

Corporate Medical Policy

Orthopedic Applications of Stem Cell Therapy

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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.

Background

MSCs are multipotent cells (also called stromal multipotent cells) that possess the ability to 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, etc.) and implantation techniques, each preparation must be individually examined.

The U.S. Food and Drug Administration (FDA) regulates human cells and tissues intended for

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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). 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 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): 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®)
- Osteoecel Plus® (NuVasive): DBM combined with viable MSCs that have been isolated from allogeneic bone marrow
- Trinity Evolution Matrix™ (Orthofix): DBM combined with viable MSCs that have been isolated from allogeneic bone marrow.
- Cellentra™ VCBM (Biomet®): an allograft that is cryopreserved containing MSCs, osteoprogenitor cells, and pre-osteoblasts.

Whether these products can be considered minimally manipulated tissue is debated. A product would not meet the criteria for FDA regulation part 1271.10 if it is dependent upon the metabolic activity of living cells for its primary function. Otherwise, a product would be considered a biologic product and would need to demonstrate safety and efficacy for the product's intended use with an investigational new drug and Biologics License Application (BLA).

Other products contain DBM and are intended to be mixed with bone marrow aspirate. Some of the products that are currently available are:

- Fusion Flex™ (Wright Medical): a dehydrated moldable DBM scaffold (strips and cubes) that will absorb autologous bone marrow aspirate.
- Ignite® (Wright Medical): an injectable graft with DBM that can be combined with autologous bone marrow aspirate.
- DBX Putty Mix and Inject (DePuy Synthes): an allograft bone void filler that may be combined with bone marrow aspirate.

Other commercially available demineralized bone matrix products are intended to be mixed with bone marrow aspirate and have received 510(k) clearance, such as:

- CopiOs® Bone Void Filler sponge and powder disc (Kensey Nash): Matrix Type 1 bovine dermal collagen.
- Collage™ Putty (Orthofix): Composed of type-1 bovine collagen and beta tricalcium phosphate.
- InQu™ (ISTO Technologies): A combination of poly(lactide-co-glycolide) (PLGA) a ceramic bone void filler with hyaluronic acid.
- FormaGraft™ Collagen Bone Graft Matrix (R and L Medical): A synthetic biologic comprised of minerals naturally occurring in the body (hydroxyapatite and beta-tricalcium phosphate) and type I bovine fibrillary collagen.

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- HEALOS®/HEALOS® FX Bone Graft Replacement (DePuy Synthes): An osteoconductive matrix constructed of cross-linked collagen fibers that are fully coated with hydroxyapatite.
- EquivaBone® (ETEX): A synthetic calcium phosphate based bone substitute.
- Vitoss® Bioactive Foam Bone Graft Substitute (Stryker, developed by OrthoVita): Vitoss is composed of Type 1 bovine collagen and beta tricalcium phosphate.
- nanOss® BVF-E (rti surgical, developed by Pioneer Surgical): nanostructured hydroxyapatite and an open structured engineered collagen carrier.
- Integra MOZAIK™ Osteoconductive Scaffold-Putty (IsoTis OrthoBiologics): Matrix type is human cancellous bone
- OrthoBlast® II Demineralized bone matrix putty and paste (SeaSpine): Matrix type is human cancellous bone chips
- DynaGraft® II Gel and Putty (IsoTis Orthobiologics): Matrix type is processed human bone particles

In 2017, the FDA published "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based 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: 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. 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.²

In 2008, the FDA determined that the mesenchymal stem cells sold by Regenerative Sciences for use in the Regenexx-C™ procedure would be considered drugs or biological products and thus require submission of a New Drug Application (NDA) or Biologics Licensing Application (BLA) to the FDA. 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

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subject to FDA regulation. In 2014, a federal appellate court upheld FDA's power to regulate adult stem cells as drugs and biologics and ruled that the Regenxx cell product fell within FDA's authority to regulate human cells, tissues, and cellular and tissue-based products (HCT/Ps). To date, no NDA or BLA has been approved by the FDA for this product. As of 2015, the expanded stem-cell procedure is only offered in the Cayman Islands. Regenxx™ network facilities in the U.S. provide same-day stem-cell and blood platelet procedures, which do not require FDA approval. These procedures, along with the Regenxx® 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.

Cartistem®, a combination of human umbilical cord blood-derived mesenchymal stem cells and sodium hyaluronate, is intended to be used as a single-dose therapeutic agent for cartilage regeneration in humans with cartilage defects of the knee as a result of aging, trauma, or degenerative diseases. A study evaluating the efficacy and safety of Cartistem® has been completed but the results have not been published at this time.

Chondrogen™ (Osiris) is an injectable stem cell product for treatment of osteoarthritis, but is currently not available in the United States.

