Medical Policy

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Title: Orthopedic Applications of Stem Cell Therapy (Including Allograft and Bone Substitute Products Used With Autologous Bone Marrow)

Related Policies:	▪ *Recombinant and Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions* ▪ *Orthopedic Applications of Platelet-Rich Plasma* ▪ *Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions*

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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
Individuals: • With joint fusion procedures	Interventions of interest are: • Stem cell therapy	Comparators of interest are: • Iliac crest bone graft	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With osteonecrosis	Interventions of interest are: • Stem cell therapy	Comparators of interest are: • Core decompression	Relevant outcomes include: • 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 evidence review 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

Mesenchymal stem cells (MSCs) are multipotent cells (also called multipotent stromal cells) that can differentiate into various tissues including organs, trabecular bone, tendon, articular cartilage, ligaments, muscle, and fat. MSCs are associated with the blood vessels within the bone marrow, synovium, fat, and muscle, where they can be mobilized for endogenous repair as occurs with the healing of bone fractures. Tissues such as cartilage, tendon, ligaments, and vertebral discs show limited capacity for endogenous repair because of the limited presence of the triad of functional tissue 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 the most accessible source and, thus, the most common place to isolate MSCs for the treatment of musculoskeletal disease. However, harvesting MSCs from bone marrow requires a procedure that may result in donor-site morbidity. Also, 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 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. 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 FDA. No products using engineered or expanded MSCs have been approved by the FDA for orthopedic applications.

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

marketing products that are dependent on living cells for their function. The following descriptions are from the product literature.

- AlloStem® (AlloSource) is a partially demineralized allograft bone seeded with adipose-derived MSCs
- Osteocel Plus® (NuVasive) is a DBM combined with viable MSCs isolated from allogeneic bone marrow.
- Trinity Evolution Matrix™ (MTF Biologics, Orthofix) is a DBM combined with viable MSCs isolated from allogeneic bone marrow.
- Trinity Elite™ (MTF Biologics, Orthofix) is an allograft with osteoconductive, osteoinductive, and osteogenic properties.
- Other products contain DBM alone and are designed to be mixed with bone marrow aspirate:
    - Fusion Flex™ (Wright Medical, now part of Stryker) is a dehydrated moldable DBM scaffold (strips and cubes) that will absorb autologous bone marrow aspirate;
    - Ignite® (Wright Medical, now part of Stryker) 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 the FDA through the 510(k) process. FDA product code: MQV.

Tables 1 and 2 provide a representative sample of these products, differentiated by whether they must be mixed with autologous MSCs.

Table 1. Examples of Demineralized Bone Matrix Products Cleared by FDA that Do Not Require Mixing with Autologous MSCs

Product	Matrix Type		Manufacturer or Sponsor	Date Cleared	510(k) No.
Vitoss® Bioactive Foam Bone Graft Substitute	Type I bovine collagen		Stryker	Nov 2008	K083033
NanOss BVF-E	Nanocrystalline hydroxyapatite		Pioneer Surgical (now Xtant Medical)	Aug 2008	K081558
OrthoBlast® II Demineralized bone matrix putty and paste	Human (mixed allograft donor-derived) cancellous bone chips		SeaSpine	Sep 2007	K070751
DBX® Demineralized bone matrix putty, paste and mix	Processed human (single allograft donor-derived) bone and sodium hyaluronate		Musculoskeletal Transplant Foundation	Dec 2006	K053218
Formagraft™ Collagen Bone Graft Matrix	Bovine fibrillary collagen		R and L Medical (now Globus Medical)	May 2005	K050789

Product	Matrix Type		Manufacturer or Sponsor	Date Cleared	510(k) No.
DynaGraft® II Gel and Putty	Processed human (mixed allograft donor-derived) bone particles		IsoTis Orthobiologics (now Orthofix)	Mar 2005	K040419

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

Table 2. Examples of Demineralized Bone Matrix Products Cleared by FDA that Require Mixing with Autologous MSCs

Product	Matrix Type	Manufacturer or Sponsor	Date Cleared	510(k) No.
CopiOs® Bone Void Filler (sponge and powder disc)	Type I bovine dermal collagen	Kensey Nash (now Highridge Medical)	May 2007	K071237
Integra MOZAIK™ Osteoconductive Scaffold-Putty	Collagen matrix with tricalcium phosphate granules	IsoTis OrthoBiologics (now Integra LifeSciences)	Dec 2006	K062353

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

In 2020, the FDA updated their guidance on "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use".[2,]

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

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

"1) The HCT/P is minimally manipulated;

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

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

4) Either:

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

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

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

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.

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.

RATIONALE

This evidence review was created using searches of the PubMed database. The most recent literature update was performed through November 25, 2025.

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, 2 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 RCT is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials 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 individuals with osteoarthritis (OA) or focal cartilage defects.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with OA or focal cartilage defects.

