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

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Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

Mesenchymal stem cell therapy **is considered experimental, investigational and/or unproven** for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue.

Allograft bone products containing viable stem cells, including but not limited to demineralized bone matrix with stem cells, **are considered experimental, investigational and/or unproven** for all orthopedic applications.

Allograft or synthetic bone graft substitutes that must be combined with autologous blood or bone marrow **are considered experimental, investigational and/or unproven** for all orthopedic applications.

Policy Guidelines

This policy does not address unprocessed allograft bone or products that do not require mixing with stem cells (product examples are shown in Tables 1 and 2 for informational purposes).

Description

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

The regulatory status of the stem cell or stem cell-containing products addressed in this policy 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.
- 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 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	Aug 2008	K081558
OrthoBlast® II Demineralized bone	Human (mixed allograft donor-	SeaSpine	Sep 2007	K070751

matrix putty and paste	derived) cancellous bone chips			
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	May 2005	K050789
DynaGraft® II Gel and Putty	Processed human (mixed allograft donor-derived) bone particles	IsoTis Orthobiologics	Mar 2005	K040419

FDA: Food and Drug Administration; MSCs: mesenchymal stem cells; No: number.

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	May 2007	K071237
Integra MOZAIK™ Osteoconductive Scaffold-Putty	Collagen matrix with tricalcium phosphate granules	IsoTis OrthoBiologics	Dec 2006	K062353

FDA: Food and Drug Administration; MSCs: mesenchymal stem cells; No: number.

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.

Rationale

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, 2 domains are examined: the relevance and the 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. 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 policy.

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.

<u>Study Selection Criteria</u>
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, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

<u>Systematic Reviews</u>
A systematic review and meta-analysis by Borakati et al. (2017) included 15 comparative studies (N=582) on the use of MSCs to treat OA or focal osteochondral lesions. (3) The studies (13 published and 2 unpublished data) included 5 RCTs, 1 case-control, and 9 cohort studies. A majority of the studies were conducted in Asia, and the source of the MSCs varied (bone marrow, blood, amniotic fluid, adipose tissue). The largest trial had only 56 participants, giving low statistical power for the individual studies. The overall quality of the evidence was

considered low, with 3 studies rated as "satisfactory" and the rest rated "poor" on the Jadad scale. Pain assessment results were noted for each of the controlled studies, resulting in a pooled standardized mean difference of -1.27 (95% confidence interval [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<0.001); although there was high heterogeneity across controlled studies (I^2=92%). There was also suggestion of publication bias; the investigators found 79 trials on clinicaltrials.gov, of which only 3 were listed as ‘complete with results,’ many trials had been inactive for several years, and 9 had ‘unknown’ status.

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

Wiggers et al. (2021) conducted a systematic review of RCTs evaluating autologous mesenchymal stem cell therapy on patient-reported outcome measures and disease severity. (5) Fourteen RCTs were identified in searches conducted through December 2020. Meta-analysis was precluded because most of the original trial data were not available for pooling and due to heterogeneity across studies. A total of 408 patients with knee osteoarthritis received MSC therapy derived from bone marrow, adipose tissue, or activated peripheral blood. After 1 year, 19 of 26 (73%) clinical outcome measures improved with MSCs compared with control. In the MSC group, patients improved by 1.8 to 4.4 points on the Visual Analogue Scale (0 to 10) and 18 to 32 points on the Knee Osteoarthritis Outcome Score (0 to 100). Four studies showed better disease severity on imaging after MSC compared with control at 1 year. Although the reviewers found a positive effect of autologous MSC therapy compared with control treatments, the certainty of the evidence was rated low to very low due to high risk of bias in the included studies (e.g., 10 of 14 RCTs were at high risk of bias on all outcomes) and high heterogeneity in the source, method of preparation, and dosage of injected stem cells in included RCTs.

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). (6) Four of the studies used bone-marrow derived MSCs, 1 used adipose-derived cells and the other cultured placental cells. Only 2 of the 6 studies were rated as low risk of bias. Pain outcomes measured with VAS and WOMAC pain scales were improved at 6 to 12 months, but there was no significant improvement in measures of WOMAC function or cartilage measured by magnetic resonance imaging.

