Molina Clinical Policy
Stem Cell Therapy for Orthopedic Applications: Policy No. 426

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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

This policy addresses stem cell therapy for orthopedic applications, specifically mesenchymal stem cells. Stem cell transplantation using hematopoietic stem cells for the treatment of blood cancer, non-cancer conditions, or solid tumors are not addressed in this policy.

Mesenchymal stem cells (MSCs) are non-hematopoietic adult stem cells that originate from mesoderm and are present in bone marrow, fat, synovium, tonsil, peripheral blood, amniotic fluid, umbilical cord blood, and other tissues. MSCs respond to osteogenic growth stimuli and promote bone repair with their ability to differentiate into resident cells to replace damaged tissues, in addition to possessing potent immunomodulatory properties to regulate surrounding cells and boost tissue repair capacity. These stem cells are capable of self-replication, self-division, self-renewal, and multidirectional differentiation to repair tissues and preserve their homeostasis. MSCs are primarily derived from bone marrow in orthopedics, but other sources include adipose tissue, umbilical cord tissue, amniotic fluid, and other extra-articular sources. MSCs have the potential to be used in orthopedic applications, such as the treatment of damaged bone, cartilage, ligaments, tendons, and intervertebral discs, and thus have an important role in tissue regeneration and regenerative medicine (Deng et al. 2022). Stem cell therapy (SCT) for musculoskeletal or orthopedic conditions is an outpatient procedure that begins with patient (autologous) or donor (allogeneic) stem cell collection. Cultured or concentrated cells are then injected into the affected area. MSC therapy has been proposed as a potential treatment for orthopedic conditions, including but not limited to the following:

- Elbow: Injuries, overuse conditions and arthritis (tendon and ligament issues)
- Hand/Wrist: Arthritis and other conditions
- Foot/Ankle: Ligament tears, sprains and instability of the ankle joint, an alternative to fusion or replacement surgery of the ankle
- Hip: Injuries, arthritis, bursitis, and other degenerative conditions
- Knee: Arthritis, meniscal tears, tendon and ligament tears, overuse injuries and other conditions
- Shoulder: Arthritis, rotator cuff tears, and other shoulder conditions
- Spine and cervical conditions: Back pain, pain from disc injury or degeneration
- Non-union fractures

The heterogeneity of the SCT treatment protocol, which includes differences in the number of stem cells injected, the use of freshly isolated versus cultured stem cells, the use of additional biomaterial, and the use of stem cells from various sources, makes it difficult to interpret results and reach treatment efficacy conclusions. The lack of large, well-designed randomized controlled trials (RCTs) across all indications, as well as the inconsistency regarding whether SCT has a positive long-term effect, are also significant limitations of SCT.

The peer-reviewed scientific literature on the use of MSCs to promote bone healing lacks sufficient evidence that SCT, alone or in combination with other biomaterials such as an allograft bone product, is effective or consistently improves health outcomes for any orthopedic indication. This includes degenerative and non-degenerative hip or knee conditions, spinal disc disorders and tendinopathies. Furthermore, no clinical practice guidelines for the use of SCT for any orthopedic condition have been proposed.

Regulatory Status

Autologous stem cell transplantation is a procedure and thus not regulated by the FDA. Medical devices, biologics, drugs, or tests used as part of this procedure may be subject to FDA regulation. Stem cells, like other medical products intended to treat, cure, or prevent disease, require FDA approval or clearance prior to marketing. **Currently, regenerative medicine therapies have not been approved for the treatment of any orthopedic condition, such as osteoarthritis, tendonitis, disc disease, tennis elbow, back pain, hip pain, knee pain, neck pain, or shoulder pain** (FDA 2021).

The FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, in accordance with the Code of Federal Regulation, Title 21, Sections 1270 and 1271. According to the FDA, "the only stem cell-based products that are FDA-approved for use in the United States consist of blood-forming stem cells (hematopoietic progenitor cells) derived from cord blood" and approval is restricted to the treatment of hematopoietic disorders.

