

Medical Policy



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Title: Orthopedic Applications of Stem Cell Therapy

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Populations	Interventions	Comparators	Outcomes
Individuals: • With cartilage defects	Interventions of interest are: • Stem cell therapy	Comparators of interest are: • Conservative management • Microfracture • Autologous chondrocyte implantation	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With meniscal defects	Interventions of interest are: • Stem cell therapy	Comparators of interest are: • Conservative management	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> • With joint fusion procedures 	Interventions of interest are: <ul style="list-style-type: none"> • Stem cell therapy 	Comparators of interest are: <ul style="list-style-type: none"> • Iliac crest bone graft 	Relevant outcomes include: <ul style="list-style-type: none"> • Symptoms • Morbid events • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> • With osteonecrosis 	Interventions of interest are: <ul style="list-style-type: none"> • Stem cell therapy 	Comparators of interest are: <ul style="list-style-type: none"> • Core decompression 	Relevant outcomes include: <ul style="list-style-type: none"> • Symptoms • Morbid events • Functional outcomes • Quality of life • Treatment-related morbidity

DESCRIPTION

Mesenchymal stem cells (MSCs) have the capability to differentiate into a variety of tissue types, including various musculoskeletal tissues. Potential uses of MSCs for orthopedic applications include treatment of damaged bone, cartilage, ligaments, tendons, and intervertebral discs.

OBJECTIVE

The objective of this policy is to evaluate whether the use of mesenchymal stem cells in conjunction with interventions for orthopedic conditions improves the net health outcome.

BACKGROUND

Mesenchymal stem cells (MSCs) 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. Tissues, such as muscle, cartilage, tendon, ligaments, and vertebral discs, show limited capacity for endogenous repair because of the limited presence of the triad of tissue functional components: vasculature, nerves, and lymphatics. *Orthobiologics* is a term introduced to describe interventions using cells and biomaterials to support healing and repair. Cell therapy is the application of MSCs directly to a musculoskeletal site. Tissue engineering techniques use MSCs and/or bioactive molecules such as growth factors and scaffold combinations to improve the efficiency of repair or regeneration of damaged musculoskeletal tissues.¹

Bone-marrow aspirate is considered to be 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.

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.

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. Mesenchymal stem cells (MSCs) are included in these regulations.

The regulatory status of the stem cell or stem cell-containing products addressed in this review is summarized below.

Concentrated autologous 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 FDA for orthopedic applications.

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

- AlloStem® (AlloSource) is a partially demineralized allograft bone seeded with adipose-derived MSCs.
- Map3™ (RTI Surgical) contains cortical cancellous bone chips, DBM, and cryopreserved multipotent adult progenitor cells (MAPC®).
- Osteocel Plus® (NuVasive) is a DBM combined with viable MSCs isolated from allogeneic bone marrow.
- Trinity Evolution Matrix™ (Orthofix) is a DBM combined with viable MSCs isolated from allogeneic bone marrow.
- Other products contain DBM alone and are designed to be mixed with bone marrow aspirate:
 - Fusion Flex™ (Wright Medical) is a dehydrated moldable DBM scaffold (strips and cubes) that will absorb autologous bone marrow aspirate.
 - Ignite® (Wright Medical) is an injectable graft with DBM that can be combined with autologous bone marrow aspirate.

A number of DBM combination products have been cleared for marketing by FDA through the 510(k) process. FDA product code: MQV.

Table 1 provides a representative sample of these products; some of which are specifically labeled for mixing with bone marrow aspirate.

Table 1. Demineralized Bone Matrix Products Cleared by FDA

Product	Matrix Type	Mix With Autologous MSCs	Manufacturer or Sponsor	Date Cleared	510(k) No.
Vitoss® Bioactive Foam Bone Graft Substitute	Type I bovine collagen	X	Stryker	Nov 2008	K083033
NanOss BVF-E	Nanocrystalline hydroxyapatite		Pioneer Surgical	Aug 2008	
OrthoBlast® II Demineralized bone matrix putty and paste	Human cancellous bone chips		SeaSpine	Sep 2007	K070751
CopiOs® Bone Void Filler (sponge and powder disc)	Type I bovine dermal collagen	X	Kensey Nash	May 2007	K071237
DBX® Demineralized bone matrix putty, paste and mix	Processed human bone and sodium hyaluronate	X	Musculoskeletal Transplant Foundation	Dec 2006	K053218
Integra MOZAIK™ Osteoconductive Scaffold-Putty	Human cancellous bone	X	IsoTis Orthobiologics	Dec 2006	K062353
Formagraft™ Collagen Bone Graft Matrix	Bovine fibrillary collagen	X	R and L Medical	May 2005	K050789
DynaGraft® II Gel and Putty	Processed human bone particles		IsoTis Orthobiologics	Mar 2005	K040419

FDA: Food and Drug Administration; MSCs: mesenchymal stem cells.

