals. Autologous MSCs were cultured from 30 mL of bone marrow from the iliac crest, tested to confirm that the cultured cells were MSCs, and
implanted beneath a periosteal patch. Concomitant procedures included patella realignment, high-tibial osteotomy, partial meniscectomy, and anterior cruciate ligament reconstruction. Clinical outcomes, measured preoperatively and at 3, 6, 12, 18, and 24 months after operation using the International Cartilage Repair Society Cartilage Injury Evaluation Package, showed improvement in patients’ scores over the 2-year follow-up in both groups, with no significant difference between groups for any of the outcome measures except for Physical Role Functioning on the 36-Item Short-Form Health Survey, which showed a greater improvement over time in the MSC group.

A 2010 publication from Centeno et al of Regenerative Sciences describes the use of percutaneously injected culture-expanded MSCs from the iliac spine in 226 patients. Following harvesting, cells were cultured with autologous platelet lysate and reinjected under fluoroscopic guidance into peripheral joints (n=213) or intervertebral discs (n=13). Follow-up for adverse events at a mean of 10.6 months showed 10 cases of probable procedure-related complications (injections or stem cell–related), all of which were considered to be self-limited or treated with simple therapeutic measures. Serial MRIs from a subset of patients showed no evidence of tumor formation at a median follow-up of 15 months. The efficacy of these procedures was not reported. This procedure is no longer offered in the United States.

**Allogeneic Bone Marrow**

In 2015, Vega et al reported a small phase 1/2 RCT of 30 patients with osteoarthritis unresponsive to conventional treatments. The MSC-treated group received intra-articular injection of expanded allogeneic bone marrow MSCs from healthy donors and the control group received an intra-articular injection of HA. Follow-up using standard outcome measures was performed at 3, 6, and 12 months after injection. In the MSC-treated group, pain scores (VAS and Western Ontario and McMasters Universities Arthritis Index [WOMAC]) decreased significantly between baseline and the 12-month follow-up, whereas pain scores in the control group did not improve significantly. A significant improvement in cartilage in the MSC group was supported by T2 MRI. Not reported was whether the patients or assessors were blinded to treatment in this trial. Additional study in a larger number of patients in a phase 3 trial with blinding of patients and assessors is needed.

**MSCs Concentrated From Bone Marrow**

In 2009, Giannini et al reported a 1-step procedure for transplanting bone marrow–derived cells for type II (>1.5 cm², <5 mm deep) osteochondral lesions of the talus in 48 patients. A total of 60-mL bone marrow aspirate was collected from the iliac crest. The bone marrow–derived cells were concentrated and implanted with a scaffold (collagen powder or HA membrane) and platelet gel. In a 2010 publication, Giannini et al reported results of a retrospective analysis based on the evolution of the investigator’s technique at the time of treatment. Outcomes following arthroscopic application of the MSC concentrate (n=25) were similar to open (n=10) or arthroscopic (n=46) ACI. ACI with a biodegradable scaffold is not commercially available in the United States.

Centeno et al reported a multicenter registry of patients treated with autologous stem cells, bone marrow concentrate, and platelet-rich plasma. This report focused on 102 patients (115 shoulders) diagnosed with either osteoarthritis of the shoulder or rotator cuff tears. Patients were treated with a protocol that included a
hypertonic dextrose solution (prolotherapy) injection to create an inflammatory response several days prior to the bone marrow concentrate injection. The bone marrow concentrate injection included platelet-rich plasma and platelet lysate. Both Disabilities of the Arm, Shoulder, and Hand scores and numeric pain scale (NPS) scores decreased by about 50%, although the absolute decrease in the NPS score was a very modest 0.9. Interpretation of these results is limited by the lack of a placebo control and blinding, subjective outcome measures, and the multiple treatments used, although it is acknowledged that neither prolotherapy nor PRP appear to have efficacy on their own. Additional study with randomized and placebo-controlled trials is needed to evaluate this treatment protocol.

