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

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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 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 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 provides limited 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.

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Regulatory Status

SCT products may be subject to FDA regulation depending on how the cells or tissues are processed and used. Stem cells products, like other medical products intended to treat, cure, or prevent disease, generally require FDA approval 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.*
>
> *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).

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

- 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.

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COVERAGE POLICY

The use of stem cells in orthopedic applications is considered **experimental, investigational, and unproven** due to insufficient evidence in the peer-reviewed medical literature to establish long-term safety, efficacy, and effect on net health outcomes.

1. Mesenchymal stem cell (MSC) therapy (e.g., Regenexx) 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

DOCUMENTATION REQUIREMENTS: Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or rendering a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

The published peer-reviewed scientific literature evaluating mesenchymal stem cells (MSCs) for treatment of these conditions included randomized controlled trials (RCTs), systematic reviews and meta-analyses, nonrandomized comparative trials, case series, case reports, and preclinical studies. The type/source of stem cell used, and methods of extraction vary across studies. Additionally, sample populations are relatively small and follow-up durations are limited, and injections sometimes include other components such as hyaluronic acid 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. Although some studies have reported improvements in pain and function, results remain inconsistent across indications and treatment protocols, with some sham-controlled trials showing no significant difference between MSC and sham. Additional, well-designed RCTs investigating long-term outcomes are needed to establish long-term safety, comparative effectiveness, and optimal treatment protocols.

Randomized Controlled Trials

Gupta et al. (2026) reported on the 2-year outcomes of a phase III, multicenter, double-blind, placebo controlled RCT evaluating single intra-articular injection of allogeneic, cultured, pooled bone marrow-derived MSCs (Stempeucel) in adults with symptomatic Kellgren-Lawrence grade 2 or 3 osteoarthritis (OA) of the knee. A total of 146 patients were randomized 1:1 to 25 million bone marrow-derived MSCs (n = 73) or placebo (n = 73), with both groups also receiving

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20 mg of hyaluronic acid. The primary efficacy outcome was a change in the total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), measured using a 0-100 visual analog scale (VAS). Secondary outcomes included pain, stiffness, MRI T2 mapping and cartilage volume, and urinary CTX-II and serum IL-10 biomarkers. At 24 months, the between-group difference in total WOMAC score was -952.43 mm (71.43% difference, 95% confidence interval [CI] -84.41% to -58.44%, $p < 0.0001$). Compared with placebo, WOMAC pain, stiffness, and physical-function scores were reduced by 73.12%, 77.25%, and 71.46%, respectively ($p < 0.0001$). Additionally, 74.0% of MSC-treated patients versus 17.8% of placebo patients demonstrated a 20-100% improvement in total WOMAC score. Pain measured by VAS also favored MSC at 24 months, with between-group difference of 64.04% (95% CI -75.99% to -52.09%, $p < 0.0001$). Mean MRI T2 relaxation values in the MSC group remained within the study's pre-specified normal range of $\leq$ 39 ms and changed from a baseline of 38.1 $\pm$ 6.57 to 36.3 $\pm$ 5.16 ms at 24 months, whereas placebo values remained above that range (41.0 $\pm$ 6.42 to 40.0 $\pm$ 4.37 ms). However, the between-group changes in T2 mapping were not statistically significant at any time point. Cartilage volume was 49.81 mm^3 greater in the MSC group at 24 months, but this difference was also not statistically significant. Differences in biomarker analyses for urinary CTX-II and serum IL-10 also were not statistically significant. During the follow-up period, 1 MSC patient and 4 placebo patients underwent total knee replacement. There were 135 treatment-emergent adverse events in 59 patients (64 events in 26 MSC patients and 71 events in 33 placebo patients). There were 11 serious adverse events in 9 patients, but none were considered treatment related, and 2 COVID-19 related deaths occurred in the MSC group. Study limitations include the absence of histologic assessment, MRI interpretation by a single blinded radiologist, lack of synovial-fluid cytokine analysis, and limited 2-year follow-up. The authors concluded that pooled allogeneic bone-marrow derived MSCs were safe and effective for grade 2-3 knee OA. The study was funded by Stempeutics Research, the developer and manufacturer of Stempeucel, with 4 of the study authors being employees of the company.