Interventions

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

Comparators

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

Outcomes

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

- Knee Injury and Osteoarthritis Outcome Score (KOOS; 5 subscales with 0-100 scale),
- Lysolm Knee Scale (LKS) score (0-100 scale),
- Tegner Activity Score (TAS); a visual analog scale (VAS) for pain (0-100 mm or 0-10 cm scale),
- Western Ontario and McMaster Universities Arthritis Index (WOMAC) which has 3 subscores: pain, which includes 5 items; stiffness, with 2 items; and physical function, with 17 items.
- WOMAC response criteria is an improvement of 20% in at least 2 items together with an improvement of 10 points in the overall scale.
- Cartilage is evaluated with the Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART, 0-100 points, where higher scores indicate better cartilage repair).
- Follow-up over months to years is of interest for relevant outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- To assess long-term outcomes and adverse events (AEs), single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Systematic Reviews

Jin et al (2025) published a systematic review and meta-analysis of RCTs comparing intra-articular MSC injections with hyaluronic acid for knee OA.[3,] Ten trials involving 818 patients (Kellgren–Lawrence grade I–III) were included. Outcomes assessed were WOMAC, VAS, and Whole-Organ Magnetic Resonance Imaging Score (WORMS) scores at 3, 6, and 12 months, along

with adverse events. Results showed that MSCs provided superior improvements in pain and function compared with hyaluronic acid. At 12 months, WOMAC total score improved by a mean difference (MD) of -10.22 points (95% CI, -14.86 to -5.59; p<.0001), and VAS pain score by -1.31 points (95% CI, -1.90 to -0.73; p<.0001). WORMS scores also indicated significantly better cartilage repair with MSCs (MD -26.01; 95% CI, -31.88 to -20.14; p<.001). No significant difference in adverse events was observed between MSCs and hyaluronic acid (relative risk, 1.54; 95% CI, 0.85 to 2.79; p=.16), with most reactions being mild (joint pain, swelling, effusion). The authors noted that their analysis had several limitations. Although only registered, prospective RCTs with high levels of evidence were included, the small number of studies reduced the reliability of some findings. There are few direct comparisons of MSCs and hyaluronic acid for knee OA, and variability in MSC sources, doses, and Kellgren–Lawrence grades may have influenced results. Additionally, while pooled minimal clinically important difference (MCID) was analyzed, none of the included trials directly assessed MCID, limiting conclusions about clinical significance.

Sadeghirad et al (2024) published a systematic review and meta-analysis of RCTs of MSCs for chronic knee pain secondary to OA.[4,] A total of 16 trials (published through September 2023) involving 807 patients were included. Individuals were evaluated for knee pain at 3-6 months and 12 months post-injection of MSCs. Results showed that MSC therapy produced little to no difference in pain relief at either time point. MSCs may slightly improve physical functioning of the knee at 12 months (weighted mean difference [WMD], 19.36 points on 100-point Short Form Survey (SF-36) physical functioning subscale, 95%CI, 0.19 to 38.9; low certainty), but MSCs may also increase risk of AEs (risk ratio [RR], 2.67; 95% CI, 1.19 to 5.99; low certainty), and pain and swelling of the knee joint (RR, 1.58; 95% CI, 1.04 to 2.38; low certainty). The authors concluded that intra-articular injection of MSCs for chronic knee pain associated with osteoarthritis likely provides little to no improvement in pain or physical function. Further rigorously conducted trials are needed to establish the role of MSC therapy in the management of chronic knee pain associated with osteoarthritis.

Giorgino et al (2024) conducted a systematic review evaluating intra-articular MSC injections for the management of hip OA.[5,] The review included 10 studies (N=316) with diverse designs and outcomes, examining pain relief, functional improvement, and cartilage repair through various imaging, pain score, and functional improvement scoring systems like WOMAC, VAS, and hip outcome score–activities of daily living (HOS-ADL). Results showed favorable outcomes regarding pain relief and functional enhancement, with minimal AEs such as transient joint pain and hematomas. Despite the promising outcomes, the authors highlighted limitations such as small sample sizes, lack of control groups, and heterogeneity in MSC sources and treatment protocols. Further large-scale controlled trials with standardized methodologies are recommended to optimize MSC therapies for hip OA.

A systematic review and meta-analysis by Borakati et al (2018) included 15 comparative studies (N=582) on the use of MSCs to treat OA or focal osteochondral lesions.[6,] The studies (13 published and 2 unpublished data, between 2002 and 2015) included 5 RCTs, 1 case-control, and 9 cohort studies. A majority of the studies were conducted in Asia, and the source of the MSCs varied (bone marrow, blood, amniotic fluid, adipose tissue). The largest trial had only 56 participants, giving low statistical power for the individual studies. The overall quality of the evidence was considered low, with 3 studies rated as "satisfactory" and the rest rated "poor" on the Jadad scale. Pain assessment results were noted for each of the controlled studies, resulting

in a pooled standardized MD of -1.27 (95% CI, -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<.001); although there was high heterogeneity across controlled studies (I^2=92%). There was also a suggestion of publication bias; the investigators found 79 trials on clinicaltrials.gov, of which only 3 were listed as 'complete with results,' many trials had been inactive for several years, and 9 had 'unknown' status.

