MEDICAL POLICY

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POLICY TITLE	ORTHOPEDIC APPLICATIONS OF STEM-CELL THERAPY
POLICY NUMBER	MP-2.080

Original Issue Date (Created):	**November 1, 2010**
Most Recent Review Date (Revised):	**November 26, 2013**
Effective Date:	**February 1, 2014**

I. POLICY

Mesenchymal stem cell therapy is considered **investigational** for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Allograft bone products containing viable stem cells, including but not limited to demineralized bone matrix (DBM) with stem cells, is considered **investigational** for all orthopedic applications. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Cross-reference

MP-2.033 Blood/Platelet-Derived Growth Factors for Wound Healing
MP-1.022 Autologous Chondrocyte Implantation

II. PRODUCT VARIATIONS

[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

[N] Capital Cares 4 Kids
[N] PPO
[N] HMO
[N] SeniorBlue HMO
[N] SeniorBlue PPO
[N] Indemnity
[N] SpecialCare
[N] POS
[Y] FEP PPO*

* Refer to FEP Medical Policy Manual MP-8.01.2 Orthopedic Applications of Stem-Cell Therapy. The FEP Medical Policy manual can be found at: www.fepblue.org

III. DESCRIPTION/BACKGROUND

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.

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. Stimulation of endogenous MSCs is the basis of procedures such as bone marrow stimulation (e.g., microfracture) and harvesting/grafting of autologous bone for fusion. 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.

Tissues such as muscle, cartilage, tendon, ligaments, and vertebral discs show limited capacity for endogenous repair. Therefore, tissue engineering techniques are being developed to improve the efficiency of repair or regeneration of damaged musculoskeletal tissues. Tissue engineering focuses on the integration of biomaterials with MSCs and/or bioactive molecules such as growth factors. 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) stated:

"A major challenge posed by SC [stem-cell] therapy is the need to ensure their efficacy and safety. Cells manufactured in large quantities outside their natural environment in the human body can become ineffective or dangerous and produce significant adverse effects, such as tumors, severe immune reactions, or growth of unwanted tissue."

Regulatory Status

No products using engineered MSCs have been approved by the FDA for orthopedic applications.

The FDA has determined that the mesenchymal stem cells sold by Regenerative Sciences for use in the Regenexx™ 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. (2) To date, no NDA or BLA has been approved by the FDA for this product.

IV. RATIONALE

Cartilage Defects: MSCs from Peripheral Blood

A 2013 report from Asia described a small randomized controlled trial with autologous peripheral blood MSCs for focal articular cartilage lesions. (13) Fifty patients with grade 3 and 4 lesions of the knee joint underwent arthroscopic subchondral drilling followed by 5 weekly injections of hyaluronic acid. Half of the patients were randomly allocated to receive injections of peripheral blood stem cells or no further treatment. There were baseline differences in age between the groups, with a mean age of 38 years for the treatment group compared to 42 for the control group. The peripheral blood stem cells were harvested after stimulation with recombinant human granulocyte colony-stimulating factor, divided in vials, and cryopreserved. At 6 months after surgery, hyaluronic acid and MSC were re-administered over 3 weekly injections. At 18 months after surgery, second look arthroscopy on 16 patients in each group showed significantly higher histological scores (by about 10%) for the MSC group (1,066 vs. 957 by independent observers) while blinded evaluation of magnetic resonance imaging (MRI) showed a higher morphologic score (9.9 vs. 8.5). There was no difference in International Knee Documentation Committee (IKDC) scores between the 2 groups at 24 months after surgery. It is uncertain how differences in patient age at baseline may have affected the response to subchondral drilling.

Cartilage Defects: Conclusions

The evidence base on MSCs for cartilage repair is increasing, although as of March 2013 only one study was identified that was randomized. This small randomized study, which is limited by group differences in age at baseline, is also the only comparative study to show an improvement in histological and morphologic outcomes. No study to date has shown an improvement in functional outcomes following treatment with MSCs for cartilage repair.

Fusion and Non-union

There is limited evidence on the use of allografts with stem cells for fusion of the extremities or spine or for the treatment of non-union. One retrospective series from 2009 was identified on the use of Trinity Evolution Matrix MSC bone allograft for revision surgery of the foot and ankle. (14) Twenty-three patients were included who had undergone

revision foot and/or ankle surgery for residual malunion, non-union, or significant segmental bone loss. Patients were followed to the point of radiographic and clinical union, which occurred at a median of 72.5 days for 21 of the 23 patients (91.3%).

Osteonecrosis

Two randomized comparative trials from Asia have been identified that evaluated the use of MSCs for osteonecrosis of the femoral head.

Osteonecrosis: MSCs Expanded from Bone Marrow

In 2012, Zhao et al. reported a randomized trial that included 100 patients (104 hips) with early stage femoral head osteonecrosis treated with core decompression and expanded bone marrow MSCs versus core decompression alone. (15) At 60 months after surgery, 2 of the 53 hips (3.7%) treated with MSCs progressed and underwent vascularized bone grafting, compared with 10 of 44 hips (23%) in the decompression group who progressed and underwent either vascularized bone grafting (n=5) or total hip replacement (n=5). The MSC group also had improved Harris Hip Scores compared with the control group on independent evaluation (data presented graphically). The volume of the lesion was also reduced by treatment with MSCs.

Osteonecrosis: MSCs Concentrated from Bone Marrow

Another small trial randomized 40 patients (51 hips) with early stage femoral head osteonecrosis to core decompression plus concentrated bone marrow MSCs or core decompression alone. (16) Blinding of assessments in this small trial was not described. Harris Hip Score was significantly improved in the MSC group (scores of 83.65 and 82.42) compared with core decompression (scores of 76.68 and 77.39). Kaplan-Meier analysis showed improved hip survival in the MSC group (mean of 51.9 weeks) compared to the core decompression group (mean of 46.7 weeks). There were no significant differences between the groups in the radiographic assessment or MRI results.