In 2008, FDA determined that the MSCs sold by Regenerative Sciences for use in the Regenexx-C™ procedure would be considered drugs or biologic products and thus require submission of a new drug application or biologic license application to FDA.² The Regenexx-C™ procedure originally used stem cells derived from bone marrow or synovial fluid and cultured the cells with autologous platelet lysate in a separate laboratory. Other compounds such as antibiotics were added before the material was returned to the patient in a separate orthopedic procedure. Regenerative Sciences asserted that the procedure was the practice of medicine and not subject to FDA regulation. In 2014, a federal appellate court upheld FDA authority to regulate adult stem cells as drugs and biologics and ruled that the Regenexx cell product fell within FDA's authority to regulate HCT/Ps.³ To date, no new drug application or biologic license application has been approved by FDA for this product. As of 2015, the expanded stem cell procedure is only offered in the Cayman Islands. Regenexx® Stem Cell Procedure is offered through a network of facilities in the United States that provide same-day stem cell and blood platelet procedures that do not require FDA approval. These procedures, along with the Regenexx® Super Concentrated Platelet Rich Plasma, are marketed as treatments for arthritis and injuries of the knee, hip, shoulder, spine, hand and wrist, foot and ankle and elbow.⁴

POLICY

- A. Mesenchymal stem-cell therapy is considered **experimental / investigational** for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue.
- B. Allograft bone products containing viable stem cells, including, but not limited to, demineralized bone matrix with stem cells, are considered **experimental / investigational** for all orthopedic applications.
- C. Allograft or synthetic bone graft substitutes that must be combined with autologous blood or bone marrow are considered **experimental / investigational** for all orthopedic applications.

Policy Guidelines

This policy does not address unprocessed allograft bone.

RATIONALE

The most recent literature update was performed through November 1, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function - including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

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 cartilage defects.

The question addressed in this evidence review is: is stem cell therapy associated with improved health outcomes for patients with cartilage defects?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with cartilage defects.

Interventions

The therapy being considered is stem cell therapy.

Comparators

Comparators of interest include conservative management, microfracture, and autologous chondrocyte implantation.

Outcomes

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

Timing

Follow-up over months to years is of interest for relevant outcomes.

Setting

Patients are actively managed by orthopedic surgeons in a primarily outpatient clinical setting.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

Studies with duplicative or overlapping populations were excluded.

The source of mesenchymal stem cells (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, we group the evidence by the source of MSC.

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

MSCs Expanded from Bone Marrow

Autologous Bone Marrow for Treatment of Osteoarthritis

Wong et al (2013) reported on an RCT of cultured MSCs in 56 patients with osteoarthritis who underwent medial opening wedge high tibial osteotomy and microfracture of a cartilage lesion.⁶ Bone marrow was harvested at the time of microfracture, and the MSCs were isolated and cultured. After three 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 score at six months, one year, and two years. Secondary outcomes were the Tegner Activity Scale (TAS) and Lysholm Knee Scale (LKS) scores through 2 years and the Magnetic Resonance Observation of Cartilage Repair Tissue scoring system (0-100 points, where higher scores indicate better cartilage repair) by magnetic resonance imaging (MRI) at 1 year. All patients completed the two-year follow-up. After adjusting for age, baseline scores, and time of evaluation, the group treated with MSCs showed significantly better scores on the International Knee Documentation Committee (mean difference, 7.65 on 0-100 scale; $p=0.001$), LKS (mean difference, 7.61 on 0-100 scale; $p=0.02$), and TAS (mean difference, 0.64 on a 0-10 scale; $p=0.02$) scores. Blinded analysis of MRI results found higher Magnetic Resonance Observation of Cartilage Repair Tissue 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%).