A more focused systematic review and meta-analysis of 6 RCTs (N=203) that evaluated cultured MSCs for OA was reported by Kim et al (2020).[7,] Four of the studies used bone marrow-derived MSCs, 1 used adipose-derived cells, and the other cultured placental cells. Only 2 (of 6) studies were rated as low risk of bias. Pain outcomes measured with VAS and WOMAC pain scales were improved at 6 to 12 months, but there was no significant improvement in measures of WOMAC function or cartilage measured by magnetic resonance imaging.

Jin et al (2022) also conducted a more focused systematic review and meta-analysis of 6 RCTs (N=452) that evaluated intra-articular MSC injection in patients undergoing high tibial osteotomy (HTO).[8,] Results demonstrated that there were no significant differences in the International Knee Documentation Committee (IKDC) score and KOOS Pain and Symptoms subscales in patients who underwent HTO with or without the MSC injection. However, patients who received MSC injection had significantly greater improvements in Lysholm scores (mean difference, 2.55; 95% CI, 0.70 to 4.40; p=.007), and greater proportions of International Cartilage Regeneration and Joint Preservation Society (ICRS) grade 1 (p=.03) and grade 2 (p=.02) cartilage repair in the medial femoral condyle and grade 2 cartilage repair in the tibial plateau (p=.04).

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

RANDOMIZED CONTROLLED TRIALS

Mesenchymal Stem Cells from Autologous Bone Marrow

The above systematic reviews included multiple studies that evaluated the use of MSCs for OA of the knee, including case series, and several small-scale RCTs (three phase 1/2 trials and one phase 3 trial).[9,10,11,12,13,] Overall, some studies found statistically significant improvements in certain clinical scores with MSC therapy, but results were often modest or of uncertain clinical significance, sometimes limited by study design. Larger trials did not find significant differences between cell therapies and standard treatment (corticosteroid or hyaluronic acid injections). In summary, while some positive findings exist, the evidence remains mixed, highlighting a need for further high-quality research. Limitations of the relevant RCTs are described in Tables 3 and 4.

Table 3. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Wong et al (2013)[9,]	3, 4. The population was restricted to patients younger than 55	4. The intervention included microfracture with/without stem cells			
Emadedin et al (2018)[10,]			2. Did not use an active control and use of analgesics was not reported	1. Evaluation of cartilage was not performed.	1, 2. Follow-up was reported out to 6 mo.
Lamo-Espinosa et al (2016, 2018)[11,12,]				1. Evaluation of cartilage was not performed.	
Mautner et al (2023)[13,]					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 4. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Wong et al (2013)[9,]	3. Patients selected from 1 of 2 identical envelopes	1, 2, 3. Not blinded except for evaluation of magnetic resonance imaging				
Emadedin et al (2018)[10,]				.	3. Details of power analysis were	1. The authors used non-inferiority compared to placebo and chi-

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
					not reported	square tests for continuous variables
Lamo-Espinosa et al (2016, 2018)[11,12,]		1, 2, 3. Not blinded			3. Details of power analysis were not reported	1. The authors used non-parametric tests for within-group comparisons rather than tests for repeated measures
Mautner et al (2023)[13,]		1, 2, 3. Single-blind (subjects only)				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Mesenchymal Stem Cells from Allogeneic Bone Marrow

Loke et al (2025) conducted a systematic review of RCTs evaluating allogeneic MSC implantation versus placebo for knee OA.[14,] The review included 7 studies (N=356), with follow-up ranging from 12 to 24 months. At 12 months, results demonstrated significant improvements in pain and function: VAS scores (n=5 studies) decreased by 30.4 points (from 59.45 to 28.02) and WOMAC scores by 40 points (from 66.3 to 26.3). Imaging studies showed increased cartilage thickness and improved cartilage quality, and one trial reported histological improvement in ICRSII scores. Adverse events were minimal, primarily transient injection-site pain and swelling, with no major complications or tumorigenesis. Limitations included small sample sizes, heterogeneous patient characteristics, and lack of long-term data beyond 2 years.

Mesenchymal Stem Cells from Bone Marrow Aspirate Concentrate

Two studies have addressed MSC from bone marrow aspirate concentrate (BMAC). Shapiro et al (2017)[15,] conducted a prospective, single-blind, placebo-controlled trial in which 25 patients

received BMAC in one knee and saline in the other, finding similar pain relief in both knees. Mautner et al (2023)[13,] compared BMAC to corticosteroid injections in a single-blind RCT (N=238), with limitations noted in Tables 3 and 4 above. These findings suggest that BMAC may not provide superior benefits over placebo or corticosteroid injections for OA-related knee pain.

Adipose-Derived Mesenchymal Stem Cells

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

Tangkanjanavelukul et al (2025) reported on a prospective, randomized, open-label, blinded-endpoint study comparing autologous adipose-derived MSC therapy with hyaluronic acid for early-stage knee osteoarthritis.[16,] Forty-eight patients (Kellgren–Lawrence grade II) were randomized to receive either a single ultrasound-guided intra-articular injection of adipose-derived MSCs (n=23) or hyaluronic acid (n=24). The primary outcome was cartilage regeneration assessed by MRI at 6 months, synovial thickness, and WOMAC scores. MRI imaging showed significant cartilage restoration in the adipose-derived MSC group, with medial femoral cartilage lesion volume decreasing by 36.44 mm^3, while the hyaluronic acid group exhibited an increase of 50.06 mm^3 (p=.029). Similar results were seen for medial patella cartilage. Synovial thickness declined more in the adipose-derived MSC group (from 3.70 mm to 2.86 mm) compared with hyaluronic acid (from 3.25 mm to 3.96 mm; $p<0.05$). WOMAC scores improved in both groups, but adipose-derived MSC therapy produced greater and sustained benefits: overall WOMAC decreased from 88.26 to 26.30 versus 96.46 to 49.09 with hyaluronic acid. No serious adverse events occurred.

