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**

Original Issue Date (Created):	**11/1/2010**
Most Recent Review Date (Revised):	**9/15/2020**
Effective Date:	**1/1/2021**

I. POLICY

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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 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 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 conclusion concerning the health outcomes or benefits associated with this procedure.

POLICY GUIDELINES

This policy does not address unprocessed allograft bone.

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

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital BlueCross and subject to benefit variations as discussed in Section VI. Please see additional information below.

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FEP PPO - Refer to FEP Medical Policy Manual MP-8.01.52 Orthopedic Applications of Stem-Cell Therapy. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

III. DESCRIPTION/BACKGROUND

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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. [1]

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 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 FDA through the 510(k) process. FDA product code: MQV.

Table 1 provides a representative sample of these products; some of which are specifically labeled for mixing with bone marrow aspirate.

Table 1. Demineralized Bone Matrix Products Cleared by FDA

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	X	Stryker	Nov 2008	K083033
NanOss BVF-E	Nanocrystalline hydroxyapatite		Pioneer Surgical	Aug 2008	

OrthoBlast® II Demineralized bone matrix putty and paste	Human cancellous bone chips		SeaSpine	Sep 2007	K070751
CopiOs® Bone Void Filler (sponge and powder disc)	Type I bovine dermal collagen	X	Kensey Nash	May 2007	K071237
DBX® Demineralized bone matrix putty, paste and mix	Processed human bone and sodium hyaluronate	X	Musculoskeletal Transplant Foundation	Dec 2006	K053218
Integra MOZAIK™ Osteoconductive Scaffold-Putty	Human cancellous bone	X	IsoTis OrthoBiologics	Dec 2006	K062353
Formagraft™ Collagen Bone Graft Matrix	Bovine fibrillary collagen	X	R and L Medical	May 2005	K050789
DynaGraft® II Gel and Putty	Processed human bone particles		IsoTis Orthobiologics	Mar 2005	K040419

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

In 2008, FDA determined that the MSCs sold by Regenerative Sciences for use in the Regenexx™ procedure would be considered drugs or biologic products and thus would require submission of a new drug application or biologic license application to FDA.[2] The Regenexx™ procedure originally used stem cells derived from bone marrow or synovial fluid and cultured the cells with autologous platelet lysate in a separate laboratory. Other compounds such antibiotics were added before the material was returned to the patient in a separate orthopedic procedure. Regenerative Sciences asserted that the procedure was the practice of medicine and not subject to FDA regulation. In 2014, a federal appellate court upheld FDA authority to regulate adult stem cells as drugs and biologics and ruled that the Regenexx cell product fell within FDA's authority to regulate human cells, tissues, and cellular and tissue-based products.[3] To date, no new drug application or biologic license application has been approved by FDA for this product. As of 2015, the expanded stem cell procedure (now termed Regenexx-C™) is only offered in the Cayman Islands. The current Regenexx® Stem Cell Procedure is offered through a network of facilities in the United States that provide same-day stem cell and blood platelet procedures that do not require FDA approval. These procedures, along with the Regenexx® Super Concentrated Platelet Rich Plasma, are marketed as treatments for arthritis and injuries of the knee, hip, shoulder, spine, hand and wrist, foot and ankle and elbow.[4]

IV. RATIONALE

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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 and nonrandomized comparative trials. 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 1/2 randomized controlled trials. Limitations in these initial trials preclude reaching conclusions, but the results to date do support future study in phase 3 trials. Alternative methods of obtaining MSCs have been reported in a smaller number of trials and with mixed results. Additional study in a larger sample of patients with longer follow-up would be needed to evaluate the long-term efficacy and safety of these procedures. Also, expanded MSCs for orthopedic applications are not 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 the effects of the technology on health outcomes.

V. DEFINITIONS

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AUTOLOGOUS- refers to originating within an individual; i.e., self-donation.

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member’s health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital BlueCross. Members and providers should consult the member’s health benefit plan for information or contact Capital BlueCross for benefit information.

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VII. DISCLAIMER

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Capital BlueCross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital BlueCross' Provider Services or Member Services. Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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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:

CPT Codes®								
0263T	0264T	0265T	0565T	0566T	20930	20931	20932	20933
20934	20939	20999	38205	38206	38232	38240	38241	

HCPC Codes®	Description
C9359	Porous purified collagen matrix bone void filler (Integra Mozaik Osteoconductive Scaffold Putty, Integra OS Osteoconductive Scaffold Putty), per 0.5 cc (synthetic)
C9362	Porous purified collagen matrix bone void filler (Integra Mozaik Osteoconductive Scaffold Strip), per 0.5 cc (bovine)

IX. REFERENCES

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2. *U.S. Food and Drug Administration. Letter from Mary A. Malarkey, Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research to Christopher J. Centeno, M.D., Medical Director, Regenerative Sciences, Inc. 2008 Jul 25; https://wayback.archive-it.org/7993/20170112214943/http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInform*

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X. POLICY HISTORY

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MP-2.080	**CAC 9/28/10.** New policy. Adopt BCBSA.
	CAC 10/25/11 Consensus review.
	CAC 10/30/12 Consensus review. No change to policy statements. References updated. Changed FEP variation to reference. MP-8.01.2 Orthopedic Applications of Stem-Cell Therapy. Updated the FDA information in the Background/Description. Codes reviewed 10/31/12
	CAC 11/26/13 Consensus review. Statement added that allograft bone products containing viable stem cells, including but not limited to demineralized bone matrix (DBM) with stem cells are also considered investigational. References updated. Rationale added**.**
	CAC 11/25/14 Consensus review. No change to policy statements. References and rationale updated. Updated and reviewed coding 11/07/2014
	CAC 11/24/15 Minor revision. 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). Background, rationale and references updated. Coding reviewed and updated.
	CAC 11/29/16 Consensus review. No changes to the policy statements. Background, references and rationale updated. Variations reformatted. Coding reviewed.
	CAC 12/19/17 Consensus review. No change to the policy statements. Background, rationale, and references updated. Added new code 20939; effective 1/1/18
	11/13/18 Consensus review. No change to policy statements. Rationale condensed. References updated.
	3/15/19 Code review. Procedure codes updated.
	10/18/19 Consensus review. Literature reviewed, references updated. No change to policy statements. Coding reviewed and updated. Additional procedure codes added as investigational. Effective 2/1/2020.
	9/15/20 Consensus review. No change to policy statements. Updated references and Summary of Evidence section. Added codes 0565T, 0566T and 20999.

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