Wakitani et al (2002) first reported on the use of expanded MSCs for repair of cartilage defects.⁷ 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 did not differ between the experimental group and a group of 12 control patients who underwent high tibial osteotomy alone. Wakitani et al (2007) have since published several cases of patients treated for isolated cartilage defects, with clinical improvement reported at up to 27 months.⁸ However, most of the defects appear to have been filled with fibrocartilage. A report from Wakitani et al (2011) 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 2008.⁹ At a mean of 75 months (range, 5-137 months) since the index procedure, no tumors or infections were identified. Functional outcomes were not reported.

Another study (2010) from Asia compared the efficacy of bone marrow-derived MSCs with autologous chondrocyte implantation in 36 matched patient pairs.¹⁰ Thirty-six consecutive patients with at least 1 symptomatic chondral lesion on the femoral condyle, trochlea, or patella were matched with 36 cases of autologous chondrocyte implantation 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. There were mixed indications based on the concomitant procedures, which 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 improvements 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 scale on the 36-Item Short-Form Health Survey, which showed a greater improvement over time in the MSC group.

A publication from Centeno et al (2010) of Regenerative Sciences has described the use of percutaneously injected culture-expanded MSCs obtained from the iliac spine in 226 patients.¹¹ 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 and indications for the injections varied. This procedure is no longer offered in the United States.

Shapiro et al (2017) reported on the results of a prospective, single-blind, placebo-controlled trial assessing 25 patients with bilateral knee pain from bilateral osteoarthritis.¹² Patients were randomized to BMAC into one knee and to saline placebo into the other. Fifty-two milliliters of bone marrow was aspirated from the iliac crests and concentrated in an automated centrifuge. The resulting BMAC was combined with platelet-poor plasma for injection into the arthritic knee and was compared with a saline injection into the contralateral knee, thereby using each patient as his or her control. Safety outcomes, pain relief, and function as measured by Osteoarthritis Research Society International measures and a visual analog scale (VAS) score were tracked initially at one week, three months, and six months postprocedure. Study patients experienced a similar relief of pain in both BMAC- and saline-treated arthritic knees. This trial is important because some previously reported studies have used an injection of high-molecular-weight HA derivatives as an active comparator. HA derivatives have been used for viscosupplementation in arthritic knee joints. However, a systematic review, prepared for the Agency for Healthcare Research and Quality on the effectiveness of HA in the treatment of degenerative joint disease in knee joints, reported that no conclusions could be drawn from available literature on avoidance or delay of total knee replacement with the use of HA.¹³ Guideline updates on viscosupplementation are included in that section of this evidence review.

A systematic review by Borakati et al (2017) included 13 studies assessed patients with osteoarthritis who were treated with MSCs or with a control treatment that was identical other than the inclusion of MSCs (ie, studies using chondrogenic cellular therapy as control were not included).¹⁴ 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 they noted high heterogeneity across controlled studies ($I^2=92%$). Additionally, 34 uncontrolled studies (n=737 patients) were summarized and evaluated qualitatively: reviewers noted consistent cartilage regrowth and reduction of pain following treatment with MSCs in these studies; however, because pain medication was often given concurrently, interpretation of the latter outcome is limited.

Allogeneic Bone Marrow for Treatment of Osteoarthritis

Vega et al (2015) reported on a small phase 1/2 RCT of 30 patients with osteoarthritis unresponsive to conventional treatments.¹⁵ The MSC-treated group received an 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 postinjection. In the MSC-treated group, pain scores (VAS and Western Ontario and McMaster Universities Arthritis Index) 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 quality in the MSC group was supported by T2 MRI. Not reported was whether the patients or assessors were blinded to treatment.

MSCs from BMAC

Giannini et al (2009) reported on 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.¹⁶ 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. Giannini et al (2010) reported the 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) autologous chondrocyte implantation.¹⁷ Both studies treated posttraumatic lesions. Autologous chondrocyte implantation with a biodegradable scaffold is not commercially available in the United States.

Centeno et al (2015) reported on a multicenter registry of patients treated with autologous stem cells, BMAC, and platelet-rich plasma (PRP).¹⁸ This study focused on 102 patients (115 shoulders) diagnosed with 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 before the BMAC injection. The BMAC injection included PRP and platelet lysate. Both Disabilities of the Arm, Shoulder, and Hand questionnaire and numeric rating scale for pain scores decreased by about 50%, although the absolute decrease in the numeric rating scale score was a very modest 0.9. Interpretation of these results is limited by the lack of placebo control and blinding, subjective outcome measures, and the multiple treatments used. Moreover, as a comparator, although it is not established whether prolotherapy or PRP have efficacy on its own (use of PRP has insufficient evidence to demonstrate improved net health outcome).