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). (7) 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).

Giorgino et al. (2024) conducted a systematic review evaluating intra-articular MSC injections for the management of hip OA. (8) 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 adverse events 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.

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.

<u>Mesenchymal Stem Cells Expanded from Bone Marrow</u>

Autologous Bone Marrow

Wakitani et al. (2002) first reported on the use of expanded MSCs for repair of cartilage defects. (9) Cells from bone marrow aspirate of 12 patients with OA knees were culture-expanded, embedded in collagen gel, transplanted into the articular cartilage defect, and covered with autologous periosteum at the time of HTO. Clinical improvement did not differ between the experimental group and a group of 12 control patients who underwent HTO 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. (10) 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. (11) 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.

A publication from Centeno et al. (2010) of Regenerative Sciences in the United States described the use of percutaneously injected culture-expanded MSCs obtained from the iliac spine in 226 patients. (12) Following harvesting, cells were cultured with autologous platelet lysate and reinjected under fluoroscopic guidance into peripheral joints (n=213) or intervertebral discs (n=13). Culture-expanded MSCs requires approval by the U.S. Food and Drug Administration (FDA) and are no longer offered in the United States.

The largest study included in the systematic review by Borakati et al. (2017) was by Wong et al. (2013), who reported on an RCT of cultured MSCs in 56 patients with OA who underwent medial opening wedge HTO and microfracture of a cartilage lesion (see Tables 3 and 4). (13) Patients received an intra-articular injection of MSCs suspended in HA, or for controls, intra-articular injection of HA alone. The primary outcome was the IKDC score at 6 months, 1 year, and 2 years. Secondary outcomes were the TAS and LKS scores through 2 years and the MOCART scoring system (0-100 points, where higher scores indicate better cartilage repair) by magnetic resonance imaging (MRI) at 1 year. All patients completed the 2-year follow-up. After adjusting for age, baseline scores, and time of evaluation, the group treated with MSCs showed significantly better scores on the IKDC (mean difference, 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 0-10 scale; p=0.02) scores. The clinical significance of these differences is uncertain. Blinded analysis of MRI results found higher MOCART scores in the MSC group. The group treated with MSCs had a higher proportion of patients who had complete cartilage coverage of their lesions (32% versus 0%), greater than 50% cartilage cover (36% versus 14%), and complete integration of the regenerated cartilage (61% versus 14%).

Emadedin et al. (2018) reported a triple-blind, placebo-controlled, phase 1/2 trial of expanded MSCs in 47 patients with OA of the knee. (14) Compared to the placebo group, the MSC group showed statistically significant improvements in WOMAC pain and function subscales but not VAS. The WOMAC stiffness subscale improved to a similar extent in the 2 groups. Minimum Clinically Important Improvement and Patient Acceptable Symptom State were not significantly different between the 2 groups. Study limitations included the short duration of follow-up, statistical analysis, and lack of information regarding use of analgesic medications (see Tables 5 and 6).

Another phase 1/2 RCT of expanded MSCs was reported by Lamo-Espinosa et al. (2016, 2018) in 30 patients with OA of the knee. (15, 16) Two doses of MSCs ($10x10^6$, $100x10^6$) were administered with HA and compared to injection of HA alone. VAS scores were significantly decreased in both MSC groups compared to baseline throughout the 12 months of follow-up, while the decrease in VAS in the control group was not statistically significant. Similarly, total WOMAC scores were statistically decreased only in the high dose group at 12 months. Four-year follow-up was available for 27 of the 30 participants. Two patients in the control group and 1 patient in the low dose group had undergone total knee arthroplasty. VAS scores group were higher than at baseline in the HA control but remained low in the 2 MSC groups. WOMAC scores at the long-term follow-up showed a similar course (see Table 4). Limitations of this study are described in Tables 5 and 6.