Adipose-Derived MSCs
The literature on adipose-derived MSCs for articular cartilage repair comes from 2 different research groups in Korea. One group appears to have been providing this treatment as an option for patients for a number of years. They compare outcomes of this new add-on treatment with those of patients who only received other cartilage repair procedures.

In 2014, Koh et al reported results of an RCT that evaluated cartilage healing after high tibial osteotomy (HTO) in 52 patients with osteoarthritis of the medial compartment. Patients were randomly assigned via sealed envelopes to HTO with application of platelet-rich plasma (PRP) or HTO with application of PRP plus MSCs. Use of PRP is considered investigational MSCs from adipose tissue were obtained through liposuction from the buttocks. The tissue was centrifuged and the stromal vascular fraction mixed with PRP for injection. A total of 44 patients completed second-look arthroscopy and 1- and 2-year clinical follow-ups. The primary outcomes were the Knee Injury and Osteoarthritis Outcome Score (KOOS; 5 subscales with 0-100 scale), the Lysholm score (0-100 scale), and a VAS for pain (0-100 scale). There were statistically significant differences for PRP only versus PRP+MSC on 2 of 5 KOOS subscales: Pain (74±5.7 vs 81.2±6.9, p<0.001) and Symptoms (75.4±8.5 vs 82.8±7.2, p=0.006). There were also statistically significant differences on the final pain score for the PRP only versus PRP+MSC groups (16.2±4.6 vs 10.2±5.7, p<0.001), but the final Lysholm score did not differ significantly between the PRP only and PRP+MSC groups (80.6±13.5 vs 84.7±16.2, all respectively, p=0.36). Articular cartilage healing was rated as improved with MSCs following video review of second-look arthroscopy; blinding of this measure is unclear. Study design and results were flawed—small sample size, short duration of follow-up, and significant improvements only on some outcomes. All significant differences in outcomes were modest in magnitude and, as a result, there is uncertainty about the clinical significance of the findings.

A 2013 publication from this Korean group reported a retrospective comparison of outcomes from 35 patients (37 ankles) who were older than 50 years of age, had focal osteochondral lesions of the talus, and were treated with microfracture alone between May 2008 and September 2010. The comparison group was 30 patients (31 ankles) who received MSC injection along with marrow stimulation between October 2010 and December 2011. MSCs were harvested from the fat pad of the buttock of the patients 1 day before surgery, concentrated, and injected after the arthroscopic procedure. With an average 22 month follow-up (range, 12-44 months), patients treated with MSCs showed greater improvements in VAS, American Orthopaedic Foot and Ankle Society Ankle–Hindfoot Scale, Tegner, and the Roles and Maudsley scores. A 2014 retrospective review from this group reported clinical outcomes and MRI results from 49 patients who
had undergone marrow stimulation with or without MSCs at their institution. Use of MSCs in addition to microfracture was determined by patient choice, and there was an overlap of 26 patients between this report and their 2013 previously discussed publication. This analysis also found modest but statistically significant improvements in clinical outcomes for the MSC group compared with microfracture alone. Blinded ratings with the MOCART scale resulted in a score of 49.4 for the conventional group and 62.1 for the MSC group (p=0.037).

Koh et al also reported a retrospective analysis of the injection of adipose-derived MSCs from the infrapatellar fat pad and PRP into arthroscopically débrided knees of 25 patients with osteoarthritis of the knee. Results were compared with a randomly selected group of patients who had previously undergone arthroscopic débridement and PRP injections without stem cells. Although there was a trend for greater improvement in the MSC group, at final follow-up, there was no significant difference between the MSC and control groups in clinical outcomes (Lysholm, Tegner, VAS).