Adipose-Derived MSCs

Adipose-derived stem cells are multipotential MSCs that can be harvested from multiple anatomic locations and with greater ease than bone marrow-derived MSCs.

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

Koh et al (2014) reported on results of an RCT that evaluated cartilage healing after high tibial osteotomy in 52 patients with osteoarthritis of the medial compartment.¹⁹ Patients were randomized via sealed envelopes to high tibial osteotomy with the application of PRP or to high tibial osteotomy with the application of PRP plus MSCs. MSCs from adipose tissue were obtained through liposuction of 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 LKS score (0-100 scale), and a VAS for pain (0-100 scale). There were statistically significant differences between PRP only and PRP plus MSC on 2 of 5 KOOS subscales: pain (74 vs 81.2, $p < 0.001$) and symptoms (75.4 vs 82.8, $p = 0.006$), all respectively. There were also statistically significant differences on the final pain score between the PRP only (16.2) and PRP plus MSC groups (10.2; $p < 0.001$), but the final LKS score did not differ significantly between the PRP only (80.6) and PRP plus MSC groups (84.7; $p = 0.36$). 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). Also, 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 retrospectively compared 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 2008 and 2010.²⁰ The comparison group was 30 patients (31 ankles) who received MSC injection along with marrow stimulation between 2010 and 2011. MSCs were harvested from the fat pad of the buttock of the patients one 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, TAS, and the Roles and Maudsley scores. A 2014 retrospective review from this group reported on clinical outcomes and MRI results from 49 patients who had undergone marrow stimulation with or without MSCs at their institution.²¹ 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.²⁰ This analysis also found modest but statistically significant improvements in clinical outcomes for the MSC group compared with microfracture alone. Blinded ratings with the Magnetic Resonance Observation of Cartilage Repair Tissue scale resulted in scores that suggested greater improvement in the MSC group (62.1) than in the conventional group (49.4; $p = 0.037$).

Koh et al (2012) also reported on 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.²² 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 statistical trend toward greater improvement in the MSC group, at final follow-up, there was no significant difference between the MSC and control groups in clinical outcomes (LKS, TAS, VAS).

Jo et al (2014) reported a phase 1/2 trial of intra-articular injection of adipose-derived MSCs for the treatment of osteoarthritis of the knee.²³ Phase 1 was a dose-escalation study of nine patients and phase 2 assessed efficacy of the highest dose in another nine patients. The study of 18 patients was approved by the Korean Food and Drug Administration. Procedures included liposuction, arthroscopy of the knee one week later with MSC injection through the portal, MRI at three and six months, and second-look arthroscopy with punch biopsy at six months. Intention-to-treat analysis showed a 39% improvement in Western Ontario and McMaster Universities Arthritis Index score and a 45% improvement in VAS score at 6 months postinjection. The knee section of the Knee Society clinical rating system showed significant increases in the low-dose group (91%) and in the high-dose group (50%), compared with baseline ($p = 0.025$ and $p < 0.001$,

respectively). The function section of the Knee Society clinical rating System was also significantly improved for the low-dose group (39%; $p=0.020$). Arthroscopy showed a significant decrease in the size of the cartilage defect: in four of the domains assessed (medial femoral and tibial condyles and lateral femoral and tibial condyles), decreases in defect ranged from 40% to 51%. There was also an increase in the volume of cartilage in the medial femoral condyle for both high- and low-dose groups, although this change was only significant in the low-dose patients, who showed a 27% increase ($p=0.26$). For the high-dose group and other domains, changes in cartilage volume were insignificant over six months. Histology showed thick, hyaline-like cartilage regeneration. The results of two-year follow-up are reported below, as are the limitations of both phases of the trial.