Related Policies:

Autologous Chondrocyte Implantation
Bone Morphogenetic Protein
Growth Factors in Wound Healing

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

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. BCBSNC does not cover investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Orthopedic Applications of Stem Cell Therapy is covered

Not Applicable

When Orthopedic Applications of Stem Cell Therapy is not covered

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 (DBM) with stem cells, are considered investigational for all orthopedic applications.

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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

Note: This policy does not address unprocessed allograft bone.

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 (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 needed to evaluate the long-term efficacy and safety of these procedures. In addition, expanded MSCs for orthopedic applications are not U.S. Food and Drug Administration (FDA)–approved (concentrated autologous MSCs do not require FDA 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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 0565T, 0566T, 0627T, 0628T, 0629T, 0630T, 20939, 38206, 38230, 38241, 38232, C9359, C9362

38220 in combination with 22510, 22511, 22512, 22513, 22514, 22515, 22533, 22534, 22548, 22551, 22552, 22554, 22558, 22585, 22586, 22590, 22595, 22600, 22612, 22614, 22630, 22632, 22633, 22634, 22800, 22802, 22804, 22808, 22810, 22812, 22856, 22857, 22861, 22864, 22865, 27279, 27280, 27299, 27702, 27703.

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.52, 4/08/10

U.S. Food and Drug Administration (FDA), Ensuring Safety and Efficacy of Stem Cell Based Products, Retrieved from <http://www.fda.gov/BiologicsBloodVaccines/ScienceResearch/BiologicsResearchAreas/ucm127182.htm>

Centeno CJ, Schultz JR, et al., Safety and complications reporting on the re-implantation of culture-expanded mesenchymal stem cells using autologous platelet lysate technique, Current Stem Cell

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Research and Therapy, 2010 (5) Retrieved on 5/03/10 from <http://www.ingentaconnect.com/content/ben/cscr/2010/00000005/00000001/art00011>

Wakitani S, Nawata, et al., Repair of articular cartilage defects in the patello-femoral joint with autologous bone marrow mesenchymal cell transplantation: three case reports involving nine defects in five knees. J Tissue Eng Regen Med 2007; 1(1):74-9. Abstract

American Academy of Orthopaedic Surgeons. Stem cells and orthopaedics. Your Orthopaedic Connection 2007; Reviewed on from <http://orthoinfo.aaos.org/topic.cfm?topic=A00501>

Senior Medical Director review 5/2010

National Institute of Health (NIH). Trinity® Evolution in Anterior Cervical Disectomy and Fusion. NCT00951938. Last reviewed on May 10, 2013 from <http://clinicaltrial.gov/ct2/show/NCT00951938>

National Institute of Health (NIH). Evaluation of Trinity® Evolution in Patients Undergoing Ankle Fusion. NCT00988338. Last reviewed on May 10, 2013 from <http://clinicaltrial.gov/ct2/show/NCT00988338>

Specialty Matched Consultant Advisory Panel review 2/2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.52, 4/14/11

National Institute of Health (NIH). Follow-up Study of Chondrogen® Delivered by Intra-Articular Injection Following Meniscectomy. NCT 00702741. Last reviewed on May 10, 2013 from <http://clinicaltrials.gov/ct2/show/NCT00702741>

National Institute of Health (NIH). Study to Compare the Efficacy and Safety of Cartistem® and Microfracture in Patients With Knee Articular Cartilage Injury or Defect. NCT 01041001. Last reviewed May 10, 2013 from <http://clinicaltrials.gov/ct2/show/NCT01041001>

Medical Director review 6/2011

Specialty Matched Consultant Advisory Panel review 2/2012

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.52, 4/12/12

Steinert AF, Rackwitz L, Gilbert F, Nöth U, Tuan RS. Concise review: the clinical application of mesenchymal stem cells for musculoskeletal regeneration: current status and perspectives. Stem Cells Transl Med. 2012 Mar;1(3):237-47. Retrieved from <http://stemcellstm.alphamedpress.org/content/1/3/237.long>

Specialty Matched Consultant Advisory Panel review 2/2013

National Institute of Health (NIH). Regenexx™ SD Versus Exercise Therapy for Rotator Cuff Tears. NCT01788683. Last reviewed May 10, 2013 from <http://clinicaltrials.gov/ct2/show/NCT01788683?term=Regenexx&rank=1>

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.52, 4/11/13

Medical Director review 5/2013

Park JJ, Hershman SH, Kim YH. Updates in the use of bone grafts in the lumbar spine. Bull Hosp Jt Dis (2013). 2013;71(1):39-48.