Mautner et al. (2023) compared multiple autologous and allogeneic cell-based therapies with gold-standard corticosteroid injection in 475 adults with OA of the knee in a single-blind phase 3 RCT (Tables 3 through 6). (17) Patients were randomized to 1 of 2 autologous cell therapies (bone marrow aspirate concentrate [BMAC] or stromal vascular fraction), allogeneic umbilical cord-derived MSCs, or intra-articular corticosteroid injection; the co-primary endpoints were changes from baseline in VAS and Knee injury and Osteoarthritis Outcome Score pain scores at 12-month follow-up. No significant differences in pain scores were noted in comparisons between corticosteroid injection and any of the cell therapy arms.

Table 3. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Wong et al. (2013) (13)	Singapore	1	NR	Patients with OA who underwent HTO and microfracture (N=56)	Microfracture followed by expanded MSCs suspended in HA	Microfracture plus HA alone
Emadedin et al. (2018) (14)	Iran	1	2012-2016	Patients who met the ACR clinical and radiological criteria for knee OA (N=47)	$40x10^6$ expanded MSCs with serum albumin (n=22)	Placebo (n=25)
Lamo-Espinosa et al. (2016, 2018) (15, 16)	Spain	2	2012-2014	Patients who met the ACR clinical and radiological criteria for knee OA (N=30)	One of 2 doses of expanded MSCs with HA $10x10^6$, $100x10^6$	HA alone
Mautner et al. (2023) (17)	U.S.	5	2019-2021	Patients with radiographic evidence of knee OA and OA pain despite conservative measures (N=475)	Autologous bone marrow aspirate concentrate (n=118) Autologous stromal vascular fraction (n=119) Allogeneic umbilical cord MSCs (n=118)	Corticosteroid injection (n=120)

ACR: American College of Rheumatology; HA: hyaluronic acid; HTO: high tibial osteotomy; MSC: mesenchymal stem cell; NR: not reported; OA: osteoarthritis; RCT: randomized controlled trial; U.S.: United States; N/n: number.

Table 4. Summary of Key RCT Results

Study					

Wong et al. (2013) (13)	*IKDC at 6 mo*	*IKDC at 2 yr*	*Tegner Activity Scale at 2 yr*	*Lysolm Knee Score at 2 yr*	*MOCART*
N	56	56	56	56	56
Diff (95% CI)	7.65 (3.04 to 12.26)		0.64 (0.10 to 1.19)	7.61 (1.44 to 13.79)	19.6 (10.5 to 28.6)
p-Value	0.001		0.021	0.016	<0.001
Emadedin et al. (2018) (14)	*WOMAC Total*	*WOMAC Pain*	*WOMAC Stiffness*	*WOMAC Function*	*VAS*
N	43	43	43	43	43
MSC (95% CI)	-25.7 (-35.4 to 16)	-35 (-44.9 to 25)	-16.9 (-30.4 to 3.5)	-22.9 (-32.9 to 12.9)	-20.8 (-34.5 to 7.1)
Placebo (95% CI)	5.5 (-2.8 to 13.8)	-12.2 (-18.5 to 5.9)	-13.1 (-20.7 to 5.4)	-9.5 (-21.8 to 2.7)	-15.7 (-33.9 to 2.4)
Diff (95% CI)	-13.5 (-24.3 to 2.7)	-21.8 (-33.8 to 9.9)	-7.4 (-25.4 to 10.5)	-11.3 (-22.1 to 0.4)	-5 (-28.1 to 18)
p-Value	0.01	0.001	0.40	0.04	0.65
Effect size (95% CI)	0.7 (0.1 to 1.4)	1.1 (0.4 to 1.7)		0.6 (0.03 to 1.2)	
Lamo-Espinosa et al. (2016, 2018) (15, 16)	*WOMAC Total at 12 mo, median (IQR)*	*WOMAC Total at 4 yr, median (IQR)*	*VAS at 4 yr, median (IQR)*		
MSC low dose	21.5 (15, 26)	17 (13, 25.5)	2 (2, 5)		
MSC high dose	16.5 (12, 19)	16.5 (8, 23)	3 (3, 4)		
Control	13.5 (8, 33)	27 (17, 30)	7 (6, 7)		
Mautner et al. (2023) (17)	*100 mm VAS for pain, mean change from baseline to 12 mo*	*KOOS pain score, mean change from baseline to 12 mo*			
Autologous BMAC	-24.3	19.1			
Autologous SVF	-19.4	17.2			
Allogeneic UCT MSCs	-20.1	16.2			
Corticosteroid injection (control)	-20.9	17.7			
p-values	BMAC vs control: .19	BMAC vs control: .49			