Osteonecrosis: Conclusions

Two small studies from Asia have compared core decompression alone versus core decompression with MSCs in patients with osteonecrosis of the femoral head. Both studies reported improvement in the Harris Hip Score in patients treated with MSCs, although it was not reported whether the patients or investigators were blinded to the treatment group. Hip survival was significantly improved following treatment with either expanded or concentrated MSCs. The effect appears to be larger with expanded MSCs compared to

concentrated MSCs. Additional studies with a larger number of patients are needed to permit greater certainty regarding the effect of this treatment on health outcomes.

Ongoing Clinical Trials

A search of online site: ClinicalTrials.gov in March 2013 identified a number of trials on use of MSCs for orthopedic indications from both within and outside the U.S. The following is a sample of some of the larger studies:

- A Phase I/II randomized, placebo controlled, double blind study of 2 doses of Chondrogen™ (Osiris Therapeutics) or a placebo intra-articular injection following meniscectomy in 60 patients is listed as completed in 2008 (NCT00225095). Chondrogen™ is a preparation of adult MSCs in a solution containing hyaluronic acid. Three-year follow-up of Chondrogen™ versus placebo injections is listed as a separate study (NCT00702741). The status of this trial is unknown.
- Medipost is sponsoring a randomized, open-label, multicenter Phase III clinical trial to compare the efficacy and safety of Cartistem® and microfracture in patients with knee articular cartilage injury or defect (NCT01041001). MSCs will be isolated from umbilical cord blood and cultured, mixed with semi-solid polymer, and administered in the cartilage tissue lesion by orthopedic surgery. The study is listed as completed as of April 2012 with an enrollment of 104 patients. Preliminary results of this study were presented at the annual meeting of the American Academy of Orthopaedic Surgeons in February 2012. As of March 2013, no peer-reviewed publications from this trial have been identified.
- Medipost is sponsoring a 60-month follow-up study (NCT01626677) of the patients who participated in the Phase III trial of Cartistem® (NCT01041001). The study has an estimated enrollment of 103 patients with completion in May 2015.
- NCT00885729 is a Phase I randomized, single-blind, active control trial of MSCs compared with chondrocytes to heal articular cartilage defects in 50 patients. The study is sponsored by an academic medical center in Norway. Both MSCs and chondrocytes will be delivered in a commercially available scaffold (not described). The estimated study completion date is 2018.
- The National University of Malaysia is sponsoring a randomized controlled trial of intra-articular MSC injection versus hyaluronic acid in patients with osteoarthritis (NCT01459640). The study has an estimated enrollment of 50 patients with completion in 2014.
- Three series are listed with Trinity Evolution Matrix for foot and ankle surgery, anterior cervical discectomy and fusion (ACDF), and posterior or transforaminal lumbar interbody fusion (PLIF or TLIF). All 3 studies are listed as ongoing but not recruiting subjects.

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Summary

Overall, the literature suggests a technology that is at an early stage of development, with the vast majority of studies focused on development of methods for tissue engineering along with preliminary testing in animal models. Despite this research into the methods of treatment, there are uncertainties regarding the optimal source of cells and the delivery method. Current available evidence on procedures using autologous bone-marrow-derived mesenchymal stem cells (MSCs) for orthopedic indications in humans consists primarily of case series and small non-randomized comparative trials with insufficient data to evaluate health outcomes. In addition, expanded MSCs for orthopedic applications are not FDA approved (concentrated autologous MSCs do not require FDA approval). Due the lack of evidence that clinical outcomes are improved, use of stem cells for orthopedic applications is considered investigational.

Practice Guidelines and Position Statements

The American Association of Orthopaedic Surgeons (AAOS) states that stem-cell procedures in orthopedics are still at an experimental stage; most musculoskeletal treatments using stem cells are performed at research centers as part of controlled, clinical trials, and results of studies in animal models provide proof-of-concept that in the future, similar methods could be used to treat osteoarthritis, nonunion of fractures, and bone defects in humans. (17)

In 2006, the Mesenchymal and Tissue Stem-Cell Committee of the International Society for Cellular Therapy proposed a minimal set of criteria to standardize the characterization of multipotent mesenchymal stem cells. (18) The proposed criteria for human MSCs included plastic-adherence when maintained in standard culture conditions; a phenotype of expression of CD105, CD73, and CD90 with a lack surface expression of CD45, CD34, CD14 or CD11b, CD79 alpha or CD19, and HLA-DR surface molecules; and the capability of differentiating into osteoblasts, adipocytes, and chondrocytes using standard *in vitro* tissue culture-differentiating conditions.

V. DEFINITIONS

AUTOLOGOUS- refers to originating within an individual; i.e., self-donation.

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VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. REFERENCES

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IX. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Mesenchymal stem cell therapy is considered investigational for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue; therefore the following codes are not covered when used for mesenchymal stem cell therapy:

CPT Codes®								
38206	38230	38241						

X. POLICY HISTORY

MP-2.080	**CAC 9/28/10.** New policy. Adopt BCBSA.
	CAC 10/25/11 Consensus
	CAC 10/30/12 Consensus. No change to policy statements. References updated. Changed FEP variation to reference MP-8.01.2 Orthopedic Applications of Stem-Cell Therapy. Updated the FDA information in the Background/Description. Code REVIEWED10/31/12 KLR
	CAC 11/26/13 Consensus review Statement added that allograft bone products containing viable stem cells, including but not limited to demineralized bone matrix (DBM) with stem cells are also considered investigational. References updated. Rationale added**.**

[Note: Final page is signature page and is kept on file, but not issued with Policy.]