Koh et al (2014), reporting on results of an RCT (N=52), found that adding MSCs to platelet-rich plasma (PRP) during HTO led to modest but statistically significant improvements in some pain and knee function scores, though the clinical significance remains uncertain due to small sample size and limited follow-up.[17,] Zaffagnini et al (2022) compared microfragmented adipose tissue with PRP (N=118) and observed significant improvements with both interventions, yet no significant differences between them, except more patients with moderate/severe OA achieved clinically meaningful improvements in the adipose tissue group.[18,] Kim et al (2023), reporting on a double-blind phase 3 RCT (N=261), found that a single injection of autologous adipose-derived MSCs resulted in significantly greater reductions in pain and functional impairment compared to placebo at 6 months, though the study's generalizability was limited by unclear prior treatment details and choice of comparator.[19,] Overall, these studies demonstrate potential benefits of cell-based therapies for knee OA, but limitations in study design and modest effect sizes raise questions about their clinical impact.

Mesenchymal Stem Cells 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. Fifty patients with grade 3 or 4 lesions of the knee joint underwent arthroscopic subchondral drilling followed by 5 weekly injections of HA.[20,]This study was included in the systematic review by Borakati (2018), as discussed above. Half the patients were randomized to injections of peripheral blood stem cells or no further treatment. 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 re-administered over 3 weekly injections. At 18 months post-surgery, 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 IKDC scores between the 2 groups at 24 months after surgery.

Mesenchymal Stem Cells from Umbilical Cord Blood

Lim et al (2021) reported on a RCT of 114 patients with large, full-thickness cartilage defects (International Cartilage Repair Society grade 4) treated with either a composite of umbilical cord-derived MSCs plus 4% hyaluronate (MSC-HA) or microfracture.[21,]The study consisted of a 48-week phase 3 clinical trial and a 5-year follow-up study. Of 114 patients randomized, 89 completed the phase 3 trial (78.1%), and 73 were enrolled in the follow-up study (64.0%). The primary outcome, proportion of participants with cartilage restoration equivalent to at least 1 grade improvement on the ICRS Macroscopic Cartilage Repair Assessment at 48-week arthroscopic evaluation, was 97.7% (42/43) in the MSC-HA group and 71.7% (33/46) in the microfracture group (odds ratio, 16.55; 95% CI, 2.06 to 133.03; p=.001). Both groups had significantly improved patient-reported pain scores (VAS pain, WOMAC, and IKDC scores) at 48 weeks versus baseline, but there was no significant difference between the 2 groups at this timepoint. From 36 to 60 months after intervention, the significant improvements from baseline were maintained in the MSC-HA group, whereas the improvements in VAS pain and WOMAC deteriorated in the microfracture group. This study had several limitations. There was no intervention group that received MSC alone, the comparator (microfracture) is not considered the standard of care for large, full-thickness cartilage defects, surgeons and participants were not blinded to treatment outcome, and there was high loss to follow-up. These limitations, along with a lack of improvement in patient-reported outcomes in the intervention group at 48 weeks, preclude drawing conclusions about the effectiveness of umbilical cord blood-derived MSCs in this population; higher quality evidence from RCTs is needed.

Xiao et al (2024) conducted a systematic review and meta-analysis on the effects of umbilical cord MSCs for the treatment of knee OA.[22,] The review included 3 RCTs (N=101), with study sample sizes ranging from 17 to 48. Results demonstrated significant reductions in WOMAC scores (mean difference, −25.85; 95% CI, −41.50 to −10.20; p=.001) and improvements in Knee Lysholm Scores (mean difference, 18.33; 95% CI, 12.89 to 23.77; p<.00001) in the MSC group compared to controls. AEs, including transient pain and joint effusion, were minimal. Limitations consisted of small sample sizes and study heterogeneity.

Mautner et al (2023) compared allogeneic umbilical cord blood-derived MSCs with corticosteroid injection in patients with OA in a single-blind RCT.[13,] The study is fully described above and in Tables 3 through 6.