	SVF vs control: .56 UCT vs control: .76	SVF vs control: .82 UCT vs control: .44			

BMAC: bone marrow aspirate concentrate; CI: confidence interval; IKDC: International Knee Documentation Committee score; IQR: interquartile range; KOOS: Knee Injury and Osteoarthritis Outcome Score; mo: month(s); MOCART; Magnetic Resonance Observation of Cartilage Repair Tissue; MSC: mesenchymal stem cell; RCT: randomized controlled trial; SEM: standard error of the mean; SVF: stromal vascular fraction; UCT: umbilical cord tissue; VAS: visual analog scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index; yr: year(s); N: number.

Table 5. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Wong et al. (2013) (13)	3, 4. The population was restricted to patients younger than 55	4. The intervention included microfracture with/without stem cells			
Emadedin et al. (2018) (14)			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) (15, 16)				1. Evaluation of cartilage was not performed	
Mautner et al. (2023) (17)					

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 6. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Wong et al. (2013) (13)	3. Patients selected from 1 of 2 identical envelopes	1, 2, 3. Not blinded except for evaluation of MRI				
Emadedin et al. (2018) (14)					3. Details of power analysis were not reported	1. The authors used non-inferiority compared to placebo and chi-square tests for continuous variables
Lamo-Espinosa et al. (2016, 2018) (15, 16)		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) (17)		1, 2, 3. Single-blind (subjects only)				

MRI: magnetic resonance imaging.
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
Vega et al. (2015) reported on a small phase 1/2 RCT of 30 patients with OA unresponsive to conventional treatments. (18) 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 post-injection. In the MSC-treated group, pain scores (VAS and WOMAC) decreased significantly between baseline and the 12-month follow-up, whereas pain scores in the control group did not improve significantly. A significant improvement in cartilage quality in the MSC group was supported by T2 MRI. Not reported was whether the patients or assessors were blinded to treatment.

Mesenchymal Stem Cells from Bone Marrow Aspirate Concentrate
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 OA. (19) Patients were randomized to BMAC into 1 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 VAS score were tracked initially at 1 week, 3 months, and 6 months post-procedure. Study patients experienced a similar relief of pain in both BMAC- and saline-treated arthritic knees.

Mautner et al. (2023) compared BMAC with corticosteroid injection in patients with OA in a single-blind RCT. (17) The study is fully described above and in Tables 3 through 6.

Adipose-Derived Mesenchymal Stem Cells
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 2 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 HTO in 52 patients with OA. (20) Patients were randomized via sealed envelopes to HTO with the application of platelet-rich plasma (PRP) or to HTO with the application of PRP plus MSCs. A total of 44 patients completed second-look arthroscopy and 1- and 2-year clinical follow-ups. The primary outcomes were the KOOS (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 versus 81.2, p<0.001) and symptoms (75.4 versus 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. There were limitations in study design (small sample size, short duration of follow-up). Also, significant improvements were found only on some outcomes, all significant differences in outcomes were modest in magnitude and, as a result, there is uncertainty about the clinical significance of the findings.

