Medical Policy Manual

**Topic:** Orthopedic Applications of Stem Cell Therapy  
**Date of Origin:** September 29, 2011

**Section:** Medicine  
**Last Reviewed Date:** April 2017

**Policy No:** 142  
**Effective Date:** May 1, 2017

**IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

**DESCRIPTION**

Mesenchymal stem cells (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. Potential uses of MSCs for orthopedic applications include treatment of damaged bone, cartilage, ligaments, tendons, and intervertebral discs.

**Background**

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. 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. Given that each tissue type requires different culture conditions, induction factors (e.g., signaling proteins, cytokines, growth factors), and implantation techniques, each preparation must be individually examined. The ability to induce cell division and differentiation, without adverse effects such as the formation of neoplasms, remains a significant concern.

The U.S. Food and Drug Administration (FDA) stated:

“Cell-based therapies are one of the most rapidly advancing approaches intended to repair, replace, restore, or regenerate cells, tissues and organs. They can be applied to damage caused by disease, injury, or aging. Many cell-based therapies use immature cells (stem cells) that are expanded outside of the body. The expanded cells are sometimes used in their immature state, but they are often manufactured into more mature cells before they are given to a patient. The resulting cells are intended to repair cell or tissue damage (efficacy) without unintended serious consequences such as tumors, severe immune reactions, or unwanted tissue development (safety). Manufacturing of large numbers of cells outside the natural environment of the human body may lead to ineffective or dangerous cells, so it is important to understand and carefully control the production process and to define measures that reliably predict safety and efficacy of the cell-based products.”[2]

**Regulatory Status**

Concentrated autologous MSCs do not require approval by the U.S. Food and Drug Administration (FDA).

Demineralized bone matrix (DBM), which is processed allograft bone, is considered minimally processed tissue and does not require FDA approval. At least 4 commercially available DBM products are reported to contain viable stem cells:

- **Allostem®** (AlloSource) is partially demineralized allograft bone seeded with adipose-derived MSCs
- **Map3™** (RTI surgical) contains cortical cancellous bone chips, DBM, and multipotent adult progenitor cells
- **Osteocell Plus®** (NuVasive): an allograft cellular bone matrix containing native MSCs.
- **Trinity Evolution Matrix™** (Orthofix): an allograft that is processed and cryopreserved to maintain viable adult MSCs and osteoprogenitor cells.

Whether these products can be considered minimally manipulated tissue is debated. A product would not meet the criteria for FDA regulation part 1271.10 if it is dependent upon the metabolic activity of living cells for its primary function. Otherwise, a product would be considered a biologic product and would need to demonstrate safety and efficacy for the product’s intended use with an investigational new drug and Biologics License Application (BLA).

Other products contain DBM and are designed to be mixed with bone marrow aspirate. Some of the products that are currently available are:
• Fusion Flex™ (Wright Medical): a dehydrated moldable DBM scaffold that will absorb autologous bone marrow aspirate.
• Ignite® (Wright Medical): an injectable graft with DBM that can be combined with autologous bone marrow aspirate.

Other commercially available products are intended to be mixed with bone marrow aspirate and have received 510(k) clearance, such as:

• CopiOs sponge or paste (Zimmer): synthetic bone graft material consisting of mineralized, lyophilized collagen.
• Collage™ Putty (Orthofix): Composed of type-1 bovine collagen and beta Tri-calcium phosphate.
• Vitoss® (Stryker, developed by Orthovita): composed of beta tricalcium phosphate.
• nanOss® Bioactive (RTI Surgical, developed by Pioneer Surgical): nanostructured hydroxyapatite and an open structured engineered collagen carrier.

