

DRAFT Medical Coverage Policy | Orthopedic Applications of Stem Cell Therapy



EFFECTIVE DATE: 01|01|2026

POLICY LAST REVIEWED: 09|17|2025

OVERVIEW

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.

MEDICAL CRITERIA

Not applicable

PRIOR AUTHORIZATION

Not applicable

POLICY STATEMENT

Medicare Advantage Plans

Mesenchymal stem cell therapy for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue is not covered as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Allograft bone products containing viable stem cells, including but not limited to demineralized bone matrix with stem cells for all orthopedic applications is not covered as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Allograft or synthetic bone graft substitutes that must be combined with autologous blood or bone marrow for all orthopedic applications is not covered as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Commercial Products

Mesenchymal stem cell therapy for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue is not medically necessary as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Allograft bone products containing viable stem cells, including but not limited to demineralized bone matrix with stem cells for all orthopedic applications is not medically necessary as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Allograft or synthetic bone graft substitutes that must be combined with autologous blood or bone marrow for all orthopedic applications is not medically necessary as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

COVERAGE

Benefits may vary between groups/contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for limitations of benefits/coverage when services are not covered/not medically necessary.

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.

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.

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

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

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

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.

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.
- 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.

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.

CODING

Medicare Advantage Plans and Commercial Products

The following CPT code(s) are not covered for Medicare Advantage Plans and not medically necessary for Commercial Products:

- 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

RELATED POLICIES

Stem Cell Therapy for Peripheral Arterial Disease

PUBLISHED

Provider Update, November 2025

REFERENCES

1. Goldberg A, Mitchell K, Soans J, et al. The use of mesenchymal stem cells for cartilage repair and regeneration: a systematic review. *J Orthop Surg Res.* Mar 09 2017; 12(1): 39. PMID 28279182
2. U.S. Food & Drug Administration. Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/regulatory-considerations-human-cells-tissues-and-cellular-and-tissue-based-products-minimal>. Accessed December 1, 2024.
3. Borakati A, Mafi R, Mafi P, et al. A Systematic Review And Meta-Analysis of Clinical Trials of Mesenchymal Stem Cell Therapy for Cartilage Repair. *Curr Stem Cell Res Ther.* Feb 23 2018; 13(3): 215-225. PMID 28914207
4. Maheshwer B, Polce EM, Paul K, et al. Regenerative Potential of Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis and Chondral Defects: A Systematic Review and Meta-analysis. *Arthroscopy.* Jan 2021; 37(1): 362-378. PMID 32497658

