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MEDICAL POLICY – 8.01.52

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

BCBSA Ref. Policy: 8.01.52

Effective Date:	April 1, 2024
Last Revised:	Jan. 1, 2025
Replaces:	N/A

RELATED MEDICAL POLICIES:

2.01.26	Prolotherapy
2.01.98	Orthopedic Applications of Platelet-Rich Plasma
2.01.543	Recombinant and Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non- Orthopedic Conditions
7.01.48	Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions
7.01.583	Amniotic Membrane and Amniotic Fluid

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Mesenchymal stem cells are adult stem cells which are usually found in the bone marrow. These stem cells can generate other types of cells that are part of the body's musculoskeletal system, such as bone, cartilage, and muscle. Stem cells are being studied as a way to treat orthopedic problems like damaged bone, ligaments, tendons, and the discs between the bones of the spine. Using stem cells to treat orthopedic problems is unproven. Studies have not yet shown the best ways to gather and deliver these cells. Studies also have not yet shown that using stem cells for orthopedic conditions leads to better health results compared to usual treatments.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a

service may be covered.

Policy Coverage Criteria

Note: This policy does not address unprocessed allograft bone or products that do not require mixing with stem cells. (See **Table2** under Regulatory Status for product examples for informational purposes).

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

Coding

Code	Description
CPT	
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

Code	Description
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
20999	Unlisted procedure, musculoskeletal system, general
38241	Hematopoietic progenitor cell (HPC); autologous transplantation

Related Information

Benefit Application

Stem cell injections are currently performed at select centers in the United States. Therefore, requests for it may be made for an out-of-network facility.

Evidence Review

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.

Background

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 individuals.

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.

Summary of Evidence

For individuals who have cartilage defects, meniscal defects, joint fusion procedures, or osteonecrosis who receive stem cell therapy, the evidence includes small randomized controlled trials (RCTs) and nonrandomized comparative trials. The relevant outcomes are symptoms,

morbid events, functional outcomes, quality of life, and treatment-related morbidity. Use of MSCs for orthopedic conditions is an active area of research. Despite continued research into the methods of harvesting and delivering treatment, there are uncertainties regarding the optimal source of cells and the delivery method. Studies have included MSCs from bone marrow, adipose tissue, 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 MSCs expanded from bone marrow, which includes several phase I and II RCTs and a phase III RCT (which also evaluated other cell therapies). The phase III 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 III 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 (FDA)–approved (concentrated autologous MSCs do not require agency approval). Overall, there is a lack of evidence that clinical outcomes are improved. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in **Table 1**.

Table 1. Summary of Key Trials

NCT No.	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 2024

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT04368806[a]	A 48-Weeks, Phase 2b/3a, Double-Blind, Randomized, Placebo Controlled, Multi-center, Superiority Study to Evaluate the Efficacy and Safety of Joint Stem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells in Patients Diagnosed as Knee Osteoarthritis	140	Dec 2024
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 106 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
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
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	Mar 2026
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.

Practice Guidelines and Position Statements

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

Guidelines or position statements will be considered for inclusion 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 the American Academy of Orthopaedic Surgeons 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 of glenohumeral joint OA.[31] 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.[32]

American Association of Neurological Surgeons

In 2014, the American Association of Neurological Surgeons guideline on fusion procedures for degenerative disease of the lumbar spine relevant to this 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. Demineralized Bone Matrix: Grade C (poor level of evidence)."[33]

American College of Rheumatology and Arthritis Foundation

In 2019, guidelines from the American College of Rheumatology and Arthritis Foundation on osteoarthritis (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.[34] No recommendation was made for hand OA, since efficacy of stem cells has not been evaluated.

Medicare National Coverage

There is no national coverage determination.

Regulatory Status

The US 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 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

Table 2 provides a representative sample of these products; some of which are specifically labeled for mixing with bone marrow aspirate.

Table 2. Demineralized Bone Matrix Products Cleared by FDA

(differentiated by whether they require mixing with autologous MSCs)

Product	Matrix Type	Mix with Autologous MSCs	Manufacturer or Sponsor	Date Cleared	510(k) No.
Vitoss Bioactive Foam Bone Graft Substitute	Type I bovine collagen	No	Stryker	Nov 2008	K083033
NanOss BVF-E	Nanocrystalline hydroxyapatite	No	Pioneer Surgical	Aug 2008	K081558
OrthoBlast II Demineralized bone matrix putty and paste	Human cancellous bone chips	No	SeaSpine	Sep 2007	K070751
CopiOs Bone Void Filler (sponge and powder disc)	Type I bovine dermal collagen	Yes	Kensey Nash	May 2007	K071237
DBX Demineralized bone matrix putty, paste and mix	Processed human bone and sodium hyaluronate	No	Musculoskeletal Transplant Foundation	Dec 2006	K053218