Another group reported a phase 1/2 trial of intra-articular injection of adipose-derived MSCs for the treatment of osteoarthritis of the knee. The phase 1 was a dose-escalation study of 9 patients, and phase 2 assessed efficacy of the highest dose of 9 patients. The study of 18 patients was approved by the Korean FDA. Procedures included liposuction, arthroscopy of the knee 1 week later with MSC injection through the portal, MRI at 3 and 6 months, and second-look arthroscopy with punch biopsy at 6 months. Intention-to-treat analysis showed a 39% improvement in WOMAC score at 6 months after injection and a 45% improvement in VAS score. Arthroscopy showed a decrease in size of the cartilage defect and an increase in the volume of cartilage. Histology showed thick, hyaline-like cartilage regeneration. Additional study is needed with a larger sample size, sham-treated controls, and longer follow-up.

MSCs From Peripheral Blood
A 2013 report from Asia described a small RCT with autologous peripheral blood MSCs for focal articular cartilage lesions. Fifty patients with grade 3 and 4 lesions of the knee joint underwent arthroscopic subchondral drilling followed by 5 weekly injections of HA. Half the patients were randomly allocated to receive injections of peripheral blood stem cells or no further treatment. There were baseline differences in age between the groups, with a mean age of 38 years for the treatment group compared with 42 for the control group. The peripheral blood stem cells were harvested after stimulation with recombinant human granulocyte colony-stimulating factor, divided in vials, and cryopreserved. At 6 months after surgery, HA and MSCs were readministered over 3 weekly injections. At 18 months postsurgery, second-look arthroscopy on 16 patients in each group showed significantly higher histologic scores (=10%) for the MSC group (1066 vs 957 by independent observers) while blinded evaluation of MRI showed a higher morphologic score (9.9 vs 8.5). There was no difference in IKDC scores between the 2 groups at 24 months after surgery. It is uncertain how differences in patient age at baseline may have affected the response to subchondral drilling.

MSCs From Synovial Tissue
Akgun et al reported a small (N=14), though without major bias, investigator-blinded RCT that compared matrix-induced autologous MSCs from synovial tissue versus matrix-induced autologous chondrocyte
implantation (MACI). Both chondrocytes from cartilage and MSCs from synovia were harvested in an arthroscopic procedure, expanded in culture, and then cultured on a collagen membrane for 2 days. Implantation was performed with the construct trimmed to the size and shape of the defect and placed with the cells facing the subchondral bone. Rehabilitation was the same for the 2 groups, with continuous passive motion for at least 1 hour daily and nonweight bearing for the first 6 weeks. The 2 groups were similar at baseline, and all patients completed the evaluations through 24 months. Outcomes on the KOOS subscales and Tegner were statistically better in the MSC group, although it is not clear if the difference observed would be considered clinically significant, with differences of around 6 on the 100-point KOOS subscales and 0.6 on the 10-point Tegner. The results of this small pilot study do suggest that cartilage repair with matrix-induced MSCs from synovial tissue may result in outcomes that are at least as good as MACI, warranting additional study in a larger sample. It should also be noted that neither of these procedures is approved for use in the United States.

Section Summary: Cartilage Defects

The evidence base on MSCs for cartilage repair is increasing, although nearly all studies to date have been performed in Asia with a variety of methods of MSC preparation. Four randomized studies reported an improvement in histologic and morphologic outcomes. Three of these studies also reported an improvement in functional outcomes. The method of preparation used in 1 positive study was to obtain MSCs from bone marrow at the time of microfracture, culture (expand) over a period of 3 weeks, and inject in the knee in a carrier of HA. Another randomized trial, using MSCs from peripheral blood, found improvement in histologic and morphologic outcomes, but not functional outcomes, following stimulation with recombinant human granulocyte colony-stimulating factor. A third small RCT found that MSCs from synovial tissue and cultured on collagen resulted in outcomes that were at least as good as those following MACI.