Safety concerns of the FDA regarding the use of unproven stem cell therapies include administration site reactions, neurologic conditions, bacterial infection, failure of cells to work as expected, the growth of tumors, and the ability of cells to move from placement sites and change into inappropriate cell types and multiply. According to the FDA statement regarding 'Development of Strategies to Improve Cell Therapy Product Characterization':

> *"A major challenge posed by 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. In response to this challenge, FDA scientists are developing laboratory techniques that will enable the agency to carefully evaluate and characterize these products in order to reliably predict whether they will be safe and effective.*
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> *Our laboratories use cell cultures and animal models to develop such techniques and to study the biochemical signals that govern cell behavior during manufacturing and after administration to patients. We are currently using mesenchymal stromal cells, or MSCs, (widely called mesenchymal stem cells) to improve strategies for predicting characteristics of stem-cell based cell products.*
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> *These studies will help us develop tests that are practical and applicable to specific manufacturing steps."*

No products using engineered or expanded MSCs have been approved by the FDA for orthopedic applications. However, several stem-cell-containing products are available for orthopedic applications:

Orthopedic MSC therapy

- **Regenexx® Stem Cell** autologous MSCs derived from bone marrow concentrate (BMC), are injected under image guidance to treat knee, hip, shoulder spine, elbow, hand, wrist, and foot-ankle defects and injuries. Regenexx network facilities in the United States offer Regenexx-SD orthopedic SCT, which harvests and re-injects patients' stem cells on the same day; procedures are not subject to FDA approval. The Regenexx procedures currently available in the U.S. are 1271.15(b) compliant and are not classified as Section 351 drugs by the FDA. The Regenexx-C Procedure is only available in the Cayman Islands through an independent vendor who has licensed the procedure. These service providers are not part of nor affiliated with any U.S. Regenexx Network provider (Regenexx date unknown).

- **Stravix®** (Osiris Therapeutics, Inc.) is a cryopreserved placental tissue, composed of the umbilical amnion and Wharton's Jelly (allogeneic matrix). As a viable wrap for surgical procedures (e.g., tendon repair, Achilles tendon rupture, bunionectomy, hallux rigidus correction, foot amputations, fibromatosis, and arthrodesis), Stravix conforms to injured tissue, can be sutured, and is arthroscopic and robotic procedure friendly. Stravix is manufactured using a proprietary process allowing the tissue to retain its native components (Stryker 2018).

The products listed below are examples of commercially available demineralized bone matrix (DBM) products marketed as containing viable stem cells (not an exhaustive list):

Allograft bone products containing viable stem cells

- **AlloStem® Cellular Bone Allograft (AlloSource)** is comprised of adipose derived MSCs with partially demineralized allograft bone.
- **Map3™ (RTI surgical)** contains cortical cancellous bone chips, DBM and multipotent adult progenitor cells.
- **OsteoCel and OsteoCel Plus (Nuvasive®)** is a DBM combined with viable MSCs that have been isolated from allogeneic bone marrow.
- **NuCel® (NuTech Medical)** is an allograft derived from amniotic membrane.
- **Trinity Evolution® and Trinity ELITE® (Orthofix®)** is a DBM combined with viable MSCs that have been isolated from allogeneic bone marrow. These cancellous bone allografts contain viable adult MSCs and are intended for the treatment of musculoskeletal defects.

NOTE: The FDA determines the safety and efficacy of a device or medication but does not establish medical necessity; however, FDA approval does not, in and of itself, establish the service, procedure, device or pharmaceutical as medically necessary.

COVERAGE POLICY

Due to the lack of evidence from existing clinical studies and published peer-reviewed literature of improved clinical outcomes, and in the absence of regulatory approval, the use of stem cells in orthopedic applications is considered experimental, investigational, and unproven.