Jafar et al. (2026) conducted a double-blind, placebo-controlled phase I/II RCT to evaluate the safety and efficacy of ultrasound-guided intra-articular allogeneic adipose-derived MSCs (ADMSCs) in adults with symptomatic Kellgren-Lawrence grade III OA of the knee. The study enrolled 55 knees in 43 participants, randomized 3:1 with 2 ADMSC injections given 2 weeks apart (mean total dose of 69.58 x 10^6 cells) or 2 equal volume saline injections; however, only 37 knees in 29 patients completed the study protocol as 14 patients were lost to follow-up. Clinical efficacy was measured with the Knee Injury and Osteoarthritis Outcome Score (KOOS) and WOMAC. At 6 months, mean KOOS increased from 50.71 $\pm$ 11.9 to 83.90 $\pm$ 10.83 in the ADMSC group versus 51.25 $\pm$ 10.28 to 53.38 $\pm$ 9.36 with placebo. At 12 months, KOOS scores were 81.87 $\pm$ 11.3 versus 45.63 $\pm$ 9.43, respectively ($p < 0.0001$). At 6 months, mean WOMAC improved from 50.12 $\pm$ 11.94 to 23.47 $\pm$ 13.02 in the ADMSC group versus 47.95 $\pm$ 8.71 to 47.80 $\pm$ 7.70 with placebo. At 12 months, WOMAC scores were 19.02 $\pm$ 11.42 versus 52.00 $\pm$ 5.81, respectively ($p < 0.0001$). At 1 year, responder rates, defined as $\geq$ 50% improvement from baseline in clinical or MRI outcomes, were 66.7% for KOOS and 71.4% for WOMAC in the ADMSC group versus 0% for those outcomes in the placebo group. However, only 8 placebo patients remained at 1 year as man placebo patients withdrew from the study when their pain and function did not improve. For MRI outcomes, at 12 months, cartilage scores decreased from 2.43 $\pm$ 0.65 to 1.50 $\pm$ 0.76 ($p < 0.01$) versus 2.10 $\pm$ 0.70 to 2.30 $\pm$ 0.48 in the placebo group. Additionally, ADMSC participants showed reduction in bone-marrow lesion scores, from 2.36 $\pm$ 0.50 to 1.36 $\pm$ 0.50 at 12 months. Adverse events were predominantly transient post-injection pain, swelling, and effusion. Study limitations include small sample size and participant attrition. The authors concluded that two intra-articular doses of allogeneic ADMSCs were safe and produced significant clinical and MRI-assessed structural improvements in stage III knee OA, with clinical benefit sustained for up to 3 years.

Pers et al. (2024) conducted a multi-center, double-blind, sham-controlled phase IIb RCT (RESPINE study) to evaluate a single intradiscal injection of 20 million allogeneic bone marrow-derived MSCs for chronic low back pain associated with intervertebral disc degeneration. The study included 114 adult participants with chronic low back pain despite $\geq$ 3 months of conservative therapy, baseline pain $\geq$ 40/100, and primarily singe-level degeneration of modified Pfirrmann grade 4-7. Participants were randomized to MSC (n = 58) or sham (n = 56), with the sham group receiving subcutaneous saline injection without intradiscal puncture. The primary endpoint at 12 months was either a $\geq$ 20% and $\geq$ 20-mm improvement in pain on the 0-100 mm VAS, or $\geq$ 20% improvement in disability on the Oswestry Disability Index (ODI). This endpoint was not met, as MSC did not demonstrate a significantly greater responder rate than sham. In the MSC group, 74.0% of patients were responders compared to 68.8% of sham patients ($p = 0.77$). Pain improvement over time in both groups, but there were no significant between-group differences at any time point through 24 months. At 12 months, mean VAS was 33.68 in the MSC group versus 43.06 with sham ($p = 0.15$) and ODI was 16.76 in the MSC group versus 21.08 in the sham group ($p = 0.41$). SF-36 quality of life scores, analgesic/NSAID use, and sick leave also did not significantly differ between the groups. For objective outcomes, MRI T2 relaxation measurements were only available for 55 patients at 12 months which limited the analysis. In the MSC group, mean

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disc-fluid content changed by -5.15% at 12 months versus -1.16% for sham (p = 0.77). At 24 months, data was available for only 20 patients: mean fluid content increased 4.58% in the MSC group versus -1.44% with sham (p = 0.55). The authors described this as a possible later increase in disc water content with MSC, but the difference was not statistically significant. Across 24 months there were 488 adverse events (272 with MSC and 216 with sham). There were 18 serious adverse events (10 with MSC and 8 with sham), 4 of which were considered related to the study treatment or procedure and involved serious but transient worsening low back pain. No serious adverse event resulted discontinuation and there were no cases of infectious spondylodiscitis, disc calcification, or lumbar surgery. The authors concluded that the trial did not conclusively demonstrate efficacy of allogeneic bone-marrow derived MSCs for intervertebral disc degeneration.

