

FEP 8.01.52 Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)

Effective Date: April 15, 2018

Related Policies:

2.01.16 Recombinant and Autologous Platelet-Derived Growth Factors as a Primary Treatment of Wound Healing and Other Miscellaneous Conditions

2.01.98 Orthopedic Applications of Platelet-Rich Plasma

7.01.48 Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

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

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.

FDA 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 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:

FEP 8.01.52 Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)

- 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.

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 as 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

FEP 8.01.52 Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)

POLICY STATEMENT

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, including but not limited to demineralized bone matrix with stem cells, are considered **investigational** for all orthopedic applications.

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

POLICY GUIDELINES

This policy does not address unprocessed allograft bone.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

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 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, peripheral blood, and synovial tissue. The largest body of evidence has evaluated the use of autologous MSCs, either concentrated or expanded in culture, for cartilage repair. This evidence includes small randomized and nonrandomized comparative trials with insufficient data to evaluate health outcomes. 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 evidence that clinical outcomes are improved. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American Association of Orthopaedic Surgeons

The 2013 and 2014 American Association of Orthopaedic Surgeons' guidelines on the treatment of glenohumeral joint osteoarthritis have indicated that:

- Treatment using allograft, autograft, biologic, and interpositional grafts in patients with glenohumeral joint osteoarthritis is inconclusive³⁵; and that
- Treatment using growth factor injections and/or platelet rich plasma for patients with symptomatic osteoarthritis of the knee is inconclusive.³⁶

American Association of Neurological Surgeons

The American Association of Neurological Surgeons 2014 guidelines on fusion procedures for degenerative disease of the lumbar spine relevant to this evidence review 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)."³⁷

FEP 8.01.52 Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)

International Society for Cellular Therapy

In 2006, the International Society for Cellular Therapy proposed a minimum set of criteria to standardize the characterization of multipotent mesenchymal stem cells.³⁸ The proposed criteria for human mesenchymal stem cells included plastic adherence when maintained in standard culture conditions; a phenotype of expression of CD105, CD73, and CD90 with a lack surface expression of CD45, CD34, CD14 or CD11b, CD79 alpha or CD19, and human leukocyte antigen–antigen D related surface molecules; and the capability of differentiating into osteoblasts, adipocytes, and chondrocytes using standard in vitro tissue culture-differentiating conditions.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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FEP 8.01.52 Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)

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FEP 8.01.52 Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)

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POLICY HISTORY

Date	Action	Description
December 2011	New Policy	
September 2012	Update Policy	Updated literature search, reference number 6 added; remaining references renumbered.
September 2013	Update Policy	Policy updated with literature review. References 4, 7, 11-16 and 18 added, renumbered and removed; addition of policy statement that allograft bone containing viable stem cells is considered investigational.
June 2014	Update Policy	Policy updated with literature review; references 5, 13, and 17 added; policy statements unchanged.
October 2015	Update Policy	Policy updated with literature review; 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. Policy title change: "Orthopedic applications of stem cell therapy (including allograft and bone substitute products used with autologous bone marrow)".
March 2018	Update Policy	Policy updated with literature review through November 29, 2017; references 1, 2, 4, 12-15, 24-25 and 27-29 added/updated. Policy statements unchanged. Title changed to "Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)."

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