Section Summary: Cartilage Defects

The evidence on MSCs for cartilage repair is increasing, although nearly all studies to date have been performed outside of the US with a variety of methods of MSC preparation. Recent systematic reviews have reported that intra-articular MSCs offer little to no pain relief for knee OA, with possible slight functional improvement and increased adverse events. For hip OA, MSCs show some benefit in pain and function but evidence is limited by small studies and inconsistent protocols. Overall, the quality of evidence is low for most studies and there is a possibility of publication bias. The strongest evidence base is on autologous MSCs expanded from bone marrow, which includes several phase 1/2 RCTs and 1 phase 3 RCT. The phase 3 RCT of autologous bone marrow-derived MSCs also evaluated 2 other autologous and allogeneic cell

therapies; the cell therapy modalities were not found to produce significant differences in pain or function after 12 months compared with intra-articular corticosteroid injection. An additional phase 3 trial evaluated autologous adipose tissue-derived MSCs; this trial enrolled patients with severe baseline symptoms and indicated significant improvements in pain, function, and other patient-reported outcomes at 6 months with intra-articular injection of adipose-derived MSCs relative to matching placebo. FDA approval for these methods has 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 individuals with meniscal defects.

The following PICO was used to select literature to inform this review.

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

Interventions
The therapy being considered is stem cell therapy.

Comparators
Comparators of interest include conservative management.

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

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- To assess long-term outcomes and adverse events (AEs), single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

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

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.[23,] The regulatory framework in the United Kingdom allows cell manipulation and requires immunohistochemical documentation of the presence and volume of mesenchymal cells. Over the first 12 months postprocedure, 3 (of 5) patients were reported to have clinical symptom relief, which persisted through 24 months. MRI scans showing lack of meniscal displacement

were the only other postoperative assessment. The 2 patients who failed to obtain symptom relief at 6 and 12 months had to repeat arthroscopic procedures with meniscectomy.

Vangsness et al (2014) reported on an industry-sponsored phase 1/2 randomized, double-blind, multicenter Study of Chondrogen - Adult Universal Cell Delivered by Intra-Articular Injection Following Meniscectomy in Patients 18-60 Years (NCT00225095, NCT00702741) of cultured allogeneic MSCs (Chondrogen; Osiris Therapeutics) injected into the knee after partial meniscectomy.[24,] The 55 patients in this US study were randomized to intra-articular injection of either $50 \acute{} 10^6$ allogeneic MSCs, $150 \acute{} 10^6$ allogeneic MSCs in HA, or an HA vehicle control at 7 to 10 days after meniscectomy. The cultured MSCs were derived from BMAC of unrelated donors. At 2-year follow-up, 3 patients in the low-dose MSC group had significantly increased meniscal volume measured by MRI (with an a priori determined threshold of at least 15%) compared with none in the control group or the high-dose MSC group. There was no significant difference between the groups in LKS scores. On subgroup analysis, patients with OA who received MSCs had a significantly greater reduction in pain at 2 years than patients who received HA alone. This trial appears to have been a post hoc analysis and, hence, should be considered preliminary. No serious AEs 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 individuals with joint fusion procedures.

The following PICO was used to select literature to inform this review.

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

Interventions
The therapy being considered is stem cell therapy.

Comparators
Comparators of interest include iliac crest bone graft.

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

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

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- To assess long-term outcomes and adverse events (AEs), single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
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.

Trinity Elite
Trinity Elite (MTF Biologics, Orthofix) is a third-generation cryopreserved allograft with a moldable matrix and viable cells. It contains the three essential components needed to support bone formation: an osteoconductive scaffold, verified osteoinductive potential, and osteogenic cells such as viable adult MSCs, osteoprogenitor cells, and osteoblasts. Trinity Elite can eliminate the need for harvesting autograft, which has the potential to reduce operative time and complications for the patients. Trinity Elite was launched with a full market release in the US in July 2013.[25,]

This launch followed the earlier introduction of Trinity Evolution allograft in 2009 (see below). Trinity Elite is built on the safety profile of Trinity Evolution and offers enhanced handling features, notably its moldability. It was made available for both spinal and extremity applications. Presented below are studies evaluating the clinical evidence for Trinity Elite cellular bone allograft (CBA) in lumbar, cervical, and foot and ankle fusion procedures.

Lumbar Spine Fusion
Wind et al (2022) conducted a prospective, multicenter, open-label clinical study (NCT 02969616) to assess the application of Trinity Elite CBA in patients undergoing lumbar spinal fusion.[26,] Fusion status was determined by independent evaluation of dynamic radiographs and CT scans, while clinical outcomes were measured using the EuroQol 5 Dimensions for quality of life, the Oswestry Disability Index (ODI) for disability, and the VAS for both back and leg pain. Data extending to 24 months were included in a post-hoc analysis. In total, 274 adult patients were enrolled across nine US sites. The cohort, with a mean age of 60 years and a collective BMI of 30.6 ± 6.5 kg/m², consisted of individuals who had not responded to at least six months of conservative treatment and were scheduled for either posterolateral (1-4 levels) or interbody (1-2 levels) lumbar fusion. Patients were divided into high-risk (>1 risk factor, n=140) and low-risk (≤1 risk factor, n=134) groups. Women represented 62% of the study population. Key exclusion criteria were prior lumbar fusion at the surgical site, active or recent malignancy (within five years, except benign skin cancer), any local or systemic infection, or ongoing adjunctive infection treatment.