More recently, Zaffagnini et al. (2022) reported on results of an RCT that evaluated a single intra-articular injection of microfragmented adipose tissue or PRP in patients (N=118) with knee OA. (21) The primary outcomes were the IKDC subjective score and the KOOS pain subscore at 6 months. Overall, both treatments provided significant improvements from baseline in clinical outcomes, with no significant differences found between treatment groups. The IKDC scores significantly improved from baseline to 6 months, from 41.1 ± 16.3 to 57.3 ± 18.8 with microfragmented adipose tissue, and from 44.8 ± 17.3 to 58.4 ± 18.1 with PRP. The improvement in the KOOS pain subscore from baseline to 6 months was 58.4 ± 15.9 to 75.8 ± 17.4 with microfragmented adipose tissue and 63.5 ± 17.8 to 75.5 ± 16.1 with PRP. As a secondary outcome, more patients in the microfragmented adipose tissue group with moderate/severe knee OA reached the minimal clinically important difference for the IKDC score at 6 months compared with the PRP group (75.0% vs 34.6%, respectively; p=.005).

Kim et al. (2023) reported a double-blind phase 3 RCT comparing a single intra-articular injection of autologous adipose tissue-derived MSCs with placebo in patients with knee OA (N=261). (22) Patients meeting American College of Rheumatology criteria for Kellgren-Lawrence grade 3 knee OA who had 100 mm VAS pain scores ≥50 and WOMAC functional impairment scores ≥40 despite >3 months of non-operative treatment were eligible for enrollment. All patients underwent abdominal subcutaneous lipoaspiration 3 weeks prior to assigned study injection (1:1 randomization to $1x10^8$ autologous adipose tissue-derived MSCs [n=131] or a mixture of saline with autologous serum [n=130]). The co-primary endpoints were change in 100 mm VAS pain score and WOMAC function score from baseline to 6 months. In the primary analysis, patients assigned to adipose tissue-derived MSCs experienced significantly greater improvements than those assigned to placebo in both VAS pain score (25.2 ±24.6 vs 15.5 ±23.7; p=.004) and WOMAC function score (21.7 ± 18.6 vs 14.3 ± 19.2; p=.002) from baseline to 6 months. Six-month changes in patient-reported outcomes (KOOS, 36-Item Short Form Health Survey Score, and International Knee Documentation Committee subjective knee score) also reflected significant improvements in patients who received adipose tissue-derived MSCs compared with those who received placebo. Study limitations include that while patients were required to have received prior non-operative therapy for at least 3 months, specific prior treatments were not reported; it is unclear whether the use of a placebo comparator was more appropriate than an active comparator in this setting.

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. (23) Fifty patients with grade 3 or 4 lesions of the knee joint underwent arthroscopic subchondral drilling followed by 5 weekly injections of HA. 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, second-look arthroscopy on 16 patients in each group showed significantly higher histologic scores (≈10%) for the MSC group (1066 versus 957 by independent observers) while blinded evaluation of MRI scans showed a higher morphologic score (9.9 versus 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. (24) 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. (25) 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. Adverse events, 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. (17) 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 United States with a variety of methods of MSC preparation. 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 policy.

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, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

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. (26) The regulatory framework in the United Kingdom allows cell manipulation and requires immunohistochemical documentation of the presence and volume of mesenchymal cells. Over the first 12 months post-procedure, 3 of the 5 patients were reported to have clinical symptom relief, which persisted through 24 months. MRI scans showing lack of meniscal displacement were the only other postoperative assessment. The 2 patients who failed to obtain symptom relief at 6 and 12 months had to repeat arthroscopic procedures with meniscectomy.

Vangsness et al. (2014) reported on an industry-sponsored phase 1/2 randomized, double-blind, multicenter Study of Chondrogen - Adult Universal Cell Delivered by Intra-Articular Injection Following Meniscectomy in Patients 18-60 Years (NCT00225095, NCT00702741) of cultured allogeneic MSCs (Chondrogen; Osiris Therapeutics) injected into the knee after partial meniscectomy. (27) The 55 patients in this U.S. study were randomized to intra-articular injection of either $50x10^6$ allogeneic MSCs, $150x10^6$ 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 a priori determined threshold of at least 15%) compared with none in the control group or the high-dose MSC group. There was no significant difference between the groups in LKS scores. On subgroup analysis, patients with OA who received MSCs had a significantly greater reduction in pain at 2 years than patients who received HA alone. This trial appears to have been a post hoc analysis and, hence, should be considered preliminary. No serious adverse events were reported as related to the investigational treatment.