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

In 2008, the FDA 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. In 2014, a federal appellate court upheld FDA’s power 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 (HCT/Ps) (Section 351).[3] To date, no NDA or BLA has been approved by the FDA for this product. As of 2015, the expanded stem cell procedure is only offered in the Cayman Islands. Regenexx™ network facilities in the U.S. provide same-day stem cell and blood platelet procedures, which do not require FDA approval.[4]

**MEDICAL POLICY CRITERIA**

I. Mesenchymal stem cell therapy is considered investigational for all orthopedic applications, including but not limited to use in repair or regeneration of musculoskeletal tissue.

II. Allograft bone products containing viable stem cells is considered investigational for all orthopedic applications, including but not limited to demineralized bone matrix (DBM) with stem cells.

**SCIENTIFIC EVIDENCE**

**Literature Appraisal**

At this time, the literature consists mainly of articles describing the potential of stem cell therapy for orthopedic applications in humans, along with basic science experiments on sources of mesenchymal stem cells (MSCs), regulation of cell growth and differentiation, and development of scaffolds.[5] Although the evidence base has been steadily increasing, authors indicate that the technology is in an
early stage of development. In order to assess the safety and efficacy of orthopedic applications of MSCs and allograft bone products, such as demineralized bone matrix, high quality randomized trials are required that compare health outcomes with versus without the use of these products.

**Cartilage Defects**

In 2015, Xu et al. published a meta-analysis on the effect of MSCs for articular cartilage degeneration treatment, including 11 controlled trials (N=558). No critical appraisal of the quality of the included studies was reported. MSC treatment significantly improved the American Orthopedic Foot and Ankle Society Scale (Standard Mean Difference [SMD] 0.91; 95% confidence interval [CI], 0.52 to 1.29) and the Osteo-Arthritis Outcome Score (SMD, 2.81; 95% CI, 2.02 to 3.60). Comprehensive evaluation indexes, such as the American Knee Society Knee Score System (SMD -0.12, 95% CI, -1.02 to 0.78), the Hospital for Special Surgery Knee Rating Scale (SMD, 0.24, 95% CI, -0.56 to 1.05) and the International Knee Documentation Committee (SMD, -0.21; 95% CI, -0.77 to 0.34), were no different between MSC use and other treatments. The reviewers concluded that there was no obvious advantage regarding the application of stem cells to treat cartilage injury, compared with other treatments.

In 2013, Filardo et al. conducted a systematic review of mesenchymal stem cells for the treatment of cartilage lesions. They identified 72 preclinical papers and 18 clinical reports. Of the 18 clinical reports, none were randomized, 5 were comparative, 6 were case series, and 7 were case reports. In 2 clinical studies the source of MSCs was adipose tissue, in 5 it was bone marrow concentrate, and in 11 studies the source of MSCs was bone marrow-derived. The authors reached the following conclusion:

“Despite the growing interest in this biological approach for cartilage regeneration, knowledge on this topic is still preliminary, as shown by the prevalence of preclinical studies and the presence of low-quality clinical studies. Many aspects have to be optimized, and randomized controlled trials are needed to support the potential of this biological treatment for cartilage repair and to evaluate advantages and disadvantages with respect to the available treatments.”

The source of MSCs may have an impact on outcomes, but this is not well understood and the available literature uses multiple different sources of MSC. Because of the uncertainty over whether these products are equivalent, the summary of the key evidence to date is grouped by source of MSC.