5. Wiggers TG, Winters M, Van den Boom NA, et al. Autologous stem cell therapy in knee osteoarthritis: a systematic review of randomised controlled trials. *Br J Sports Med.* Oct 2021; 55(20): 1161-1169. PMID 34039582
6. Kim SH, Djaja YP, Park YB, et al. Intra-articular Injection of Culture-Expanded Mesenchymal Stem Cells Without Adjuvant Surgery in Knee Osteoarthritis: A Systematic Review and Meta-analysis. *Am J Sports Med.* Sep 2020; 48(11): 2839-2849. PMID 31874044
7. Jin L, Yang G, Men X, et al. Intra-articular Injection of Mesenchymal Stem Cells After High Tibial Osteotomy: A Systematic Review and Meta-analysis. *Orthop J Sports Med.* Nov 2022; 10(11): 23259671221133784. PMID 36452339
8. Giorgino R, Alessandri Bonetti M, Migliorini F, et al. Management of hip osteoarthritis: harnessing the potential of mesenchymal stem cells-a systematic review. *Eur J Orthop Surg Traumatol.* Dec 2024; 34(8): 3847-3857. PMID 39254726
9. Wakitani S, Imoto K, Yamamoto T, et al. Human autologous culture expanded bone marrow mesenchymal cell transplantation for repair of cartilage defects in osteoarthritic knees. *Osteoarthritis Cartilage.* Mar 2002; 10(3): 199-206. PMID 11869080
10. Wakitani S, Nawata M, Tensho K, et al. Repair of articular cartilage defects in the patello-femoral joint with autologous bone marrow mesenchymal cell transplantation: three case reports involving nine defects in five knees. *J Tissue Eng Regen Med.* 2007; 1(1): 74-9. PMID 18038395
11. Wakitani S, Okabe T, Horibe S, et al. Safety of autologous bone marrow-derived mesenchymal stem cell transplantation for cartilage repair in 41 patients with 45 joints followed for up to 11 years and 5 months. *J Tissue Eng Regen Med.* Feb 2011; 5(2): 146-50. PMID 20603892
12. Centeno CJ, Schultz JR, Cheever M, et al. Safety and complications reporting on the re-implantation of culture-expanded mesenchymal stem cells using autologous platelet lysate technique. *Curr Stem Cell Res Ther.* Mar 2010; 5(1): 81-93. PMID 19951252
13. Wong KL, Lee KB, Tai BC, et al. Injectable cultured bone marrow-derived mesenchymal stem cells in varus knees with cartilage defects undergoing high tibial osteotomy: a prospective, randomized controlled clinical trial with 2 years' follow-up. *Arthroscopy.* Dec 2013; 29(12): 2020-8. PMID 24286801
14. Emadedin M, Labibzadeh N, Liastani MG, et al. Intra-articular implantation of autologous bone marrow-derived mesenchymal stromal cells to treat knee osteoarthritis: a randomized, triple-blind, placebo-controlled phase 1/2 clinical trial. *Cytotherapy.* Oct 2018; 20(10): 1238-1246. PMID 30318332
15. Lamo-Espinosa JM, Mora G, Blanco JF, et al. Intra-articular injection of two different doses of autologous bone marrow mesenchymal stem cells versus hyaluronic acid in the treatment of knee osteoarthritis: long-term follow up of a multicenter randomized controlled clinical trial (phase I/II). *J Transl Med.* Jul 31 2018; 16(1): 213. PMID 30064455
16. Lamo-Espinosa JM, Mora G, Blanco JF, et al. Intra-articular injection of two different doses of autologous bone marrow mesenchymal stem cells versus hyaluronic acid in the treatment of knee osteoarthritis: multicenter randomized controlled clinical trial (phase I/II). *J Transl Med.* Aug 26 2016; 14(1): 246. PMID 27565858
17. Mautner K, Gottschalk M, Boden SD, et al. Cell-based versus corticosteroid injections for knee pain in osteoarthritis: a randomized phase 3 trial. *Nat Med.* Dec 2023; 29(12): 3120-3126. PMID 37919438
18. Vega A, Martín-Ferrero MA, Del Canto F, et al. Treatment of Knee Osteoarthritis With Allogeneic Bone Marrow Mesenchymal Stem Cells: A Randomized Controlled Trial. *Transplantation.* Aug 2015; 99(8): 1681-90. PMID 25822648
19. Shapiro SA, Kazmerchak SE, Heckman MG, et al. A Prospective, Single-Blind, Placebo-Controlled Trial of Bone Marrow Aspirate Concentrate for Knee Osteoarthritis. *Am J Sports Med.* Jan 2017; 45(1): 82-90. PMID 27566242
20. Koh YG, Kwon OR, Kim YS, et al. Comparative outcomes of open-wedge high tibial osteotomy with platelet-rich plasma alone or in combination with mesenchymal stem cell treatment: a prospective study. *Arthroscopy.* Nov 2014; 30(11): 1453-60. PMID 25108907
21. Zaffagnini S, Andrioli L, Boffa A, et al. Microfragmented Adipose Tissue Versus Platelet-Rich Plasma for the Treatment of Knee Osteoarthritis: A Prospective Randomized Controlled Trial at 2-Year Follow-up. *Am J Sports Med.* Sep 2022; 50(11): 2881-2892. PMID 35984721