The 2-year follow-up of this phase 1/2 trial was published by Jo et al (2017); functional outcomes were assessed by Western Ontario and McMaster Universities Osteoarthritis Index, Knee Society clinical rating System, KOOS, and VAS; almost exclusively, the high-dose group showed significantly improved scores at 2 years compared with baseline and 1-year follow-up, while the medium- and low-dose groups showed insignificant changes or deterioration from 1-year to 2-year follow-up.²⁴ In the high-dose group, the Western Ontario and McMaster Universities Osteoarthritis Index score decreased from baseline 54.2 to 16.0 at 1-year follow-up; after 2 years, the score was 19.0, which reflected the tendency of high-dose patients to improve early in treatment and remain at a stable level of improvement. Those in the medium- and low-dose groups, on the other hand, were more likely to show signs of deterioration after two years, a finding supported by structural measures (eg, no significant changes in cartilage defects were reported for these patients, as assessed by MRI). In the high-dose group, measurement of the medial femoral defect showed a 49.4% decrease after 2 years ($p=0.005$), and measurement of lateral tibial condyles defect showed a 64.4% decrease ($p=0.037$); additionally, no adverse events were reported, prompting investigators to call for more randomized trials of the treatment. Among the trial's limitations were a lack of a control group and the absence of data at one year for both MRI results and patients receiving a medium stem cell dose. Another factor potentially influencing results was the use of arthroscopic exploration with lavage.

MSCs from Peripheral Blood

A 2013 report from Asia has described a small RCT assessing the use of autologous peripheral blood MSCs for focal articular cartilage lesions.²⁵ Fifty patients with grade 3 or 4 lesions of the knee joint underwent arthroscopic subchondral drilling followed by five weekly injections of HA. Half the patients were randomized to 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 and a mean of 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 six months after surgery, HA and MSCs were re-administered over three 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 scans showed a higher morphologic score (9.9 vs 8.5). There was no difference in International Knee Documentation Committee scores between the 2 groups at 24 months after surgery. It is uncertain whether differences in patient age at baseline affected the response to subchondral drilling.

MSCs from Synovial Tissue

Akgun et al (2015) reported on a small (n=14), though without major bias, investigator-blinded RCT that compared matrix-induced autologous MSCs from synovial tissue with matrix-induced autologous chondrocyte implantation.²⁶ 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 two 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 two groups, with a continuous passive motion for at least one hour daily and no weight bearing for the first six weeks. The 2 groups were similar at baseline, and all patients completed the evaluations through 24 months. Outcomes on KOOS subscales and TAS 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 TAS. The results of this small pilot study would suggest that cartilage repair with matrix-induced MSCs from synovial tissue might provide outcomes at least as good as matrix-induced autologous chondrocyte implantation, warranting additional study in a larger sample. Neither procedure 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 trials have reported improvements in histologic and morphologic outcomes. Three of them also reported improvements in functional outcomes. A meta-analysis of 13 studies found a consistent reduction of pain in groups treated with MSCs, although the studies included were highly heterogeneous and did not consistently distinguish between improvements due to MSCs and those due to pain medication. The method of preparation used in one positive study was to obtain MSCs from bone marrow at the time of microfracture, culture (expand) over a period of three weeks and inject into the knee in HA. Another randomized trial, using MSCs from peripheral blood, found improvements 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 in collagen resulted in outcomes at least as good as those following matrix-induced autologous chondrocyte implantation.

The literature on adipose-derived MSCs includes a phase 1/2 trial with cultured MSCs and follow-up results after two years, as well as 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 have shown modest improvements in health outcomes of uncertain clinical significance. The potential for bias from the nonblinded use of a novel procedure on subjective outcome measures is also a limitation of these studies. The phase 1/2 trial of cultured MSCs from adipose tissue showed promising results for this technology. Additional study in a larger sample of patients with longer follow-up would be needed to evaluate the long-term efficacy and safety of the procedure. U.S. Food and Drug Administration approval for this method has also not been obtained.

Meniscal 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 meniscal defects.

The question addressed in this evidence review is: is stem cell therapy associated with improved health outcomes for patients with meniscal defects?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are 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, QOL, and TRM.

Timing

Follow-up over months to years is of interest for relevant outcomes.

Setting

Patients are actively managed by orthopedic surgeons in a primarily outpatient clinical setting.

Study Selection Criteria

Methodologically credible studies were selected using principles detailed above.

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

Whitehouse et al (2017) 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.²⁷ The regulatory framework in the U.K. allows cell manipulation and requires immunohistochemical documentation of the presence and volume of mesenchymal cells. Over the first 12 months postprocedure, 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.

Vangsnest et al (2014) reported on 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.²⁸ 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 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 osteoarthritis who received MSCs had a significantly greater reduction in pain at two 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.

Section Summary: Meniscal Defects

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.

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.

