**ORTHOPEDIC APPLICATIONS OF STEM CELL THERAPY (INCLUDING ALLOGRAFTS AND BONE SUBSTITUTES USED WITH AUTOLOGOUS BONE MARROW)**

**Medical Benefit**
- **Effective Date:** 10/01/15
- **Next Review Date:** 07/19

**Preauthorization**
- **No**
- **Review Dates:** 09/10, 07/11, 07/12, 07/13, 07/14, 07/15, 07/16, 07/17, 07/18

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*This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.*

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

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<th>Populations</th>
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<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
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<td>With cartilage defects</td>
<td>• Stem cell therapy</td>
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<td>• Microfracture</td>
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<td>• Autologous chondrocyte implantation</td>
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<td>• Treatment-related morbidity</td>
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<td>Individuals:</td>
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<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
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<td>With meniscal defects</td>
<td>• Stem cell therapy</td>
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<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
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<td>Individuals:</td>
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<td>With osteonecrosis</td>
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<td>• Core decompression</td>
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**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.
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 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 has evaluated the 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. 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 the effects of the technology on health outcomes.

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.

POLICY GUIDELINES

Note: This protocol does not address unprocessed allograft bone.

BACKGROUND

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.1

Bone marrow aspirate is considered 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 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 three-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 three-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.

**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, 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 FDA. No products using engineered or expanded MSCs have been approved by 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) 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. 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.
In 2008, FDA determined that the MSCs sold by Regenerative Sciences for use in the Regenexx™ procedure would be considered drugs or biologic products and thus would require submission of a new drug application or biologic license application to 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 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. To date, no new drug application or biologic license application has been approved by FDA for this product. As of 2015, the expanded stem cell procedure (now termed Regenexx-C™) is only offered in the Cayman Islands. The current 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.

**RELATED PROTOCOLS**

- Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions
- Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions
- Orthopedic Applications of Platelet-Rich Plasma
- Prolotherapy
Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