Centeno et al. (2024) reported on the 2-year results of the RCT comparing the use of BMC and platelet-rich plasma to exercise therapy for treating rotator cuff tears. Patient-reported outcome measures (PROMs), including DASH, NPS, and a modified Single Assessment Numeric Evaluation (SANE), showed continued improvement for both the BMC treatment and crossover groups throughout the 24-month follow-up (p = 0.06). In the BMC group, 40 out of 44 patients met or exceeded the minimal clinically important difference (MCID) for DASH and NPS, while 41 out of 44 exceeded the SANE MCID. Long-term PROMs from a patient registry indicated sustained positive outcomes beyond the 2-year follow-up. Overall, BMC with platelet injections significantly improved PROMs, with effects lasting through the 2-year study period.

Mautner et al. (2023) conducted a multi-center, randomized, controlled phase III trial to evaluate the efficacy of stem cell injections compared to corticosteroid injections for the treatment of knee OA. The study enrolled 480 patients across multiple United States sites and compared three types of stem cell preparations: autologous bone marrow aspirate concentrate, autologous stromal vascular fraction, and allogenic human umbilical cord tissue derived mesenchymal stem cells. These were evaluated against the standard of care corticosteroid injection. Primary outcomes included changes in pain intensity measured by the VAS and functional improvement assessed by the Knee Injury and Osteoarthritis Outcome Score (KOOS) over a 12-month period. All treatment groups including the stem cell and corticosteroid arms demonstrated measurable improvements in pain and function. However, no statistically significant differences were observed between any of the stem cell groups and the corticosteroid group in either VAS or KOOS scores at the 12-month follow up period. Importantly, the study reported no serious treatment related adverse events across all groups, supporting the safety profile of both stem cell and corticosteroid injections. The authors concluded that while stem cell therapies may offer benefit, they did not demonstrate superiority over corticosteroids in reducing pain or improving function over one year. These findings reinforce the current view that stem cell and productions for knee OA remain investigational, and further research is needed to identify potential subgroups that may benefit from specific cell-based therapies.

Kim et al. (2023) conducted a phase III, double-blind, placebo-controlled trial to evaluate the evaluate the safety and effectiveness of autologous ADMSCs for knee OA. The trial involved 261 patients with K-L grade 3 symptomatic knee OA, with 125 receiving ADMSC injections and 127 in the control group. Primary outcomes, including pain (measured by VAS) and function (assessed by WOMAC), were evaluated at baseline, 3 months, and 6 months. At 6 months, the ADMSC group showed significant improvements in both VAS (p = 0.004) and WOMAC scores (p = 0.002) compared to the control group. There were no significant differences in radiologic outcomes or adverse events. Study limitations included the short 6-month follow-up and incomplete participation. While long-term data is needed to confirm the disease-modifying effects, ADMSC injections significantly improved pain and function in patients with knee OA.

Lee et al. (2019) conducted a phase IIb, randomized, double-blinded, placebo-controlled clinical trial to assess the effectiveness and safety of intra-articular injection of autologous ADMSCs. Twenty-four patients between 18 and 75 years of age with OA of the knee joint were enrolled in the study. Twelve patients were in the 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 WOMAC. Secondary measurements included the VAS for knee pain, OA 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

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improvements reported in the control group. In the MSC group, range of motion was significantly improved, from 127.9° ± 10.3° to 134.6° ± 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 ADMSCs in patients with osteoarthritic knees led to satisfactory clinical and functional improvement over six months of follow-up.

Centeno et al. (2018) conducted an RCT to evaluate Regenexx treatment for knee OA. Patients with symptomatic knee OA 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.