At 12 months, 201 patients (73%) had successfully completed both radiographic and clinical follow-up after surgery.[27,] Fusion was deemed successful in 90% of cases. At 24 months, clinical outcomes showed significant improvement from baseline in ODI, VAS-back, and VAS-leg scores ($p<.001$).[28,] When outcomes were stratified by patient risk profile, CBA was found to achieve

similarly high fusion rates in both high-risk (94%) and low-risk (90%) cohorts (p>.05).[29,] Both groups maintained statistically significant improvements in clinical outcomes at all measured time points (p<.05), and the choice of surgical approach did not significantly affect the likelihood of successful fusion. A total of 665 adverse events (AEs) were reported, with pain (53 events, 8%) and back pain (37 events, 5.6%) being the most common. Two serious AEs (0.7%), both in high-risk patients, were linked to the bone graft.[27,] Attributing surgical success solely to the allograft remains challenging due to the interplay of surgical technique, patient risk factors, and post-operative care. Future controlled studies are necessary to clarify the comparative efficacy of CBA and to better define its independent contribution to patient outcomes.

Saeed et al. (2024), in a retrospective case series based on review of a single surgeon's practice database, evaluated radiographic fusion in 39 patients undergoing posterolateral lumbar fusion using unilateral CBA compared to contralateral local bone autograft.[30,] Fusion was assessed by CT at 9 months, with demographic and patient-reported outcomes monitored up to 12 months post-surgery. Across 81 attempted fusion levels, the overall fusion rate (bony bridging at least one side per level) was 85%. Fusion rates between CBA and local bone were similar (79% vs. 76%, p=.35). The ODI significantly improved by 3 months (p=.01) and was sustained. Two patients underwent revision for nonunion. Study limitations include use of internal controls, retrospective design, side interdependence, and small sample size.

Cervical Spine Fusion

Goldman et al (2024) conducted a retrospective, US single-center, consecutive case series (N=73) to evaluate the efficacy and safety of Trinity Elite CBA as an osteopromotive bone, in anterior cervical discectomy and fusion (ACDF) procedures.[31,] Fusion status was assessed at 6 and 12 months by independent evaluation of dynamic radiographs and CT scans. Complete fusion was defined as: evidence of bridging bone across the disc space on CT, angular motion. At 12 months, the fusion rate was 97%, including 100% fusion in one-, two-, and four-level cases, and 92% in three-level procedures. No cases of cage migration, graft-related complications, or graft removal were reported. Two patients (3%) required supplemental fixation due to traumatic falls post-operatively, and both ultimately achieved successful fusion.

Foot & Ankle Arthrodesis

Donaghue et al (2024) conducted a retrospective, single-site study evaluating the safety and efficacy of Trinity Elite CBA in foot and ankle arthrodesis among patients with high risk for non-union.[32,] The study included 22 patients (spanning 29 joints), the majority of whom possessed at least one risk factor undermining bone healing - such as nicotine use, diabetes, osteoporosis, neuropathy, or a history of failed fusions. The surgical procedures ranged from single- to triple-joint fusions involving the tibiotalar, subtalar, calcaneocuboid, and talonavicular joints. Fusion success was defined by radiographic evidence of bridging bone across three standard radiographic views or confirmed via CT scan. By 12 months, 95% of patients (21 of 22) achieved radiographic fusion, with an average time to union of approximately 6 months. All patients with diabetes, nicotine use, osteoporosis, or prior non-union achieved successful fusion. Statistical analysis revealed no significant differences in time to fusion when comparing those with fewer (≤1) versus multiple (≥2) risk factors, nor between obese and non-obese groups, smokers and non-smokers, or between younger and older cohorts. No postoperative complications or adverse events were reported.

Trinity Evolution
A prospective, clinical, and radiographic 12-month outcomes study (Vanichkachorn et al, 2016) of patients undergoing single-level ACDF for symptomatic cervical degenerative disc disease using Trinity EvolutionCBA was reported using historical controls as the comparator.[33,] The ACDF procedure was performed using the polyetheretherketone interbody spacer and CBA 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 post-procedure. Reported AEs included carpal tunnel syndrome, minor pain, numbness, permanent and/or unresolved pain, and swelling. Independent medical adjudication of the 26 AEs occurring in 31 patients found that no AEs were definitely or probably related to CBA. However, 5 AEs were found to be possibly related to CBA with 3 events of mild severity and 2 of moderate severity.

A similar study (Peppers et al, 2017) involving several of the same investigators and clinical sites reported on the clinical and radiographic evaluation of Trinity Evolution CBA in patients undergoing 2-level ACDF.[34,] 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 Trinity Evolution CBAwas performed in patients undergoing foot and/or ankle arthrodesis with surgeons' preferred technique.[35,] A total of 103 subjects were prospectively enrolled at 10 participating sites. No restrictions were placed on the diagnosis, which included arthritis (primary OAs, posttraumatic OA, 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 6 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.

Osteocel
Eastlack et al (2014) reported on outcomes from a series of 182 patients treated with ACDF using Osteocel Plus (NuVasive) in a polyetheretherketone cage and anterior plating.[36,] 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
Current evidence regarding the application of allografts combined with stem cells for bone fusion in the extremities or spine, as well as for the treatment of nonunion, remains limited. Several early-phase, industry-sponsored trials have been reported. Outcomes included radiologic assessments of fusion, sometimes made independently, and patient-reported measures (e.g., VAS scores). Clinical studies involving moldable cellular bone allografts have demonstrated high fusion rates at 12 months in lumbar, cervical, and foot and ankle procedures. These studies also note significant improvements in disability and pain scores, with few serious graft-related adverse events. However, the data are drawn primarily from nonrandomized, small-scale, and largely retrospective studies.