The literature on adipose-derived MSCs includes a phase 1/2 study with cultured MSCs and an RCT from a separate group in Asia that has been using uncultured MSCs as an adjunctive procedure in clinical practice. Comparisons between patients who have and have not received uncultured adipose-derived MSCs shows modest improvement in health outcomes that are of uncertain clinical significance. Potential for bias from nonblinded use of a novel procedure on subjective outcome measures is also a limitation of these studies. The phase 1/2 study of cultured MSCs from adipose tissue shows promising results for this technology. Additional study in a larger sample of patients with longer follow-up is needed to evaluate the long-term efficacy and safety of the procedure. U.S. FDA approval for this method has also not been obtained.

Meniscectomy

In 2014, Vangsness et al reported an industry-sponsored phase 1/2 randomized, double-blind, multicenter study (NCT00225095, NCT00702741) of cultured allogeneic MSCs (Chondrogen™, Osiris Therapeutics) injected into the knee after partial meniscectomy. The 55 patients in this U.S. study were randomized to intra-articular injection of either 50×10^6 allogeneic MSCs, 150×10^6 allogeneic MSCs in HA, or HA vehicle control at 7 to 10 days after meniscectomy. The cultured MSCs were derived from bone-marrow aspirates from 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 in the high-dose MSC group. There was no significant
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difference between the groups in the Lysholm score. On subgroup analysis, patients with osteoarthritis who received MSCs had a significantly greater reduction in pain at 2 years than patients who received HA alone. This appears to be a post hoc analysis and should be considered preliminary. No serious adverse events were thought to be related to the investigational treatment.

Spinal Fusion
There is limited evidence on the use of allografts with stem cells for fusion of the extremities or spine or for the treatment of nonunion, although several large observational studies are ongoing (see Table 1). In 2014, Eastlack et al reported outcomes from a series of 182 patients who were treated with anterior cervical disectomy and fusion using Osteocel Plus in a PEEK cage and anterior plating. At 24 months, 74% of patients (180/249 levels treated) were available for follow-up. These patients had significant improvements in clinical outcomes; 87% of levels achieved solid bridging and 92% of levels had range of motion less than 3°. With 26% loss to follow-up at 24 months and lack of a standard of care control group, interpretation of these results is limited.

Osteonecrosis
Two randomized comparative trials from Asia have been identified that evaluated the use of MSCs for osteonecrosis of the femoral head.

MSCs Expanded From Bone Marrow
In 2012, Zhao et al reported a randomized trial that included 100 patients (104 hips) with early-stage femoral head osteonecrosis treated with core decompression and expanded bone marrow MSCs versus core decompression alone. At 60 months after surgery, 2 (3.7%) of the 53 hips treated with MSCs progressed and underwent vascularized bone grafting, compared with 10 (23%) of 44 hips in the decompression group who progressed and underwent either vascularized bone grafting (n=5) or total hip replacement (n=5). The MSC group also had improved Harris Hip Scores compared with the control group on independent evaluation (data presented graphically). The volume of the lesion was also reduced by treatment with MSCs.

MSCs Concentrated From Bone Marrow
Another small trial randomized 40 patients (51 hips) with early-stage femoral head osteonecrosis to core decompression plus concentrated bone marrow MSCs or core decompression alone. Blinding of assessments in this small trial was not described. Harris Hip Score was significantly improved in the MSC group (scores of 83.65 and 82.42) compared with core decompression (scores of 76.68 and 77.39). Kaplan-Meier analysis showed improved hip survival in the MSC group (mean, 51.9 weeks) compared with the core decompression group (mean, 46.7 weeks). There were no significant differences between groups in radiographic assessment or MRI results.

Section Summary: Osteonecrosis
Two small studies from Asia have compared core decompression alone versus core decompression with MSCs in patients with osteonecrosis of the femoral head. Both studies reported improvement in the Harris Hip Score in patients treated with MSCs, although it was not reported whether the patients or investigators
were blinded to the treatment group. Hip survival was significantly improved following treatment with either expanded or concentrated MSCs. The effect appears to be larger with expanded MSCs than with concentrated MSCs. Additional studies with a larger number of patients are needed to permit greater certainty on the effect of this treatment on health outcomes.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1. A 2014 review on FDA regulations of adult stem cell therapies for sports medicine identified over 45 ongoing clinical trials on this topic. Many are observational studies with commercially available products (Cartistem®, AlloStem, Trinity Evolution, Osteocel Plus).