Product	Matrix Type	Mix with Autologous MSCs	Manufacturer or Sponsor	Date Cleared	510(k) No.
Integra MOZAIK Osteoconductive Scaffold-Putty	Human cancellous bone	Yes	IsoTis OrthoBiologics	Dec 2006	K062353
Formagraft Collagen Bone Graft Matrix	Bovine fibrillary collagen	No	R and L Medical	May 2005	K050789
DynaGraft II Gel and Putty	Processed human bone particles	No	IsoTis Orthobiologics	Mar 2005	K040419

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:

- The HCT/P is minimally manipulated;
- The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;
- 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
- Either:
    - 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

- 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.

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History

Date	Comments
08/09/11	New policy; add to Therapy section. Policy created with literature review through January 2011; considered investigational. ICD-10 codes included in policy.
07/20/12	Replace policy. Policy updated with literature review through February 2012; reference 6 added and references reordered; policy statement unchanged.
08/15/12	Update Related Policies: remove 7.01.48, it was archived.
08/20/12	Update Related Policies – add 2.02.18.
10/09/12	Update Coding Section – ICD-10 codes are now effective 10/01/2014.
04/26/13	Clarification only. Statement within the Benefit Application section stating, "Therefore, requests may be made for an out-of-network facility" was removed, as this conflicts with the FDA statements in the rest of the policy. No other changes.
06/10/13	Replace policy. New policy statement added that allograft bone containing viable stem cells is considered investigational. New policy guideline added that policy does not address unprocessed allograft bone. Regulatory status section updated regarding allograft bone. Rationale updated based on a literature review through March 2013.

Date	Comments
	References 4, and 11-15 added; others renumbered or removed. Policy statement changed as noted.
08/20/13	Update Related Policies. Change title to 2.02.18.
06/19/14	Annual Review. Policy updated with literature review through March 3, 2014; references 5, 13, and 17 added; policy statements unchanged. ICD-10 codes removed in line with code mapping project and implementation delay.
06/09/15	Annual Review. Policy updated with literature review through February 26, 2015; references 3, 14, 16, 18, 20, and 22 added; investigational statement added on bone graft substitutes that must be used with autologous blood or bone marrow aspirate; title changed to "Orthopedic applications of stem cell therapy (including allograft and bone substitute products used with autologous bone marrow)". Related policies removed: 2.02.18, 7.01.15 and 8.01.55. CPT code 20999 added to policy.
09/01/15	Update Related Policies. Add 2.01.98 and 7.01.149.
04/01/16	Annual Review, approved March 8, 2016. Policy updated with literature review through November 17, 2015; references 12 and 15 added. Policy statements unchanged. Title changed to "Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)".
06/09/17	Coding update; updated description for CPT codes 38230 and 38241.
09/01/17	Annual Review, approved August 22, 2017. Policy updated with literature review through June 9, 2017; references 1, 4, 12-13, 25, and 27-29 were added. Policy statements unchanged.
05/01/18	Annual Review, approved April 3, 2018. Policy updated with literature review through November 2017; references 14 and 24 added; references 2 and 4 updated. Policy statements unchanged. Removed CPT code 38230.
04/01/19	Annual Review, approved March 19, 2019. Policy updated with literature review through November 2018; no references added. Policy statements unchanged.
04/01/20	Annual Review, approved March 19, 2020. Policy updated with literature review through November 2019; references added. Policy statements unchanged. Removed CPT code 38206. Added CPT codes 0263T, 0264T, and 0265T.
08/01/20	Update related policies. 7.01.149 is now 7.01.583.
04/01/21	Annual Review, approved March 2, 2021. Policy updated with literature review through December 4, 2020; references added. Policy statements unchanged. Added CPT codes 0565T & 0566T.
04/01/22	Annual Review, approved March 7, 2022. Policy updated with literature review through December 17, 2021; references added. Policy statements unchanged.
05/04/22	Minor update to related policy 7.01.48 – renumbered to 7.01.569 Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions.

Date	Comments
04/01/23	Annual Review, approved March 6, 2023. Policy updated with literature review through December 5, 2022; references added. Policy statements unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization.
08/01/23	Minor update to Related Policies. Removed 7.01.569 and replaced with 7.01.48 Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions.
04/01/24	Annual Review, approved March 11, 2024. Policy updated with literature review through November 10, 2023; references added. Policy statements unchanged. Note added to policy to clarify that bone matrix products that do not involve stem cell use are not evaluated in this policy.
01/01/25	Minor update to related policy. 2.01.16 was replaced with 2.01.543 Recombinant and Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.