1. Mesenchymal stem cell (MSC) therapy (e.g., Regenexx, Stravix) is considered **experimental, investigational, and unproven** for all orthopedic applications. This includes but is not limited to allogeneic or autologous stem cells, harvested bone marrow, adipose tissue, peripheral blood, synovial or amniotic fluid. Examples include:
   - Bone repair or fracture repair (non-union or delayed union)
   - Degenerative conditions
   - Joint disease (e.g., articular cartilage repair, joint capsular injury)
   - Osteonecrosis of the knee and hip
   - Osteoarthritis
   - Chondral / Osteochondral Defect
     - Osteochondritis dissecans of the knee
   - Other knee indications (e.g., pain from ligament or meniscus repair, knee cartilage defects)
   - Regeneration and/or repair of musculoskeletal tissue
   - Spinal disc disorders
   - Tendinopathies

2. Allograft bone products containing viable stem cells, including but not limited to demineralized bone matrix with stem cells (e.g., BIO4, OSTEOCEL Plus, OSTEOCEL Pro, OsteoVive, Trinity Evolution, Trinity ELITE, VIA Form, VIA Graft, ViviGen) are considered **experimental, investigational, and unproven** for all orthopedic applications.

3. Allograft or synthetic bone graft substitutes that must be combined with autologous blood or bone marrow are considered **experimental, investigational, and unproven** for all orthopedic applications.

SUMMARY OF MEDICAL EVIDENCE

The published peer-reviewed scientific literature evaluating Mesenchymal stem cells (MSCs) for treatment of these conditions consists primarily of preliminary animal studies, case reports, case series, nonrandomized comparative trials, systematic reviews/meta-analyses, and randomized trials. The type/source of stem cell used, and methods of extraction vary across studies. Additionally, sample populations are small, reported outcomes are two years or less in most studies, and injections sometimes include other components such as hyaluronan or platelet rich plasma, making it difficult to attribute the sole effect of MSCs as a treatment response. Furthermore, the optimal source of MSC, the number of cells to inject, processes for extraction and concentration of MSC, infusion procedures, and indications for use have not been standardized. To establish the safety and efficacy of MSCs utilized for therapy of orthopedic and/or musculoskeletal diseases, additional randomized controlled trials (RCTs) investigating long-term outcomes are

required since it has not yet been demonstrated that the clinical benefit of MSC treatments outweighs the risk of potential adverse effects.

Lee et al. (2019) conducted a phase IIb, randomized, doubled-blinded, placebo-controlled clinical trial to assess the effectiveness and safety of intra-articular injection of autologous adipose-derived mesenchymal stem cells (AD-MSCs). Twenty-four patients between 18 and 75 years of age with osteoarthritis of the knee joint were enrolled in the study. Twelve patients were in the mesenchymal stem cells (MSC) group that underwent a lipoaspiration procedure and 12 were in the control group that received a normal saline injection. Patients experienced a mean pain intensity of 4 or more on a 10-point visual analog scale (VAS) for at least 12 weeks and had at least one focal or localized grades 3 or 4 lesion on MRI scan. The primary outcome measurement was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Secondary measurements included the VAS for knee pain, osteoarthritis outcome score, range of motion, quadriceps power, presence of joint effusion, presence of joint crepitus, presence of medial joint line tenderness, presence of pes anserinus tenderness, radiologic evaluation, and adverse events.