The question addressed in this evidence review is: is stem cell therapy associated with improved health outcomes for patients with joint fusion procedures?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are 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, morbid events, functional outcomes, QOL, and TRM.

Timing

Follow-up over months to years is of interest for relevant outcomes.

Setting

Patients are actively managed by orthopedic surgeons in a primarily outpatient clinical setting.

Study Selection Criteria

Methodologically credible studies were selected using principles detailed above.

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

A prospective, clinical, and radiographic 12-month outcomes study (2016) of patients undergoing single-level anterior cervical discectomy and fusion (ACDF) for symptomatic cervical degenerative disc disease using a novel viable allogeneic stem cell and cancellous bone matrix (Trinity Evolution) was reported using historical controls as the comparator.²⁹ 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, the primary endpoint of radiographic fusion was evaluated as determined by an independent radiographic review and the fusion rate was 78.6% at 6 months and 93.5% at 12 months. Secondary endpoints included a function as assessed by Neck Disability Index scores, and neck and arm pain as assessed by individual VAS scores. Neck function and neck and arm pain were reported as significantly improved at both 6 and 12 months postprocedure. 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, five adverse events were found to be possibly related to Trinity Evolution with three events of mild severity and two of moderate severity.

A similar study (2017) involving several of the same investigators and clinical sites reported on the clinical and radiographic evaluation of an allogeneic bone matrix containing stem cells (Trinity Evolution Viable Cellular Bone Matrix) in patients undergoing 2-level ACDF.³⁰ This study involved 40 patients exposed to the ACDF and bone graft substitute procedure at 2 adjacent disc levels. A panel blinded to clinical outcomes reviewed 12-month dynamic motion plain radiographs and thin-cut computed tomography with multiplanar reconstruction. At 12 months, the per-subject and per-level fusion rates were 89.4% and 93.4%, respectively. The clinical function assessments using the Neck Disability Index and VAS scores were reported to have improved from baseline.

A 2015 prospective, multicenter, open-label clinical trial using a cryopreserved, donor mesenchymal cell scaffold (Trinity Evolution) was performed in subjects undergoing foot and/or ankle arthrodesis with surgeons' preferred technique.³¹ A total of 103 subjects were prospectively enrolled at 10 participating sites. No restrictions were placed on the diagnosis, which included arthritis (primary osteoarthritis, posttraumatic osteoarthritis, and rheumatoid), deformity, neuropathy (Charcot and diabetic), revision surgery, and degenerative joint disease, and arthrodesis was performed in 171 joints. The per-protocol population consisted of 92 patients at 6 months and 76 patients at 12 months, with 153 and 129 total arthrodeses, respectively. The primary endpoint was fusion at six months, as assessed from computed tomography scans and standard radiographs by an independent radiology consultant. At 6 months, the fusion rate for all patients was 68.5% and 81.1% for all joints. American Orthopaedic Foot and Ankle Society Hindfoot Scale scores for disability improved over time.

Eastlack et al (2014) reported on outcomes from a series of 182 patients treated with ACDF using Osteocel Plus in a polyetheretherketone cage and anterior plating.³² 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°. With 26% loss to follow-up at 24 months and lack of a standard of care control group, interpretation of these results is limited.

Section Summary: Joint Fusion Procedures

The evidence on the use of MSCs as a component of joint fusion procedures primarily comes from industry-sponsored, prospective, open-label procedures. Outcomes included radiologic assessments of fusion, sometimes made independently, and patient-reported measures (eg, VAS scores). The MSCs used were cryopreserved allogeneic in origin. Presumptive benefits of allogeneic MSCs are that patients undergoing an orthopedic intervention procedure do not need another graft harvesting procedure and that dose of stem cells can be managed.

OsteonecrosisClinical 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 osteonecrosis.

The question addressed in this evidence review is: is stem cell therapy associated with improved health outcomes for patients with osteonecrosis?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with osteonecrosis.

Interventions

The therapy being considered is stem cell therapy.

Comparators

Comparators of interest include core decompression.

Outcomes

The general outcomes of interest are symptoms, morbid events, functional outcomes, QOL, and TRM.

Timing

Follow-up over months to years is of interest for relevant outcomes.

Setting

Patients are actively managed by orthopedic surgeons in a primarily outpatient clinical setting.

Study Selection Criteria

Methodologically credible studies were selected using principles detailed above.

