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

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Policy Number: 254
BCBSA Reference Number: 8.01.52 (For Plans internal use only)
NCD/LCD: NA

Related Policies
- Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions, #374
- Orthopedic Applications of Platelet-Rich Plasma, #737
- Prolotherapy, #183

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

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, including, but not limited to:
- AlloStem® (AlloSource)
- Map3® (RTI Surgical)
- Osteocel Plus® (NuVasive)
- Trinity Evolution Matrix™ (Orthofix).

Allograft or synthetic bone graft substitutes that must be combined with autologous blood or bone marrow are considered INVESTIGATIONAL for all orthopedic applications, including, but not limited to:
- Fusion Flex™ (Wright Medical)
- Ignite® (Wright Medical)
- Vitoss® Bioactive Foam Bone Graft Substitute (Stryker)
- NanOss BVF-E (Pioneer Surgical)
- DBX® Putty (DePuy Synthes)
- Integra MOZAIK™ Osteoconductive Scaffold (IsoTis OrthoBiologics)
• Formagraft™ Collagen Bone Graft Matrix (R and L Medical)
• CopiOs® Bone Void Filler (Kensey Nash)
• OrthoBlast® II (Sea Spine)
• DynaGraft® II (Sea Spine)

Supplemental Information
The purpose of the following information is to provide reference material. Inclusion of table 1, Demineralized Bone Matrix Products Cleared by FDA, does not indicate coverage. Orthopedic Applications of Stem Cell Therapy is considered investigational.

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

<table>
<thead>
<tr>
<th>Product</th>
<th>Matrix Type</th>
<th>Mix With Autologous MSCs</th>
<th>Manufacturer or Sponsor</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>
</tr>
<tr>
<td>NanOss BVF-E</td>
<td>Nanocrystalline hydroxyapatite</td>
<td></td>
<td>Pioneer Surgical</td>
</tr>
<tr>
<td>OrthoBlast® II Demineralized bone matrix putty and paste</td>
<td>Human cancellous bone chips</td>
<td></td>
<td>SeaSpine</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>
</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>
</tr>
<tr>
<td>Integra MOZAIK™ Osteoconductive Scaffold-Putty</td>
<td>Human cancellous bone</td>
<td>X</td>
<td>IsoTis OrthoBiologics</td>
</tr>
<tr>
<td>Formagraft™ Collagen Bone Graft Matrix</td>
<td>Bovine fibrillar collagen</td>
<td>X</td>
<td>R and L Medical</td>
</tr>
<tr>
<td>DynaGraft® II Gel and Putty</td>
<td>Processed human bone particles</td>
<td></td>
<td>IsoTis Orthobiologics</td>
</tr>
</tbody>
</table>

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

Prior Authorization Information

Inpatient
• For services described in this policy, precertification/preauthorization IS REQUIRED for all products if the procedure is performed inpatient.

Outpatient
• For services described in this policy, see below for products where prior authorization might be required if the procedure is performed outpatient.

<table>
<thead>
<tr>
<th>Outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
</tr>
<tr>
<td>Medicare HMO BlueSM</td>
</tr>
</tbody>
</table>
This is not a covered service.

### CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

According to the policy statement above, the following CPT code is considered investigational for the conditions listed for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

### CPT Codes

<table>
<thead>
<tr>
<th>CPT codes</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>20930</td>
<td>Allograft, morselized, or placement of osteopromotive material, for spine surgery only (List separately in addition to code for primary procedure). NOTE: This is a generic graft add on injection code to spine surgery which could be used for stem cells injection.</td>
</tr>
</tbody>
</table>

The following CPT codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

### CPT Codes

<table>
<thead>
<tr>
<th>CPT codes</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0263T</td>
<td>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</td>
</tr>
<tr>
<td>0264T</td>
<td>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</td>
</tr>
<tr>
<td>0265T</td>
<td>Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; unilateral or bilateral bone harvest only for intramuscular autologous bone marrow cell therapy</td>
</tr>
<tr>
<td>0489T</td>
<td>Autologous adipose-derived regenerative cell therapy for scleroderma in the hands; adipose tissue harvesting, isolation and preparation of harvested cells including incubation with cell dissociation enzymes, removal of non-viable cells and debris, determination of concentration and dilution of regenerative cells</td>
</tr>
<tr>
<td>0490T</td>
<td>Autologous adipose-derived regenerative cell therapy for scleroderma in the hands; multiple injections in one or both hands</td>
</tr>
<tr>
<td>0565T</td>
<td>Autologous cellular implant derived from adipose tissue for the treatment of osteoarthritis of the knees; tissue harvesting and cellular implant creation</td>
</tr>
<tr>
<td>0566T</td>
<td>Autologous cellular implant derived from adipose tissue for the treatment of osteoarthritis of the knees; injection of cellular implant into knee joint including ultrasound guidance, unilateral</td>
</tr>
</tbody>
</table>

### Description

Mesenchymal Stem Cells
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 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.1

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 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
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 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 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 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. 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 that the technology results in an improvement in the net health outcome.

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/2023</td>
<td>Policy clarified. Table 1. Demineralized Bone Matrix Products Cleared by FDA added.</td>
</tr>
<tr>
<td>5/2023</td>
<td>Clarified coding information</td>
</tr>
</tbody>
</table>
### References