Systematic Reviews and Meta-Analyses

Rahyussalim et al. (2026) conducted a systematic review and meta-analysis to evaluate the safety and efficacy of intradiscal MSC therapy for chronic low-back pain attributable to degenerative disc disease. The review included 7 RCTs for a total of 594 participants. Five studies used saline placebo controls while two used sham injections with mepivacaine. Follow-up ranged from 3 to 42 months. MSC were predominantly allogeneic and bone-marrow derived and one study evaluated autologous bone marrow concentrate. Pain was assessed with the 0-100 VAS and disability with the 0-100% ODI, with higher scores indicating greater pain or disability. Across all 7 RCTs, MSC therapy produced a statistically greater VAS reduction for pain compared to sham/placebo (mean difference [MD], -6.67 points, 95% CI -9.31 to -4.02, p < 0.00001), I^2 = 29%). Differences in pain were not significant at 1, 3, or 6 months, but became significant at 12, (MD -9.82), 24 (MD -11.85), and 36 (MD -17.04) months. MSC participants were also more likely to achieve ≥ 30% pain reduction (odds ratio [OR] 1.82, 95% CI 1.43-2.33) and ≥ 50% pain reduction (OR 1.96, 95% CI 1.38-2.79. For functional disability, pooled ODI reduction favored MSC participants by 4.05 percentage points (95% CI -5.24 to -2.87, p < 0.00001, I^2 =32%), with significant differences beginning at 3 months and increasing through 36 months. However, the authors noted that the overall pooled -6.67-point VAS and -4.05-point ODI differences were below commonly cited minimal clinically important differences (15-20 for VAS and 10-15 for ODI), meaning that the statistically significant average effects may not represent substantial clinically significant improvement. Safety outcomes were not significantly different between MSC and sham/placebo groups, with an OR 1.07 (95% CI 0.64-1.77) for treatment-emergent adverse events, OR 0.58 (95% CI 0.18-1.91) for serious adverse events, and OR 1.42 (95% CI 0.28-7.19) for discontinuation due to adverse events. The authors noted inadequate reporting of participant/provider blinding and outcome-assessor blinding, which is important since VAS and ODI are subjective outcomes. The authors concluded that intradiscal MSC injections reduce pain and improve function in patients with chronic low-back pain due to degenerative disc disease and appear safe compared with sham or placebo.

Whittle et al. (2025) conducted a Cochrane systematic review to evaluate the efficacy and safety of stem cell injections for individuals with knee OA. The review included 25 randomized controlled trials involving a total of 1,342 participants. Of these, 8 trials (459 participants) compared stem cell injections to placebo, while 17 trials (882 participates) evaluated stem cells against other comparators such as glucocorticoid injections, exercise, or usual care. In the placebo-

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controlled trials, stem cell injections showed a small improvement in pain at three to six months post treatment, with a mean difference of 1.2 points and a 0-10 pain scale (95% CI: 0 to 2.5). Function also improved modestly, with the mean difference of 14.2 points on a scale 0-100 (95% CI: 3.1 to 25.3). However, these findings were rated as low certainty due to variability in stem cells source, preparation methods, and dosing, as well as suspected publication bias. Evidence for improvements in quality of life, global treatment success, and joint structure was rated very low certainty, and radio graphic progression was not assessed in any of the included studies. Safety data was limited, with serious adverse effects infrequently reported, and no consistent conclusions could be drawn regarding long-term risks. The authors concluded that, due to the low to very low certainty of evidence, stem cell injections for knee OA should be considered investigational.

Non-Randomized Studies, Retrospective Reviews, and Other Evidence
Hayes (2026) conducted a Health Technology Assessment to examine the effectiveness and safety of bone marrow-derived stem cells (BMSC) for treating knee OA, compared with placebo and minimally invasive therapies. The body of evidence was considered low quality. While BMSC treatment is reasonably safe compared to placebo, hyaluronic acid injections, or no treatment, there were inconsistent results in improving knee pain, function, and radiographically visible damage reported. The small sample sizes and differing BMSC protocols across studies contributed to the lack of consistent benefits reported. Additionally, only one study included follow-up beyond one year, leaving the long-term benefits of BMSC unknown. Further studies with extended follow-up periods and larger sample sizes are necessary to establish optimal treatment protocols and determine benefits of BMSC treatment.

National and Specialty Organizations

The **American Academy of Orthopaedic Surgeons (AAOS)** published evidence-based clinical practice guidelines for the treatment of OA of the hip and knee. The guidelines do not address SCT or provide recommendations regarding its use (AAOS 2021, 2023). Additionally, the AAOS published a clinical practice guideline on the management of glenohumeral joint OA. The AAOS stated that in the absence of reliable evidence, injectable biologics, such as stem cells, cannot be recommended for the treatment of glenohumeral joint OA. The panel reached a consensus that definitive evidence on the efficacy of biologics in glenohumeral OA requires improved standardization and high-quality clinical trial evidence (AAOS 2020). The AAOS also published a clinical practice guideline on the management of ankle OA. In the absence of sufficient evidence, the workgroup concluded by consensus that “there is no reliable evidence regarding intra-articular SCT for symptomatic ankle OA.” No studies that evaluated this treatment met the inclusion criteria, and its safety, efficacy optimal protocols, and appropriate patient selection cannot be determined (AAOS 2026).