Six months after injection the reduction of the WOMAC score in the MSC group from the baseline was 55%, from 60.0 ± 17.0 to 26.7 ± 13.3 ($p < 0.001$). All sub scores of the WOMAC at 6 months significantly improved from the baseline in the MSC group only ($p < 0.05$). The VAS for the knee pain significantly decreased from 6.8 ± 0.6 to 3.4 ± 1.5 in the MSC group ($p < 0.001$) with no significant improvements reported in the control group. In the MSC group, range of motion was significantly improved, from $127.9° \pm 10.3°$ to $134.6° \pm 12.5°$ at 6 months after the injection ($p = 0.0299$). Quadriceps power, presence of joint effusion, presence of joint crepitus, presence of medial joint line tenderness, and presence of pes anserinus tenderness showed no significant change in either group compared with baseline. For radiologic evaluation, the size of the cartilage defect and the amount of change in cartilage defect was measured. The size of the cartilage defect in MRI at 6 months was not significantly changed in the MSC group ($p = 0.5803$) and was significantly increased in the control group ($p = 0.0049$). There was a significant difference between the two groups in the amount of change in cartilage defect after the injection ($p = 0.0051$). Adverse events were reported in eight patients in the study. In the MSC group six patients experienced arthralgia and two patients experienced joint effusion. In the control group one patient experienced joint effusion. Limitations of the study included the small sample size and short-follow up time of six months. The study concluded a single intra-articular injection of autologous AD-MSCs in patients with osteoarthritic knees led to satisfactory clinical and functional improvement over six months of follow-up.

Ding et al. (2021) conducted a systematic review and meta-analysis to determine the efficacy and safety of intra-articular cell-based therapy for osteoarthritis (OA). Thirteen studies were analyzed and met the inclusion criteria of having an RCT design, included OA patients, included a study arm with cell-based treatment, and included a control group with non-cell-based therapy. The included studies also reported outcomes with WOMAC, Knee Injury and Osteoarthritis Outcome Score (KOOS), or the VAS. Studies were excluded if they had a non-RCT design, examined non-OA patients, used non-cell-based interventions or non-cell-based interventions with surgical treatment, or lacked a non-cell-based control group. All in vitro studies, animal studies, conference abstracts, and comments were also excluded. Results showed that intra-articular cell-based therapy of OA did not significantly reduce the 6-month follow-up WOMAC score ($p = 0.1928$). After 12-month the results showed cell-based therapy did significantly improve the KOOS ($p = 0.0288$) and relieved pain ($p < 0.0001$). Limitations included the inability to demonstrate the effects of cell-based therapy in OA patients of different ages or Kellgren-Lawrence grades. The meta-analysis was also limited by the large numbers of arms resulting in a small sample size of each arm and publication bias. Overall, the study was only suitable for making recommendation for the design of future RCTs. Further studies on long-term effect of high-dose MSC treatment for OA is needed.

Regenexx® Stem Cell (Regenexx)

Centeno et al. (2018) conducted a RCT to evaluate Regenexx treatment for knee osteoarthritis. Patients with symptomatic knee osteoarthritis were assigned to either an exercise therapy control group (n=22) or a treatment group with image-guided injection of autologous bone marrow concentrate (BMC) and platelet products (n=26). At 3 months, participants were permitted to crossover to the group receiving bone marrow treatment. Measured outcomes included the Knee Society Score, Pain VAS, Short Form-12 Scales (SF-12), and Lower Extremity Activity Scale. Follow-up for clinical outcomes occurred at 6-weeks, 3, 6, 12 and 24 months. A total of 14 patients were lost to follow-up. All 22 patients in the control group crossed over to BMC treatment after 3 months. Compared to patients who participated in a 3-month home exercise treatment program, those who received a specific protocol of BMC and platelet products had substantial improvements in activity levels, discomfort, range of motion, and stability. Pain decreased in both the exercise therapy and BMC groups, and function improved in the BMC group; nevertheless, these results did not differ substantially between the two groups. Compared to baseline, exercise therapy resulted in significant improvements in

range of motion and activity levels at 3 months. There were no reports of major side effects. This RCT is limited by its small sample size and the fact that participants in the exercise group were permitted to switch to the BMC group after three months. To establish safety and efficacy, additional RCTs examining Regenexx techniques, treatments, and products are necessary.

Centeno et al. (2020) published the mid-term results of a RCT comparing the use of BMC and platelet rich plasma versus exercise therapy as treatment for rotator cuff tears (n=25; 14 subjects in the bone marrow group, 11 subjects in the exercise therapy group). The trial is still underway, and the authors highlight that enrollment is ongoing, however, the interim analysis includes the reported results of participants who have reached 12-month follow-up (n=24). The preliminary findings indicate a reduction in the size of most tears following bone marrow treatment, as well as improvements in Disability of the Arm, Shoulder, and Hand Questionnaire (DASH) and Numeric Pain Scale (NPS) scores at 3 and 6 months compared to exercise. However, final outcomes are pending study completion.