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 policy.

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, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

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. (28) The ACDF procedure was performed using the polyetheretherketone (PEEK) interbody spacer and bone graft substitute (Trinity Evolution™) in 31 patients at multiple clinical sites. At 6 and 12 months, the primary end point of radiographic fusion was evaluated as determined by independent radiographic review and the fusion rate was 78.6% at 6 months and 93.5% at 12 months. Secondary endpoints included function as assessed by Neck Disability Index (NDI) 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 adverse events included carpal tunnel syndrome, minor pain, numbness, permanent and/or unresolved pain, and swelling. Independent medical adjudication of the 26 adverse events occurring in 31 patients found that no adverse events were definitely or probably related to Trinity Evolution. However, 5 adverse events were found to be possibly related to Trinity Evolution with 3 events of mild severity and 2 of moderate severity.

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. (29) 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 (CT) 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 NDI 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. (30) A total of 103 subjects were prospectively enrolled at 10 participating sites. No restrictions were placed on the diagnosis, which included arthritis (primary OA, post-traumatic 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 CT 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 PEEK cage and anterior plating. (31) 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^{o}. 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 (e.g., 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.

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 policy.

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, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

At least 2 RCTs from Asia have evaluated the use of MSCs for osteonecrosis of the femoral head.

Mesenchymal Stem Cells Concentrated from Bone Marrow Aspirate Concentrate

Sen et al. (2012) randomized 40 patients (51 hips) with early-stage femoral head osteonecrosis to core decompression plus concentrated bone marrow MSCs or core decompression alone. (32) Blinding of assessments in this small trial was not described. Harris Hip Score (HHS) was significantly improved in the core decompression plus MSC group compared with the core decompression alone group at 12 months (scores, 83.65 versus 76.68, p<0.016) but not at 24 months (scores, 82.42 versus 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.

Mesenchymal Stem Cells 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. (33) At 60 months post-surgery, 2 (3.7%) of the 53 hips treated with MSCs progressed and underwent vascularized bone grafting compared with 10 (23%) of 44 hips in the decompression group who progressed and underwent either vascularized bone grafting (n=5) or total hip replacement (n=5). The MSC group also had improved HHS 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 RCTs 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 randomized controlled trials (RCTs) and nonrandomized comparative trials. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. Use of mesenchymal stem cells (MSCs) for orthopedic conditions is an active area of research. Despite continued research into the methods of harvesting and delivering treatment, there are uncertainties regarding the optimal source of cells and the delivery method. Studies have included MSCs from bone marrow, adipose tissue, and peripheral blood. Overall, the quality of evidence is low and there is a possibility of publication bias. The strongest evidence to date is on autologous MSCs expanded from bone marrow, which includes several phase 1/2 RCTs and a phase 3 RCT (which also evaluated other cell therapies). The phase 3 trial did not indicate significant improvements with the cell therapy modalities relative to active-control intra-articular corticosteroid injections for patients with knee osteoarthritis after 12 months of follow-up. Another recent phase 3 RCT evaluated autologous MSCs expanded from abdominal adipose tissue for treatment of knee osteoarthritis; this trial indicated autologous adipose-derived MSCs were more effective than matching placebo injections in improving pain, function, and other patient-reported outcomes after 6 months of follow-up. These phase 3 trials' mixed findings may be related to differences in the cell therapy modalities used, baseline cohort characteristics, and/or the use of an active vs placebo control. Alternative methods of obtaining MSCs have been reported in a smaller number of trials and with mixed results. Additional study with longer follow-up is needed to evaluate the long-term efficacy and safety of these procedures. 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 clear evidence that clinical outcomes are improved. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American Association of Orthopaedic Surgeons (AAOS)

A 2020 guideline from the AAOS on the management of glenohumeral joint OA, endorsed by several other societies, states that injectable biologics such as stem cells cannot be recommended in the treatment glenohumeral joint OA. (34) 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 OA of the knee does not address stem cell injections. (35)

The 2023 guidelines on treatment of osteoarthritis of the hip do not address stem cell injections. (36)

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 medical policy 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. DBM: Grade C (poor level of evidence)." (37)

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. (38) No recommendation was made for hand OA, since efficacy of stem cells has not been evaluated.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this medical policy are listed in Table 7.