Specialty Matched Consultant Advisory Panel review 2/2014

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Medical Director review 2/2014

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.52, 4/13/14

Specialty Matched Consultant Advisory Panel review 2/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.52, 4/23/15

Specialty Matched Consultant Advisory Panel review 2/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.52, 1/14/2016

Specialty Matched Consultant Advisory Panel review 2/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.52, 7/13/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.52, 1/11/2018

Specialty Matched Consultant Advisory Panel review 2/2018

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.52, 1/17/2019

Specialty Matched Consultant Advisory Panel review 2/2019

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.52, 1/16/2020

Specialty Matched Consultant Advisory Panel review 2/2020

Policy Implementation/Update Information

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| 7/6/10 | New Medical Policy implemented. Mesenchymal stem cell therapy is considered investigational for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue. (mco) |
| 8/31/10 | Policy Guideline section updated with clinical trial and product information. References updated. (mco) |
| 3/15/11 | Specialty Matched Consultant Advisory Panel review 2/2011. Added new product titled, "AlloStem Stem Cell Bone Growth Substitute" in the Policy Guidelines section. (mco) |
| 6/21/11 | Medical Director review 6/2011. References updated. No changes to policy statements. (mco) |
| 3/20/12 | Specialty Matched Consultant Advisory Panel review 2/2012. References update. Policy Guidelines updated. (mco) |
| 6/12/12 | References updated. No changes to policy statements. (mco) |
| 3/12/13 | Specialty Matched Consultant Advisory Panel review 2/2013. References updated. Policy Guidelines updated. Added Related Policies to Description section. (mco) |
| 6/11/13 | Description section updated. References updated. Policy Guidelines updated. New Policy Statement added: "Allograft bone products containing viable stem cells, including but not limited to demineralized bone matrix (DBM) with stem cells, is considered investigational |

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for all orthopedic applications.” The following statement added to Policy Guidelines: “Note: This policy does not address unprocessed allograft bone.” Medical Director review 5/2013. (mco)

- 8/13/13 Added new product to Description section: InQu™ (ISTO Technologies): A combination of poly(lactide-co-glycolide) (PLGA) a ceramic bone void filler with hyaluronic acid. (mco)
- 4/15/14 Specialty Matched Consultant Advisory Panel review 2/2014. Medical Director review 2/2014. Additional products added to the Description section. The following statement added to the “When not Covered” section: “Allograft bone products that are intended to be mixed with autologous bone marrow aspirate are considered investigational.” CPT codes 38232 and 38220 in combination with 22520, 22521, 22522, 22523, 22524, 22525, 22533, 22534, 22548, 22551, 22552, 22554, 22558, 22585, 22586, 22590, 22595, 22600, 22612, 22614, 22630, 22632, 22633, 22634, 22800, 22802, 22804, 22808, 22810, 22812, 22856, 22857, 22861, 22864, 22865, 27280, 27299, 27702, 27703 added to “Billing/Coding” section. References updated. Policy noticed 4/15/14 for effective date 7/1/14. (mco)
- 12/30/14 Codes 22520, 22521, 22522, 22523, 22524, and 22525 deleted from Billing/Coding section. Codes 22510, 22511, 22512, 22513, 22514, 22515, and 27279 added to Billing/Coding section for effective date 1/1/2015. (sk)
- 5/26/15 Specialty Matched Consultant Advisory Panel review 2/25/2015. Reference added. New products added to the Background section. The following statement added to the Policy statement “Allograft or synthetic bone graft substitutes that must be combined with autologous blood or bone marrow are considered investigational for all orthopedic applications”. (sk)
- 7/1/16 Specialty Matched Consultant Advisory Panel review 2/24/2016. Reference added. Policy Guidelines updated. (sk)
- 3/31/17 Specialty Matched Consultant Advisory Panel review 2/22/2017. (sk)
- 8/11/17 Reference added. Codes C9359 and C9362 added to Billing/Coding section. Notification given 8/11/2017 for effective date 10/13/2017. (sk)
- 12/29/17 Code 20939 added to Billing/Coding section for effective date 1/1/2018. (sk)
- 7/13/18 Reference added. Specialty Matched Consultant Advisory Panel review 2/28/2018. (sk)
- 3/12/19 Reference added. Specialty Matched Consultant Advisory Panel review 2/20/2019. (sk)
- 12/31/19 CPT codes 0565T and 0566T added to Billing/Coding section. (sk)
- 3/10/20 Reference added. Background section and Policy Guidelines section updated. Specialty Matched Consultant Advisory Panel review 2/19/2020. (sk)
- 12/31/20 Codes 0627T, 0628T, 0629T, and 0630T added to Billing/Coding section for effective date 1/1/2021. (sk)

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