Table 1. Summary of Key Trials

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<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>Mesenchymal Stem Cells in a Clinical Trial to Heal Articular Cartilage Defects</td>
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<td>Jul 2018</td>
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<td><strong>Unpublished</strong></td>
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<td>NCT00951938a</td>
<td>A Radiographic and Clinical Study Evaluating a Novel Allogeneic, Cancellous, Bone Matrix Containing Viable Stem Cells (Trinity Evolution Viable Cryopreserved Cellular Bone Matrix) in Patients Undergoing Anterior Cervical Discectomy and Fusion</td>
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<td>NCT00988338a</td>
<td>A Radiographic and Clinical Study Evaluating a Novel Allogeneic, Cancellous, Bone Matrix Containing Viable Stem Cells (Trinity Evolution Matrix) in Subjects Undergoing Foot and Ankle Fusion</td>
<td>106</td>
<td>Jan 2013</td>
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<tr>
<td>NCT00965380a</td>
<td>A Radiographic and Clinical Study Evaluating a Novel Allogeneic, Cancellous, Bone Matrix Containing Viable Stem Cells (Trinity Evolution Viable Cryopreserved Cellular Bone Matrix) in Posterior Lumbar or Transforaminal Lumbar Interbody Fusion (PLIF or TLIF)</td>
<td>200</td>
<td>Jun 2014</td>
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<td>NCT01626677/</td>
<td>Randomized, Open-Label, Multi-Center and Phase 3 Clinical Trial to Compare the Efficacy and Safety of Cartistem and Microfracture in Patients With Knee Articular Cartilage Injury or Defect/ Long Term Follow-Up Study of CARTISTEM Versus Microfracture</td>
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<td>May 2015</td>
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<td>NCT01041001a</td>
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NCT: national clinical trial.
*a* Denotes industry-sponsored or cosponsored trial.
Summary of Evidence
The evidence for stem cell therapy in individuals who have various orthopedic conditions (cartilage defects, meniscectomy, spinal fusion procedures, osteonecrosis) includes small randomized controlled trials and nonrandomized comparative trials. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. Use of 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. Studies have included MSCs from bone marrow, adipose tissue, peripheral blood, and synovial tissue. The largest body of evidence is on use of autologous MSCs, either concentrated or expanded in culture, for cartilage repair. This evidence includes small randomized and nonrandomized comparative trials with insufficient data to evaluate health outcomes. In addition, expanded MSCs for orthopedic applications are not U.S. FDA–approved (concentrated autologous MSCs do not require FDA approval). Overall, there is a lack of evidence that clinical outcomes are improved. The evidence is insufficient to determine the effects of the technology on health outcomes.

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05/18/2011 Medical Policy Implementation Committee approval. No change to coverage.
05/03/2012 Medical Policy Committee review
05/16/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/04/2013 Coding updated
05/02/2013 Medical Policy Committee review
05/22/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/01/2014 Medical Policy Committee review
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05/21/2014 Medical Policy Implementation Committee approval. New investigational indication added.
05/07/2015 Medical Policy Committee review
05/20/2015 Medical Policy Implementation Committee approval. No change to coverage.
05/05/2016 Medical Policy Committee review
05/18/2016 Medical Policy Implementation Committee approval. Investigational statement added on bone graft substitutes that must be used with autologous blood or bone marrow aspirate. Title changed.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
05/04/2017 Medical Policy Committee review
05/17/2017 Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date: 05/2018

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®), copyright 2016 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>38206, 38230, 38241</td>
</tr>
<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-10</td>
<td>All related diagnoses</td>
</tr>
</tbody>
</table>

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)

Policy # 00258
Original Effective Date: 06/16/2010
Current Effective Date: 05/17/2017

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

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