MEDICAL POLICY – 8.01.52
Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used with Autologous Bone Marrow)

BCBSA Ref. Policy: 8.01.52
Effective Date: May 1, 2018
Last Revised: April 3, 2018
Replaces: N/A

RELATIVE MEDICAL POLICIES:
2.01.16 Recombinant and Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other Non-Orthopedic Conditions
2.01.98 Orthopedic Applications of Platelet-Rich Plasma
7.01.149 Amniotic Membrane and Amniotic Fluid

Select a hyperlink below to be directed to that section.
POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Mesenchymal stem cells are adult stem cells which are usually found in the bone marrow. These stem cells can generate other types of cells that are part of the body’s musculoskeletal system, such as bone, cartilage, and muscle. Stem cells are being studied as a way to treat orthopedic problems like damaged bone, ligaments, tendons, and the discs between the bones of the spine. Using stem cells to treat orthopedic problems is unproven. Studies have not yet shown the best ways to gather and deliver these cells. Studies also have not yet shown that using stem cells for orthopedic conditions leads to better health results compared to usual treatments.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
Policy Coverage Criteria

**Note:** This policy does not address unprocessed allograft bone.

<table>
<thead>
<tr>
<th>Service</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesenchymal stem cell therapy</td>
<td>Mesenchymal stem cell therapy is considered investigational for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue.</td>
</tr>
<tr>
<td>Allograft bone products containing viable stem cells</td>
<td>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.</td>
</tr>
<tr>
<td>Allograft or synthetic bone graft substitutes</td>
<td>Allograft or synthetic bone graft substitutes that must be combined with autologous blood or bone marrow are considered investigational for all orthopedic applications.</td>
</tr>
</tbody>
</table>

**Coding**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).</td>
</tr>
<tr>
<td>20999</td>
<td>Unlisted procedure, musculoskeletal system, general</td>
</tr>
<tr>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous</td>
</tr>
<tr>
<td>38241</td>
<td>Hematopoietic progenitor cell (HPC); autologous transplantation</td>
</tr>
</tbody>
</table>

**Related Information**
Benefit Application

The Regenexx® procedure is currently performed at select centers in the United States. Therefore, requests for it may be made for an out-of-network facility.

Evidence Review

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.

Background

*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.

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, peripheral blood, and synovial tissue. The largest body of evidence is on 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. 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.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1. Many are observational studies with commercially available products (eg, Cartistem, AlloStem, Trinity Evolution, Osteocel Plus).
Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01413061a</td>
<td>Study of Subtalar Arthrodesis Using AlloStem® Versus Autologous Bone Graft</td>
<td>140</td>
<td>Sep 2017 (ongoing)</td>
</tr>
<tr>
<td>NCT00885729</td>
<td>Mesenchymal Stem Cells in a Clinical Trial to Heal Articular Cartilage Defects</td>
<td>50</td>
<td>Jul 2018</td>
</tr>
<tr>
<td><strong>Unpublished</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01626677 / NCT01041001a</td>
<td>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/ Long Term Follow-Up Study of CARTISTEM® Versus Microfracture</td>
<td>104</td>
<td>May 2015 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
a Denotes industry-sponsored or cosponsored trial.

Practice Guidelines and Position Statements

**American Association of Orthopaedic Surgeons**

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

- Treatment using allograft, autograft, biologic, and interpositional grafts in patients with glenohumeral joint osteoarthritis is inconclusive, and that

- Treatment using growth factor injections and/or platelet rich plasma for patients with symptomatic osteoarthritis of the knee is inconclusive.

**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).”

**International Society for Cellular Therapy**

In 2006, the International Society for Cellular Therapy proposed a minimal set of criteria to standardize the characterization of multipotent mesenchymal stem cells. 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 of 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.

**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.

**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. 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 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 multipotent adult progenitor cells (MAPC®)
- Osteocel Plus® (NuVasive) is a DBM combined with viable MSCs isolated from allogeneic bone marrow
- Trinity Evolution Matrix™ (Orthofix) DBM combined with viable MSCs isolated from allogeneic bone marrow

Other products contain DBM and are designed to be mixed with bone marrow aspirate:
- Fusion Flex™ (Wright Medical) is 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 2 provides a representative sample of these products; some of which are specifically labeled for mixing with bone marrow aspirate.