22. Kim KI, Lee MC, Lee JH, et al. Clinical Efficacy and Safety of the Intra-articular Injection of Autologous Adipose-Derived Mesenchymal Stem Cells for Knee Osteoarthritis: A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial. *Am J Sports Med.* Jul 2023; 51(9): 2243-2253. PMID 37345256
23. Lim HC, Park YB, Ha CW, et al. Allogeneic Umbilical Cord Blood-Derived Mesenchymal Stem Cell Implantation Versus Microfracture for Large, Full-Thickness Cartilage Defects in Older Patients: A Multicenter Randomized Clinical Trial and Extended 5-Year Clinical Follow-up. *Orthop J Sports Med.* Jan 2021; 9(1): 2325967120973052. PMID 33490296
24. Xiao Z, Wang X, Li C, et al. Effects of the umbilical cord mesenchymal stem cells in the treatment of knee osteoarthritis: A systematic review and meta-analysis. *Medicine (Baltimore).* Nov 15 2024; 103(46): e40490. PMID 39560593
25. Whitehouse MR, Howells NR, Parry MC, et al. Repair of Torn Avascular Meniscal Cartilage Using Undifferentiated Autologous Mesenchymal Stem Cells: From In Vitro Optimization to a First-in-Human Study. *Stem Cells Transl Med.* Apr 2017; 6(4): 1237-1248. PMID 28186682
26. Vangsness CT, Farr J, Boyd J, et al. Adult human mesenchymal stem cells delivered via intra-articular injection to the knee following partial medial meniscectomy: a randomized, double-blind, controlled study. *J Bone Joint Surg Am.* Jan 15 2014; 96(2): 90-8. PMID 24430407
27. Vanichkachorn J, Peppers T, Bullard D, et al. A prospective clinical and radiographic 12-month outcome study of patients undergoing single-level anterior cervical discectomy and fusion for symptomatic cervical degenerative disc disease utilizing a novel viable allogeneic, cancellous, bone matrix (trinity evolution™) with a comparison to historical controls. *Eur Spine J.* Jul 2016; 25(7): 2233-8. PMID 26849141
28. Peppers TA, Bullard DE, Vanichkachorn JS, et al. Prospective clinical and radiographic evaluation of an allogeneic bone matrix containing stem cells (Trinity Evolution® Viable Cellular Bone Matrix) in patients undergoing two-level anterior cervical discectomy and fusion. *J Orthop Surg Res.* Apr 26 2017; 12(1): 67. PMID 28446192
29. Jones CP, Loveland J, Atkinson BL, et al. Prospective, Multicenter Evaluation of Allogeneic Bone Matrix Containing Viable Osteogenic Cells in Foot and/or Ankle Arthrodesis. *Foot Ankle Int.* Oct 2015; 36(10): 1129-37. PMID 25976919
30. Eastlack RK, Garfin SR, Brown CR, et al. Osteocel Plus cellular allograft in anterior cervical discectomy and fusion: evaluation of clinical and radiographic outcomes from a prospective multicenter study. *Spine (Phila Pa 1976).* Oct 15 2014; 39(22): E1331-7. PMID 25188591
31. Sen RK, Tripathy SK, Aggarwal S, et al. Early results of core decompression and autologous bone marrow mononuclear cells instillation in femoral head osteonecrosis: a randomized control study. *J Arthroplasty.* May 2012; 27(5): 679-86. PMID 22000577
32. Zhao D, Cui D, Wang B, et al. Treatment of early stage osteonecrosis of the femoral head with autologous implantation of bone marrow-derived and cultured mesenchymal stem cells. *Bone.* Jan 2012; 50(1): 325-30. PMID 22094904
33. American Academy of Orthopaedic Surgeons. Management of Glenohumeral Joint Osteoarthritis Evidence-Based Clinical Practice Guideline. <https://www.aaos.org/globalassets/quality-and-practice-resources/glenohumeral/gjo-cpg.pdf>. Updated March 23, 2020. Accessed December 1, 2024.
34. American Academy of Orthopaedic Surgeons. Management of Osteoarthritis of the Knee (Non-Arthroplasty). <https://www.aaos.org/globalassets/quality-and-practice-resources/osteoarthritis-of-the-knee/oak3cpg.pdf>. Updated August 31, 2021. Accessed December 2, 2024.
35. American Academy of Orthopaedic Surgeons. Management of Osteoarthritis of the Hip. <https://www.aaos.org/globalassets/quality-and-practice-resources/osteoarthritis-of-the-hip/oah-cpg.pdf>. Updated December 1, 2023. Accessed December 4, 2024.
36. Kaiser MG, Groff MW, Watters WC, et al. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 16: bone graft extenders and substitutes as an adjunct for lumbar fusion. *J Neurosurg Spine.* Jul 2014; 21(1): 106-32. PMID 24980593
37. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Care Res (Hoboken).* Feb 2020; 72(2): 149-162. PMID 31908149

DRAFT

[CLICK THE ENVELOPE ICON BELOW TO SUBMIT COMMENTS](#)

This medical policy is made available to you for informational purposes only. It is not a guarantee of payment or a substitute for your medical judgment in the treatment of your patients. Benefits and eligibility are determined by the member's subscriber agreement or member certificate and/or the employer agreement, and those documents will supersede the provisions of this medical policy. For information on member-specific benefits, call the provider call center. If you provide services to a member which are determined to not be medically necessary (or in some cases medically necessary services which are non-covered benefits), you may not charge the member for the services unless you have informed the member and they have agreed in writing in advance to continue with the treatment at their own expense. Please refer to your participation agreement(s) for the applicable provisions. This policy is current at the time of publication; however, medical practices, technology, and knowledge are constantly changing. BCBSRI reserves the right to review and revise this policy for any reason and at any time, with or without notice. Blue Cross & Blue Shield of Rhode Island is an independent licensee of the Blue Cross and Blue Shield Association.

