MEDICAL POLICY

POLICY TITLE	**ORTHOPEDIC APPLICATIONS OF STEM-CELL THERAPY (INCLUDING ALLOGRAFT AND BONE SUBSTITUTE PRODUCTS USED WITH AUTOLOGOUS BONE MARROW)**
POLICY NUMBER	**MP 2.080**

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective date:	**7/1/2026**

POLICY

Mesenchymal stem cell therapy is considered **investigational** for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Allograft bone products containing viable stem cells, including but not limited to demineralized bone matrix (DBM) with stem cells, is considered **investigational** for all orthopedic applications. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Allograft or synthetic bone graft substitutes that must be combined with autologous blood or bone marrow are considered **investigational** for all orthopedic applications. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

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).

Regenexx is an example of mesenchymal stem cell therapy.

AlloStem, Osteocel, Osteocel Plus, and Trinity Evolution are examples of demineralized bone matrix with stem cells.

Cross-references:
MP 2.033 Recombinant and Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other Non-Orthopedic Conditions
MP 4.039 Orthopedic Applications of Platelet Rich Plasma

PRODUCT VARIATIONS

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations. Please see additional information below.

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FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

DESCRIPTION/BACKGROUND

MESENCHYMAL STEM CELLS

Mesenchymal stem cells (MSCs) are multipotent cells (also called stromal multipotent 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 bone marrow, synovium, fat, and muscle, where they can be mobilized for endogenous repair as occurs with healing of bone fractures. Tissues, such as muscle, cartilage, tendon, ligaments, and vertebral discs, show limited capacity for endogenous repair because of the limited presence of the triad of tissue functional components: vasculature, nerves, and lymphatics. Orthobiologics is a term introduced to describe interventions using cells and biomaterials to support healing and repair. Cell therapy is the application of MSCs directly to a musculoskeletal site. Tissue engineering techniques use MSCs and/or bioactive molecules such as growth factors and scaffold combinations to improve the efficiency of repair or regeneration of damaged musculoskeletal tissues.

Bone marrow aspirate is considered the most accessible source and, thus, the most common place to isolate MSCs for treatment of musculoskeletal disease. However, harvesting MSCs from bone marrow requires a procedure that may result in donor-site morbidity. In addition, the number of MSCs in bone marrow is low, and the number and differentiation capacity of bone marrow–derived MSCs decreases with age, limiting their efficiency when isolated from older patients.

In vivo, the fate of stem cells is regulated by signals in the local 3-dimensional microenvironment from the extracellular matrix and neighboring cells. It is believed that the success of tissue engineering with MSCs will also require an appropriate 3-dimensional scaffold or matrix, culture conditions for tissue-specific induction, and implantation techniques that provide appropriate biomechanical forces and mechanical stimulation. The ability to induce cell division and differentiation without adverse effects, such as the formation of neoplasms, remains a significant concern. Given that each tissue type requires different culture conditions, induction factors (signaling proteins, cytokines, growth factors), and implantation techniques, each preparation must be individually examined.

REGULATORY STATUS

The U.S. Food and Drug Administration (FDA) regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation (CFR) Title 21, parts 1270 and 1271. MSCs are included in these regulations.

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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 FDA. No products using engineered or expanded MSCs have been approved by FDA for orthopedic applications.

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

- AlloStem® (AlloSource) is a partially demineralized allograft bone seeded with adipose-derived MSCs.
- Osteocel Plus® (NuVasive) is a DBM combined with viable MSCs isolated from allogeneic bone marrow.
- Trinity Evolution Matrix™ (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 Sponser	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 matrix putty and paste	Human (mixed allograft donor-derived) cancellous bone	SeaSpine	Sep 2007	K070751

	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	Iso Tis Orthobiologics	Mar 2005	K040419

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

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

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

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

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

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:
   a) 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

   b) 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

SUMMARY OF EVIDENCE

For individuals who have cartilage defects, meniscal defects, joint fusion procedures, or osteonecrosis who receive stem cell therapy, the evidence includes systematic reviews, randomized controlled trials (RCTs) and observational studies. 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. Recent systematic reviews have reported that intra-articular MSCs offer little to no pain relief for knee osteoarthritis (OA), with possible slight functional improvement and increased adverse events. For hip OA, MSCs show some benefit in pain and function but evidence is limited by small studies and inconsistent protocols. Overall, the quality of evidence is low 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 OA after 12 months of follow-up. Another recent phase 3 RCT evaluated autologous MSCs expanded from abdominal adipose tissue for treatment of knee OA ; 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. Current evidence regarding the application of allografts combined with stem cells for bone fusion in the extremities or spine, as well as for the treatment of nonunion, remains limited. Several early-phase, industry-sponsored trials have been reported. Clinical studies involving moldable cellular bone allografts have demonstrated high fusion rates at 12 months in lumbar, cervical, and foot and ankle procedures. These studies also note significant improvements in disability and pain scores, with few serious graft-related adverse events. However, the data are drawn primarily from nonrandomized, small-scale, and largely retrospective studies. 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.

DEFINITIONS

Allograft - a tissue graft from a donor of the same species as the recipient but not genetically identical.

Autologous - originating within an individual, (i.e., self-donation.)

Mesenchymal Stem Cells (MSC) – adult stem cells that are multipotent and can differentiate into several different specialized cell types.

DISCLAIMER

Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as permitted by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These polices are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

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CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore, not covered:

Procedure Codes								
0263T	0264T	0265T	0489T	0490T	0565T	0566T	20999*	

*Use for aspiration of bone marrow for the purpose of bone grafting, other than spine surgery and other therapeutic musculoskeletal applications (e.g. Regenexx)

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POLICY HISTORY

MP 2.080	**09/15/2020 Consensus review.** No change to policy statements. Updated references and Summary of Evidence section. Added codes 0565T, 0566T and 20999.
	08/19/2021 Consensus review. Updated FEP, regulatory status, definition, and references. To align with BCBSA, deleted codes 20931-20934, 38205-38206, 38232, 38240-38241, and added codes 0489T-0490T.
	03/07/2022 Consensus review. No changes to policy statements. References updated.
	02/14/2023 Retirement review.
	08/30/2023 Minor review. Determined retirement is not best course at this time. Added examples of MSC therapy**.**
	01/19/2024 Administrative update. Clinical benefit added.
	03/01/2024 Consensus review. No change to policy statement. References updated.
	03/14/2025 Consensus review. Examples of products in the policy statement were moved to policy guidelines; no change to intent. Updated policy guidelines, background, benefits, disclaimer, and references. No changes to coding.
	03/16/2026 Consensus Review. Updated background, rationale, and references. No changes to coding.