



Louisiana

Orthopedic Applications of Stem Cell Therapy (Including Allograft and Bone Substitute Products Used With Autologous Bone Marrow)

Policy # 00258

Original Effective Date: 06/16/2010

Current Effective Date: 06/14/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Recombinant and Autologous Platelet Derived Growth Factors for Wound Healing and Other Non Orthopedic Conditions is addressed separately in medical policy 00262.

Note: Prolotherapy is addressed separately in medical policy 00106.

Note: Orthopedic Applications of Platelet-Rich Plasma is addressed separately in medical policy 00476.

Note: Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions is addressed separately in medical policy 00006.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of mesenchymal stem cell therapy for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue to be **investigational**.*

Based on review of available data, the Company considers allograft bone products containing viable stem cells, including but not limited to demineralized bone matrix with stem cells, for all orthopedic applications to be **investigational**.*

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Based on review of available data, the Company considers allograft or synthetic bone graft substitutes that must be combined with autologous blood or bone marrow for all orthopedic applications to be **investigational**.*

Policy Guidelines

This policy does not address unprocessed allograft bone.

Background/Overview

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 muscle, 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.

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 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 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

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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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

The U.S. 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:

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- 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.

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	K081558
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

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Product	Matrix Type	Mix With Autologous MSCs	Manufacturer or Sponsor	Date Cleared	510(k) No.
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: 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;

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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:

i) 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

ii) 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/Source

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.

For individuals who have cartilage defects, meniscal defects, joint fusion procedures, or osteonecrosis who receive stem cell therapy, the evidence includes small RCTs 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 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 a smaller number of trials and with mixed results. Additional study in a larger sample of patients with longer follow-up would be

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needed to evaluate the long-term efficacy and safety of these procedures. Also, expanded MSCs for orthopedic applications are not U.S. 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.

Supplemental Information

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, 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. No recommendation was made for hand OA, since efficacy of stem cells has not been evaluated.

American Academy of Orthopaedic Surgeons

A 2020 guideline from American Association 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 glenohumeral joint OA. 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 2013 guideline on treatment of osteoarthritis of the knee does not address stem cell injections.

American Association of Neurological Surgeons

In 2014, the American Association of Neurological Surgeons guidelines on fusion procedures for degenerative disease of the lumbar spine relevant to this evidence review have indicated that “The use of 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).”

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U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
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
NCT03818737	Randomized Multicenter Phase 3 Single-blind Trial Comparing the Efficacy of Corticosteroid Control to Mesenchymal Stem Cell Preparations From Autologous Bone Marrow Concentrate (BMAC), Adipose-derived Stem Cells in the Form of Stromal Vascular Fraction (SVF), and Third-party Human Mesenchymal Stem Cells Manufactured From Umbilical Cord Tissue for the Treatment of Unilateral Knee Osteoarthritis (OA)	480	Dec 2021
NCT04310215 ^a	A Multi-center, Single-blind, Randomized, Phase III Clinical Trial to Evaluate the Efficacy and Safety of	100	Dec 2021

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	Adding CARTISTEM [®] ‡ on Microfracture in Patients With Talar Chondral or Osteochondral Defect		
NCT02582489	Prospective, Randomized, Double-blind Clinical Trial to Investigate the Efficacy of Autologous Bone Marrow Aspirate Concentrate Post-Meniscectomy	100	Jan 2022
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
NCT04368806 ^a	A 48-Weeks, Phase 2b/3a, Double-Blind, Randomized, Placebo Controlled, Multi-center, Superiority Study to Evaluate the Efficacy and Safety of JointStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells in Patients Diagnosed as Knee Osteoarthritis	140	Dec 2022
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 10 ⁶ 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	153	Jun 2023
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	Jan 2024
<i>Unpublished</i>			

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NCT01413061 ^a	Study of Subtalar Arthrodesis Using AlloStem ^{®‡} Versus Autologous Bone Graft	140	Mar 2018 (completed)
NCT01041001 ^a	Randomized, Open-Label, Multi-Center and Phase 3 Clinical Trial to Compare the Efficacy and Safety of Cartistem ^{®‡} and Microfracture in Patients With Knee Articular Cartilage Injury or Defect	104	Jan 2011 (completed)
NCT01626677 ^a	Long Term Follow-Up Study of CARTISTEM ^{®‡} Versus Microfracture for the Treatment of Knee	104	May 2015 (completed)
NCT01504464	Evaluation the Effects of Intra-articular Injection of Mesenchymal Stem Cells in Patients With Knee Joint Osteoarthritis, Triple Blind Randomized Clinical Trial	40	Oct 2015 (completed)
NCT03990805 ^a	Multi-center, Randomized, Double-Blind, Placebo Controlled Phase 3 Clinical Trial to Evaluate Efficacy and Safety of Mesenchymal Stem Cells JointStem in Patients With Knee Osteoarthritis	260	Nov 2020

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

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|------------|---|
| 05/06/2010 | Medical Policy Committee approval |
| 06/16/2010 | Medical Policy Implementation Committee approval. |
| 05/05/2011 | Medical Policy Committee approval |
| 05/18/2011 | Medical Policy Implementation Committee approval. No change to coverage. |
| 05/03/2012 | Medical Policy Committee review |
| 05/16/2012 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 03/04/2013 | Coding updated |
| 05/02/2013 | Medical Policy Committee review |

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Orthopedic Applications of Stem Cell Therapy (Including Allograft and Bone Substitute Products Used With Autologous Bone Marrow)

Policy # 00258

Original Effective Date: 06/16/2010

Current Effective Date: 06/14/2021

05/22/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

05/01/2014 Medical Policy Committee review

05/21/2014 Medical Policy Implementation Committee approval. New investigational indication added.

05/07/2015 Medical Policy Committee review

05/20/2015 Medical Policy Implementation Committee approval. No change to coverage.

05/05/2016 Medical Policy Committee review

05/18/2016 Medical Policy Implementation Committee approval. Investigational statement added on bone graft substitutes that must be used with autologous blood or bone marrow aspirate. Title changed.

01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes

05/04/2017 Medical Policy Committee review

05/17/2017 Medical Policy Implementation Committee approval. No change to coverage.

12/01/2017 Coding update

05/03/2018 Medical Policy Committee review

05/16/2018 Medical Policy Implementation Committee approval. No change to coverage.

05/02/2019 Medical Policy Committee review

05/15/2019 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

05/07/2020 Medical Policy Committee review

05/13/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Title changed to “Orthopedic Applications of Stem Cell Therapy (Including Allograft and Bone Substitute Products Used With Autologous Bone Marrow)”.

05/06/2021 Medical Policy Committee review

05/12/2021 Medical Policy Implementation Committee approval. No change to coverage

Next Scheduled Review Date: 05/2022

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2020

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by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0263T, 0264T, 0265T, 0489T, 0490T, 0565T, 0566T, 20939, 38206, 38220, 38230, 38232, 38241
HCPCS	C9359
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

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- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. Reference to federal regulations.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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