### Table 2. Demineralized Bone Matrix Products Cleared by FDA

<table>
<thead>
<tr>
<th>Product</th>
<th>Matrix Type</th>
<th>Mix With Autologous MSCs</th>
<th>Manufacturer or Sponsor</th>
<th>Date Cleared</th>
<th>510(k) No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitoss® Bioactive Foam Bone Graft Substitute</td>
<td>Type I bovine collagen</td>
<td>X</td>
<td>Stryker</td>
<td>Nov 2008</td>
<td>K083033</td>
</tr>
<tr>
<td>NanOss BVF-E</td>
<td>Nanocrystalline hydroxyapatite</td>
<td></td>
<td>Pioneer Surgical</td>
<td>Aug 2008</td>
<td></td>
</tr>
<tr>
<td>OrthoBlast® II Demineralized bone matrix putty and paste</td>
<td>Human cancellous bone chips</td>
<td></td>
<td>SeaSpine</td>
<td>Sep 2007</td>
<td>K070751</td>
</tr>
<tr>
<td>CopiOs® Bone Void Filler (sponge and powder disc)</td>
<td>Type I bovine dermal collagen</td>
<td>X</td>
<td>Kensey Nash</td>
<td>May 2007</td>
<td>K071237</td>
</tr>
<tr>
<td>Product</td>
<td>Matrix Type</td>
<td>Mix With Autologous MSCs</td>
<td>Manufacturer or Sponsor</td>
<td>Date Cleared</td>
<td>510(k) No.</td>
</tr>
<tr>
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</tr>
<tr>
<td>DBX® Demineralized bone matrix putty, paste and mix</td>
<td>Processed human bone and sodium hyaluronate</td>
<td>X</td>
<td>Musculoskeletal Transplant Foundation</td>
<td>Dec 2006</td>
<td>K053218</td>
</tr>
<tr>
<td>Integra MOZAIK™ Osteoconductive Scaffold-Putty</td>
<td>Human cancellous bone</td>
<td>X</td>
<td>IsoTis OrthoBiologics</td>
<td>Dec 2006</td>
<td>K062353</td>
</tr>
<tr>
<td>Formagraft™ Collagen Bone Graft Matrix</td>
<td>Bovine fibrillary collagen</td>
<td>X</td>
<td>R and L Medical</td>
<td>May 2005</td>
<td>K050789</td>
</tr>
<tr>
<td>DynaGraft® II Gel and Putty</td>
<td>Processed human bone particles</td>
<td></td>
<td>IsoTis Orthobiologics</td>
<td>Mar 2005</td>
<td>K040419</td>
</tr>
</tbody>
</table>

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

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 Biologic License Application (BLA) to FDA. The Regenexx-C™ 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 (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. 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.

References


History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/09/11</td>
<td>New policy; add to Therapy section. Policy created with literature review through January 2011; considered investigational. ICD-10 codes included in policy.</td>
</tr>
<tr>
<td>07/20/12</td>
<td>Replace policy. Policy updated with literature review through February 2012; reference 6 added and references reordered; policy statement unchanged.</td>
</tr>
<tr>
<td>08/15/12</td>
<td>Update Related Policies: remove 7.01.48, it was archived.</td>
</tr>
<tr>
<td>08/20/12</td>
<td>Update Related Policies – add 2.02.18.</td>
</tr>
<tr>
<td>10/09/12</td>
<td>Update Coding Section – ICD-10 codes are now effective 10/01/2014.</td>
</tr>
<tr>
<td>04/26/13</td>
<td>Clarification only. Statement within the Benefit Application section stating, “Therefore, requests may be made for an out-of-network facility” was removed, as this conflicts with the FDA statements in the rest of the policy. No other changes.</td>
</tr>
<tr>
<td>06/10/13</td>
<td>Replace policy. New policy statement added that allograft bone containing viable stem cells is considered investigational. New policy guideline added that policy does not address unprocessed allograft bone. Regulatory status section updated regarding allograft bone. Rationale updated based on a literature review through March 2013. References 4, and 11-15 added; others renumbered or removed. Policy statement changed as noted.</td>
</tr>
<tr>
<td>08/20/13</td>
<td>Update Related Policies. Change title to 2.02.18.</td>
</tr>
<tr>
<td>06/19/14</td>
<td>Annual Review. Policy updated with literature review through March 3, 2014; references 5, 13, and 17 added; policy statements unchanged. ICD-10 codes removed in line with code mapping project and implementation delay.</td>
</tr>
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</table>
| 06/09/15 | Annual Review. Policy updated with literature review through February 26, 2015; 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; title changed to “Orthopedic applications of stem cell therapy (including allograft and
<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>bone substitute products used with autologous bone marrow). Related policies removed: 2.02.18, 7.01.15 and 8.01.55. CPT code 20999 added to policy.</td>
</tr>
<tr>
<td>09/01/15</td>
<td>Update Related Policies. Add 2.01.98 and 7.01.149.</td>
</tr>
<tr>
<td>04/01/16</td>
<td>Annual Review, approved March 8, 2016. Policy updated with literature review through November 17, 2015; references 12 and 15 added. Policy statements unchanged. Title changed to “Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)”.</td>
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<tr>
<td>06/09/17</td>
<td>Coding update; updated description for CPT codes 38230 and 38241.</td>
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<tr>
<td>09/01/17</td>
<td>Annual Review, approved August 22, 2017. Policy updated with literature review through June 9, 2017; references 1, 4, 12-13, 25, and 27-29 were added. Policy statements unchanged.</td>
</tr>
<tr>
<td>05/01/18</td>
<td>Annual Review, approved April 3, 2018. Policy updated with literature review through November 2017; references 14 and 24 added; references 2 and 4 updated. Policy statements unchanged. Removed CPT code 38230.</td>
</tr>
</tbody>
</table>

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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
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