BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

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

Policy #: 430
Category: Surgical

Latest Review Date: January 2021
Policy Grade: B

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*

    - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
    - *Furnished in a setting appropriate to the patient's medical needs and condition;*
    - *Ordered and furnished by qualified personnel;*
    - *One that meets, but does not exceed, the patient's medical need; and*
    - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Effective for dates of service on or after May 1, 2015:

Blue Advantage will treat **mesenchymal stem cell therapy for all orthopedic applications**, including use in repair or regeneration of musculoskeletal tissue, as a **non-covered** benefit and as **investigational.**

Blue Advantage will treat **allograft bone products containing viable stem cells**, including but not limited to demineralized bone matrix (DBM) with stem cells, **for all orthopedic applications** as a **non-covered benefit** and as **investigational.**

Blue Advantage will treat **allograft or synthetic bone graft substitutes** that must be combined with autologous blood or bone marrow as a **non-covered benefit** and as **investigational**.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

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.

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 to be 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 an additional 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.

KEY POINTS:

This policy has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through December 4, 2020.

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 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 peripheralblood. Overall, the quality of evidence is low and there is a possibility of publication bias. The strongest evidence to date is on MSCsexpanded from bone marrow, which includes several phase 1/2 RCTs. 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 asmaller number of trials and with mixed results. Additional study in a larger sample of patients with longer follow-up would be neededto evaluate the long-term efficacy and safety of these procedures. Also, expanded MSCs for orthopedic applications are not FDAapproved (concentrated autologous MSCs do not require agency approval). Overall, there is a lack of evidence that clinical outcomesare improved. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

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, andknee gave a strong recommendation against stem cell injections in patients with knee and/or hip OA, noting the heterogeneity inpreparations and lack

of standardization of techniques.No recommendation was made for hand OA, since efficacy of stem cellshas not been evaluated.

American Association of Orthopaedic Surgeons
A 2020 guideline from American Association of Orthopaedic Surgeons on the management of glenohumeral joint OA, endorsed byseveral other societies, states that injectable biologics such as stem cells cannot be recommended in the treatment glenohumeral jointOA.26, There was consensus from the panel that better standardization and high-quality evidence from clinical trials is needed toprovide definitive evidence on the efficacy of biologics in glenohumeral OA. The strength of evidence was rated as no reliable scientificevidence to determine benefits and harms.

The 2013 guideline on treatment of osteoarthritis of the knee does not address stem cell injections.

American Association of Neurological Surgeons
The American Association of Neurological Surgeons 2014 guidelines on fusion procedures for degenerative disease of the lumbar spine related 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)."

U.S. Preventive Services Task Force Recommendations
Not Applicable

KEY WORDS:
Allostem®,Chondrogen™, Cartistem®, stem cell therapy for orthopedic applications, mesenchymal stem cells (MSCs), bone matrix containing viable stem cell, Osteocel®, map3, nanOss®, Regenexx™, Regenerative Sciences, Trinity Evolution Matrix, Vitoss®, demineralized bone matrix (DBM)

APPROVED BY GOVERNING BODIES:
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. Mesenchymal stem cells (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 U.S. Food and Drug Administration (FDA).

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.

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

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 2017, the FDA U.S. Food and Drug Administration published "Regulatory Considerations for

Human Cells, Tissues, and Cellular and TissueBased Products: Minimal Manipulation and Homologous Use" https://www.fda.gov/media/124138/download

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. In June 2019, the FDA issued a statement on a stem cell clinic permanent injunction and FDA's ongoing efforts to protect patients from risks of unapproved stem cell products.

BENEFIT APPLICATION:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

CURRENT CODING:

CPT Codes:

38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation per collection, autologous
38230	Bone marrow harvesting for transplantation; allogeneic
38232	; autologous
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
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
0565T	Autologous cellular implant derived from adipose tissue for the treatment of osteoarthritis of the knees; tissue harvesting and cellular implant creation (Effective 01/01/20)

0566T	; injection of cellular implant into knee joint including ultrasound guidance, unilateral (Effective 01/01/20)

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POLICY HISTORY:

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