The **American College of Rheumatology (ACR)** published updated guidelines on the management of hand, hip, and knee OA. The ACR strongly advises against stem cell injections in patients with knee and/or hip OA, citing a moderate certainty of evidence. The guidelines make no recommendations for SCT in patients with hand OA (ACR 2026).

The **International Society for Stem Cell Research (ISSCR)** published *Guidelines for Stem Cell Research and Clinical Translation (v.1.2).* The ISSCR states that for the vast majority of medical conditions there is insufficient evidence of safety and efficacy to justify routine or commercial use. Serious adverse events have been reported, and the long-term safety of most stem cell, cord blood, bone marrow, and other cell-based interventions, including MSC, remains undetermined. The ISSCR recommends that clinical use of unproven stem cell-based interventions be limited to well-regulated clinical trials and guideline compliant medical innovation. The routine clinical use of novel products should depend on substantial evidence of effectiveness from appropriately powered, well-controlled clinical trials (ISSCR 2025). In its *2024 Guide to Stem Cell Treatments*, the ISSCR advises patients to exercise caution regarding unproven stem cell treatments that have not undergone rigorous clinical testing or appropriate regulatory review and may result in physical, psychological, or financial harm (ISSCR 2024).

The **American Association of Hip and Knee Surgeons (AAHKS)** published a 2025 position statement on biologic therapies for advanced hip and knee OA. The AAHKS states that biologic therapies, including BMAC and MSC injections, “cannot currently be recommended for the routine treatment of advanced hip or knee OA.” The AAHKS notes that biologic injections have not been shown to restore cartilage in OA of the hip or knees, and that although intra-articular culture-expanded MSCs may provide mild improvement compared with placebo, MSCs derived from multiple tissue sources have not demonstrated superiority to corticosteroid injections for advanced knee OA. The AAHKS cites the lack of significant improvement over existing non-biologic therapies and high out-of-pocket costs and recommends further rigorous clinical trials to establish the safety, efficacy and cost-effectiveness of biologic treatments before any widespread adoption (AAHKS 2025).

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The **American Society of Interventional Pain Physicians (ASIPP)** published *Comprehensive Evidence-Based Guidelines for Regenerative Therapies in the Management of Chronic Low Back Pain* (Manchikanti et al. 2025). The authors rated the evidence for BMAC therapy as Level III (fair), with a moderate consensus-based clinical recommendation. The authors also rated MSC therapy as Level III (fair), with low to moderate certainty and a moderate strength of recommendation. For intra-articular facet joint injections with platelet-rich plasma and MSCs, the authors rated the evidence as Level IV (limited) with a moderate consensus-based clinical recommendation. The authors emphasize that regenerative medicine remains in the early stages of clinical validation and that the available evidence is limited by a "scarcity if high-quality studies," with many studies being small or heterogeneous.

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)

Code	Description
20999	Unlisted procedure, musculoskeletal system, general
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)
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
0627T	Percutaneous injection of allogeneic cellular and/or tissue-based product, intervertebral disc, unilateral or bilateral injection, with fluoroscopic guidance, lumbar; first level
0628T	Percutaneous injection of allogeneic cellular and/or tissue-based product, intervertebral disc, unilateral or bilateral injection, with fluoroscopic guidance, lumbar; each additional level (List separately in addition to code for primary procedure
0629T	Percutaneous injection of allogeneic cellular and/or tissue-based product, intervertebral disc, unilateral or bilateral injection, with CT guidance, lumbar; first level
0630T	Percutaneous injection of allogeneic cellular and/or tissue-based product, intervertebral disc, unilateral or bilateral injection, with CT guidance, lumbar; each additional level (List separately in addition to code for primary procedure)
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

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0737T	Xenograft implantation into the articular surface

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APPROVAL HISTORY

10/14/2026	Policy reviewed. No changes to coverage criteria. IRO peer reviewed on October 1, 2026 by a practicing physician board certified in orthopaedic surgery.
10/08/2025	Policy reviewed. No changes to coverage criteria.
10/09/2024	Policy reviewed. No changes to coverage criteria.
12/13/2023	Policy reviewed. No changes to coverage criteria.
12/14/2022	New policy. IRO Peer Review. Oct 28, 2022. Practicing physician board-certified in Orthopedic Surgery.

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