Table 7. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			

NCT02582489	Prospective, Randomized, Double-blind Clinical Trial to Investigate the Efficacy of Autologous Bone Marrow Aspirate Concentrate Post-Meniscectomy	100	Dec 2025
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 2024 (unknown status)
NCT02838069	A Phase IIb, Prospective, Multicentre, Double-blind, Triple-arm, Randomized Versus Placebo Trial, to Assess the Efficacy of a Single Injection of Either 2 or 10 x 10^6 Autologous Adipose Derived Mesenchymal Stromal Cells (ASC) in the Treatment of Mild to Moderate Osteoarthritis (OA) of the Knee, Active and Unresponsive to Conservative Therapy for at Least 12 Months	100	Mar 2024 (active, not recruiting)
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
NCT05288725	A Study to Evaluate the Safety, and Efficacy of Minimally Manipulated Autologous Bone Marrow Aspirate to Treat Knee Osteoarthritis in Patients	120	Dec 2024 (unknown status)
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	148	Mar 2026

	ABLE OA Double-Blinded Randomized Clinical Trial		
Unpublished			
NCT04310215[a]	A Multi-center, Single-blind, Randomized, Phase III Clinical Trial to Evaluate the Efficacy and Safety of Adding CARTISTEM® on Microfracture in Patients With Talar Chondral or Osteochondral Defect	102	Jun 2022
NCT04043819[a]	Evaluation of Safety and Exploratory Efficacy of PSC-01, an Autologous Adipose-derived Stromal Vascular Fraction Cell Therapy Product for the Treatment of Knee Osteoarthritis	125	Jan 2021
NCT03067870	Transplantation of Autologous Purified Bone Marrow Derived Specific Populations of Stem Cells and Mesenchymal Stem Cells in Patients With Rheumatoid Arthritis	100	Feb 2022

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	20930, 20939, 20999, 0263T, 0264T, 0265T, 0489T, 0490T, 0565T, 0566T
HCPCS Codes	C9359, C9362

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
06/15/2025	Document updated with literature review. Coverage unchanged. Added references 8, 25 and 36; others updated.
08/15/2024	Document updated with literature review. Coverage unchanged. Added references 16 and 21.
09/15/2023	Document updated with literature review. Coverage unchanged. Added references 5, 7, 19, and 21.
05/15/2022	Reviewed. No changes.
09/15/2021	Document updated with literature review. Coverage unchanged. Added/updated references: 2, 4-5, and 26-27. Title changed from: Orthopedic Applications of Stem Cell Therapy (Including Allograft and Bone Substitute Products Used With Autologous Bone Marrow).
05/01/2021	Document updated with literature review. Coverage unchanged. Added/updated references: 9-11 and 24. Title changed from: Orthopedic Applications of Stem-Cell Therapy.
05/01/2019	Reviewed. No changes.
08/15/2018	Document updated with literature review. Coverage unchanged. References 1, 4, 12-14, 24, 27, and 29-31 were added, with several references removed.
10/15/2017	Reviewed. No changes.
11/01/2016	Document updated with literature review. The following coverage statement was added: "Allograft or synthetic bone graft substitutes that must be combined with autologous blood or bone marrow are considered experimental, investigational and/or unproven for all orthopedic applications."
08/15/2015	Reviewed. No changes.
08/15/2014	New medical document. Mesenchymal stem-cell (MSC) therapy, including but not limited to bone-marrow aspirate concentrate (BMAC), is considered experimental, investigational and/or unproven for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue. Allograft bone products containing viable stem-cells, including but not limited to demineralized bone matrix (DBM) with stem-cells, is considered experimental, investigational and/or unproven for all orthopedic applications. NOTE: This policy does not address unprocessed allograft bone.