OSTEONECROSIS

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 individuals with osteonecrosis.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with osteonecrosis.

Interventions
The therapy being considered is therapy with MSCs.

Comparators
Comparators of interest include core decompression.

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

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

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- To assess long-term outcomes and adverse events (AEs), single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Systematic Reviews
Li et al (2021) published the results of a systematic review and meta-analysis evaluating stem cell therapy combined with core decompression versus single biomechanical support as treatment

of osteonecrosis of the femoral head.[37,] The analysis included 10 RCTs involving 498 patients (719 hips). A majority of the RCTs were not high quality, involved small sample size (n=18 to 125), and had short term follow-up (2 to 3 yrs on average). Stem cell counts and source varied among studies. Clinical outcomes were assessed using Harris hip score, VAS, and AEs. Publication bias was not able to be assessed and there was heterogeneity in outcome indicators. The Harris hip score and VAS both differed when compared with the control group, favoring stem cell therapy for relief of pain and were statistically significant (MD, 8.87; 95% CI, 5.53 to 12.22; p<0.000; MD, -14.07; 95% CI, -18.32 to -9.82; p<0.000, respectively). The was no significant difference in AEs among groups (RR, 1.57, 95% CI, 0.62 to 3.97; p=.34). According to the authors stem cell combined with core decompression was effective with few complications, however further high quality, large sample, multicenter long term RCTs are needed to establish safety and efficacy.

Randomized Controlled Trials
No additional relevant RCTs were found apart from those included in the Li et al (2021) systematic review.

Section Summary: Osteonecrosis
A 2021 systematic review analyzed 10 RCTs (N=498) comparing stem cell therapy plus core decompression to single biomechanical support in femoral head osteonecrosis. The studies, mostly small and short-term, showed stem cell therapy significantly improved Harris hip scores and VAS for pain, with no significant difference in adverse events. Limitations included study quality and heterogeneity. Additional, well-designed RCTs with a large number of patients are needed to permit greater certainty on the efficacy of this treatment for osteonecrosis.

SUPPLEMENTAL INFORMATION
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Orthopaedic Surgeons
A 2020 guideline from American Association of Orthopaedic Surgeons on the management of glenohumeral joint osteoarthritis (OA), endorsed by several other societies, states that injectable biologics such as stem cells cannot be recommended in the treatment of glenohumeral joint OA.[38,] There was consensus from the panel that better standardization and high-quality evidence from clinical trials is needed to provide definitive evidence on the efficacy of biologics in glenohumeral OA. The strength of evidence was rated as no reliable scientific evidence to determine benefits and harms.

The 2021 guideline on treatment of osteoarthritis of the knee does not address stem cell injections.[39,]

The 2023 guidelines on treatment of osteoarthritis of the hip do not address stem cell injections.[40,]

In May 2023, AAOS released a series of frequently asked questions on orthobiologics, aiming to provide clarity and guidance for treatment choices:

- "According to the Food and Drug Administration (FDA), … Unproven stem cell therapies can be particularly unsafe." Because stems cells do not come from your own body, and are further manipulated in a laboratory, these treatments pose additional risks and can be offered only in an FDA-approved clinical trial. Ask your doctor if the stem cell treatment they offer is part of an FDA-approved trial."[41,]

American Association of Neurological Surgeons
In 2014, the American Association of Neurological Surgeons guidelines on fusion procedures for degenerative disease of the lumbar spine relevant 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)."[42,]

American College of Rheumatology and Arthritis Foundation
In 2019, guidelines from the American College of Rheumatology and Arthritis Foundation on OA of the hand, hip, and knee gave a strong recommendation against stem cell injections in patients with knee and/or hip OA, noting the heterogeneity in preparations and lack of standardization of techniques.[43,] No recommendation was made for hand OA, since efficacy of stem cells has not been evaluated.

Department of Veterans Affairs and the Department of Defense
In a 2020 clinical practice guideline for the non-surgical management of hip and knee OA, the Department of Veterans Affairs and the Department of Defense (VA/DoD) gave a "weak against" recommendation for the use of stem cell injections (e.g., mesenchymal, adipose derived, and bone marrow-derived) for the treatment of osteoarthritis of the knee. The guideline was based on evidence published prior to 2020 and limited by inconsistency and imprecision with study designs and outcome measures, lack of studies evaluating the therapy in individuals with hip OA, and incomplete reporting.[44,]

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 7.