At least two randomized comparative trials from Asia have evaluated the use of MSCs for osteonecrosis of the femoral head.

MSCs Concentrated from BMAC

Another small trial (2012) randomized 40 patients (51 hips) with early-stage femoral head osteonecrosis to core decompression plus concentrated bone marrow MSCs or core decompression alone.³³ Blinding of assessments in this small trial was not described. Harris Hip Score was significantly improved in the core decompression plus MSC group compared with the

core decompression alone group at 12 months (scores, 83.65 vs 76.68, $p < 0.016$) but not at 24 months (scores, 82.42 vs 77.39; $p = 0.09$), all respectively. 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.

MSCs Expanded from Bone Marrow

Zhao et al (2012) reported on a randomized trial that included 100 patients (104 hips) with early-stage femoral head osteonecrosis treated with core decompression and expanded bone marrow MSCs or with core decompression alone.³⁴ At 60 months postsurgery, 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). Lesion volume was also reduced by treatment with MSCs.

Section Summary: Osteonecrosis

Two small studies have compared core decompression alone with core decompression plus MSCs in patients with osteonecrosis of the femoral head. Both 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, well designed RCTs with a large number of patients are needed to permit greater certainty on the efficacy of this treatment for osteonecrosis.

SUMMARY OF EVIDENCE

For individuals who have cartilage defects, meniscal defects, joint fusion procedures, or osteonecrosis who receive stem cell therapy, the evidence includes small RCTs and nonrandomized comparative trials. The relevant outcomes are symptoms, morbid events, functional outcomes, QOL, and TRM. 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 has evaluated the 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. Also, expanded MSCs for orthopedic applications are not U.S. Food and Drug Administration–approved (concentrated autologous MSCs do not require agency 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.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Association of Orthopaedic Surgeons

The 2013 and 2014 American Association of Orthopaedic Surgeons' guidelines on treatment of glenohumeral joint osteoarthritis have indicated:

- Treatment using allograft, autograft, biologic, and interpositional grafts in patients with glenohumeral joint osteoarthritis is inconclusive.³⁵

- Treatment using growth factor injections and/or platelet rich plasma for patients with symptomatic osteoarthritis of the knee is inconclusive.³⁶

American Association of Neurological Surgeons

The American Association of Neurological Surgeons 2014 guidelines on fusion procedures for degenerative disease of the lumbar spine related to this evidence review have indicated that "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)."³⁷

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 2. Many are observational studies with commercially available products (eg, Cartistem, AlloStem).

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Unpublished			
NCT01413061 ^a	Study of Subtalar Arthrodesis Using AlloStem® Versus Autologous Bone Graft	140	Mar 2018 (completed)
NCT01626677; NCT01041001 ^a	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	104	May 2015 (completed)
NCT02291926 ^a	Phase I Study of Human Umbilical Cord Mesenchymal Stem Cell Implantation in the Treatment of Articular Cartilage Defect of Knee	20	Dec 2016

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
0263T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure including unilateral or bilateral bone marrow harvest

- 0264T Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure excluding bone marrow harvest
- 0265T Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; unilateral or bilateral bone marrow harvest only for intramuscular autologous bone marrow cell therapy

Diagnoses

Experimental / investigational for all diagnoses related to this policy.

REVISIONS

09-19-2013	Policy added to the bcbsks.com web site on 08-20-2013 for an effective date of 09-19-2013 for professional and institutional.
08-07-2015	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> ▪ In Item B, removed "is" and added "are" to read, "Allograft bone productions containing viable stem cells including, but not limited to, demineralized bone matrix (DBM) with stem cells are considered experimental/investigational for all orthopedic applications. ▪ Added Item C, "Allograft or synthetic bone graft substitutes that must be combined with autologous blood or bone marrow are considered experimental/investigational for all orthopedic applications." ▪ In Policy Guidelines, removed "Note:", to read "This policy does not address unprocessed allograft bone."
	Updated Rationale section.
	Updated References section.
03-02-2016	Updated Description section.
	Updated Rationale section.
	Updated References section.
08-15-2017	Updated Description section.
	Updated Rationale section.
	Updated References section.
02-15-2018	Updated Description section.
	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> ▪ Added CPT codes: 0263T, 0264T, 0265T. ▪ Removed CPT code: 38241.
	Updated References section.
02-18-2019	Updated Description section.
	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> ▪ Added CPT code: 38232.
	Updated References section.

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