National and Specialty Society Guidelines

The **American Association of Orthopedic Surgeons (AAOS)** published evidence-based clinical practice guidelines for the treatment of osteoarthritis of the hip and knee. Evidence reviews of SCT versus other comparators for these indications did not identify sufficient high-quality evidence to formally address the treatment in their recommendations (AAOS 2017; AAOS 2021). An additional guideline was published on the management of glenohumeral joint osteoarthritis, which was endorsed by several societies. Injectable biologics, such as stem cells, are not recommended for the treatment of glenohumeral joint osteoarthritis, according to the guideline. The consensus of the panel is that definitive evidence on the efficacy of biologics in glenohumeral osteoarthritis requires improved standardization and high-quality clinical trial evidence (AAOS 2020).

The **American College of Rheumatology and Arthritis Foundation (ACRA)** published guidelines on hand, hip, and knee osteoarthritis and strongly advises against stem cell injections in patients with knee and/or hip osteoarthritis, citing "heterogeneity in preparations and lack of standardization of techniques". The guideline made no recommendations for hand because SCT has not been evaluated for this condition (Kolasinski et al. 2019).

The **International Society of Stem Cell Research (ISSCR)** published information about stem cell types and uses, stating that there is scant evidence that they are advantageous. MSC therapy is still in its early stages of development. Various MSCs are thought to have stem cell and immunomodulatory properties that could be used to treat a variety of disorders. The precise nature of these cells, as well as the types of cells they can produce, is unknown. Researchers are in general agreement that not all MSCs are identical, and that their properties vary based on where they originate in the body and how they are isolated and cultivated. Since certain types of stem cells might migrate following transplantation, off-target effects and incorrect integration are possible (ISSCR date unknown).

CODING & BILLING INFORMATION

NOTE: Stem cell therapy applications for orthopedic conditions are not specifically coded. For reporting this procedure, the appropriate CPT code is 20999, or the code for an unlisted procedure of the body part where the procedure is being performed.

CPT (Current Procedural Terminology) Codes

CPT	Description
20939	Bone marrow aspiration for bone grafting, spine surgery only, through separate skin or fascial incision (List separately in addition to code for primary procedure)
20999	Unlisted procedure, musculoskeletal system, general
21899	Unlisted procedure, neck, or thorax
22899	Unlisted procedure, spine
23929	Unlisted procedure, shoulder
24999	Unlisted procedure, humerus, or elbow
25999	Unlisted procedure, forearm, or wrist
26989	Unlisted procedure, hands, or fingers
27299	Unlisted procedure, pelvis, or hip joint
27599	Unlisted procedure, femur, or knee
27899	Unlisted procedure, leg, or ankle

28899	Unlisted procedure, foot, or toes
29999	Unlisted procedure, arthroscopy
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
0565T	Autologous cellular implant derived from adipose tissue for the treatment of osteoarthritis of the knees; tissue harvesting and cellular implant creation
0566T	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
0717T	Autologous adipose-derived regenerative cell (ADRC) therapy for partial thickness rotator cuff tear; adipose tissue harvesting, isolation and preparation of harvested cells, including incubation with cell dissociation enzymes, filtration, washing and concentration of ADRCs
0718T	Autologous adipose-derived regenerative cell (ADRC) therapy for partial thickness rotator cuff tear; injection into supraspinatus tendon including ultrasound guidance, unilateral
0737T	Xenograft implantation into the articular surface

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

12/13/2023 Policy reviewed. No changes to criteria. Updated references and summary of medical evidence.
12/14/2022 New policy. IRO Peer Review. Oct 28, 2022. Practicing physician board-certified in Orthopedic Surgery.

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