Table 7. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT06570291	A Multicenter, Randomized, Double-blind, Controlled Phase III Trial of Allogenic Adipose Tissue-Derived Mesenchymal Stem Cells (AlloJoin®) Therapy for Knee Osteoarthritis	520	Dec 2028
NCT07106229	A Phase 3, Multicentre, Randomised, Double Blind, Placebo-controlled Study to Evaluate the Effectiveness, Safety, and Tolerability of MAG200 (an Allogeneic Adipose-derived Mesenchymal Stem Cell Preparation) Administered by Intra-articular Injection to Adult Participants With Symptomatic Osteoarthritis of the Knee	573	Feb 2030
NCT02582489	Prospective, Randomized, Double-blind Clinical Trial to Investigate the Efficacy of Autologous Bone Marrow Aspirate Concentrate Post-Meniscectomy	100	Dec 2026
NCT04368806[a]	A 48-Weeks, Phase 2b/3a, Double-Blind, Randomized, Placebo Controlled, Multi-center, Superiority Study to Evaluate the Efficacy and Safety of JointStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells in Patients Diagnosed as Knee Osteoarthritis	140	Dec 2026
NCT04448106[a]	Clinical Study for Subjects With Osteoarthritis of Knees, Hips, and Shoulders Using a Combination of Intravenous Infusions With Intra-articular Injection of Autologous Adipose Tissue-Derived Mesenchymal Stem Cells (AdMSCs)	300	Aug 2026
NCT04427930	Long-Term Safety and Efficacy Extension Study Of Autologous Adipose-Derived MesenchymalStem Cells (JOINTSTEM) in Patients With Knee Osteoarthritis: A Phase III Extension Study	129	Dec 2027
NCT05517434	Intra-Articular Autologous Bone Marrow Aspirate Concentrate vs Placebo Injection and Lipoaspirate Concentrate With Leukocyte-Poor Platelet Rich Plasma vs Placebo Injection Evaluations for Treatment of Knee OsteoArthritis: The ABLE OA Double-Blinded Randomized Clinical Trial	148	Dec 2026

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. This may not be a comprehensive list of procedure codes applicable to this policy.

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.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
20930	Allograft, morselized, or placement of osteopromotive material, for spine surgery only (List separately in addition to code for primary procedure). NOTE: This is a generic graft add on injection code to spine surgery which could be used for stem cells injection.
20999	Unlisted procedure, musculoskeletal system, general (Use for aspiration of bone marrow for the purpose of bone grafting, other than spine surgery and other therapeutic musculoskeletal applications)
0263T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure including unilateral or bilateral bone marrow harvest
0264T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure excluding bone marrow harvest
0265T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; unilateral or bilateral bone marrow harvest only for intramuscular autologous bone marrow cell therapy
0489T	Autologous adipose-derived regenerative cell therapy for scleroderma in the hands; adipose tissue harvesting, isolation and preparation of harvested cells including incubation with cell dissociation enzymes, removal of non-viable cells and debris, determination of concentration and dilution of regenerative cells
0490T	Autologous adipose-derived regenerative cell therapy for scleroderma in the hands; multiple injections in one or both hands
0565T	Autologous cellular implant derived from adipose tissue for the treatment of osteoarthritis of the knees; tissue harvesting and cellular implant creation
0566T	Autologous cellular implant derived from adipose tissue for the treatment of osteoarthritis of the knees; injection of cellular implant into knee joint including ultrasound guidance, unilateral
0717T	Autologous adipose-derived regenerative cell (ADRC) therapy for partial thickness rotator cuff tear; adipose tissue harvesting, isolation and preparation of harvested cells, including incubation with cell dissociation enzymes, filtration, washing and concentration of ADRCs

CPT/HCPCS	
0718T	Autologous adipose-derived regenerative cell (ADRC) therapy for partial thickness rotator cuff tear; injection into supraspinatus tendon including ultrasound guidance, unilateral
C9359	Porous purified collagen matrix bone void filler (Integra Mozaik Osteoconductive Scaffold Putty, Integra Os Osteoconductive Scaffold Putty), per 0.5 cc
C9362	Porous purified collagen matrix bone void filler (Integra Mozaik Osteoconductive Scaffold Strip), per 0.5 cc

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: ▪ 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: ▪ 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: ▪ Added CPT code: 38232.
	Updated References section.
02-25-2021	Changed title from "Orthopedic Applications Of Stem Cell Therapy" to "Orthopedic Applications of Stem Cell Therapy (Including Allograft and Bone Substitute Products Used With Autologous Bone Marrow)"
	Updated Description section
	Updated Rationale section
	In coding section: • Added CPT codes: 20932, 20933, 20934, 20999, 38205, 38240, 38241, 0565T, 0566T, C9359, C9362
	Updated Reference section

REVISIONS	
04-11-2022	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Added CPT codes: 20930, 0489T, 0490T ▪ Removed CPT codes: 20932, 20933, 20934
	Updated References Section
07-01-2022	Updated Coding Section • Added 0717T and 0718T
02-28-2023	Updated Description Section
	Updated Rationale Section
	Updated References Section
02-27-2024	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Removed ICD-10 Diagnoses Box ▪ Removed 38205, 38206, 38230, 38232, 38240, 38241
	Updated References Section
02-25-2025	Updated Description Section
	Updated Rationale Section
	Updated Reference Section
01-05-2026	Updated Description Section
	Updated Rationale Section
	Updated Reference Section
02-24-2026	Updated Description Section
	Updated Rationale Section
	Updated Reference Section

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