**Cartilage Defects: MSCs Expanded From Bone Marrow**

Since the systematic review by Filardo et al. one RCT was published. Wong et al. reported on the use of cultured MSCs in 56 patients with osteoarthritis who underwent medial opening-wedge high tibial osteotomy and microfracture of a cartilage lesion. Bone marrow was harvested at the time of microfracture and the MSCs were isolated and cultured. After 3 weeks, the cells were assessed for viability and delivered to the clinic, where patients received an intra-articular injection of MSCs suspended in hyaluronic acid (HA) or, for controls, intra-articular injection of HA alone. The primary outcome was the International Knee Documentation Committee (IKDC) score at 6 months, 1 year, and 2 years. Secondary outcomes were the Tegner and Lysholm scores through 2 years and the Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) scoring system by MRI at 1 year. All patients completed the 2-year follow-up. After adjusting for age, baseline scores, and time of evaluation, the group treated with MSCs showed significantly better scores on the IKDC (mean difference, 7.65 on 0-100 scale; p=0.001), Lysholm (mean difference, 7.61 on 0-100 scale; p=0.02), and Tegner (mean difference, 0.64 on a 0-10 scale; p=0.02). Blinded analysis of MRI results found higher MOCART scores in the MSC group. The group treated with MSCs had a higher proportion of patients who had
complete cartilage coverage of their lesions (32% vs 0%), greater than 50% cartilage cover (36% vs 14%) and complete integration of the regenerated cartilage (61% vs 14%). This study is ongoing and recruiting additional patients.

**Cartilage Defects: MSCs Concentrated From Bone Marrow**

A small RCT was recently published by Vega et al. that assessed the efficacy of bone marrow derived MSCs as a treatment for knee osteoarthritis, randomizing 30 patients with chronic knee pain unresponsive to conservative treatments and showing radiological evidence of osteoarthritis.[9] Fifteen patients were treated with allogeneic bone marrow MSCs by intra-articular injection, while 15 controls received intra-articular hyaluronic acid (HA). Clinical outcomes were followed for 1 year and included evaluations of pain, disability, and quality of life. Articular cartilage quality was assessed by quantitative magnetic resonance imaging T2 mapping. The MSC-treated patients displayed significant improvement in algofunctional indices versus the active controls. Quantification of cartilage quality by T2 relaxation measurements showed a significant decrease in poor cartilage areas, with cartilage quality improvements in MSC-treated patients.

Centeno et al reported a multicenter registry of patients treated with autologous stem cells, bone marrow concentrate, and platelet-rich plasma.[10] This report focused on 102 patients (115 shoulders) diagnosed with either osteoarthritis of the shoulder or rotator cuff tears. Patients were treated with a protocol that included a hypertonic dextrose solution (prolotherapy) injection to create an inflammatory response several days prior to the bone marrow concentrate injection. The bone marrow concentrate injection included platelet-rich plasma and platelet lysate. Both DASH (Disabilities of the Arm, Shoulder, and Hand) score and numeric pain scores (NPS) decreased by about 50%, although the absolute decrease in the NPS was a very modest 0.9. Interpretation of these results is limited by the lack of a placebo control and blinding, subjective outcome measures, and the multiple treatments used, although it is acknowledged that neither prolotherapy nor PRP appear to have efficacy on their own. Additional study with randomized and placebo-controlled trials is needed to evaluate this treatment protocol.

**Cartilage Defects: Adipose-Derived MSCs**

The literature on adipose-derived MSCs for articular cartilage repair is very limited, coming from two research groups in Korea. One of the groups appears to have been providing this treatment as an option for patients for a number of years and recently published a RCT that evaluated cartilage healing after high tibial osteotomy (HTO) in 52 patients with osteoarthritis of the medial compartment.[11] Patients were randomly assigned to HTO with application of platelet-rich plasma (PRP) or HTO with application of PRP plus MSCs. MSCs from adipose tissue were obtained through liposuction from the buttocks. The tissue was centrifuged and the stromal vascular fraction mixed with PRP for injection. A total of 44 patients completed second look arthroscopy and 1- and 2-year clinical follow-up. There were statistically significant differences for PRP only versus PRP+MSC on the Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales for pain (74±5.7 vs 81.2±6.9, p<0.001) and symptoms (75.4±8.5 vs 82.8±7.2, p=0.006). There were also statistically significant differences on the final pain score for the PRP only versus PRP+MSC groups (16.2±4.6 vs 10.2±5.7, p<0.001), but the Lysholm score, which is more scientifically proven, was not significantly different between the PRP only and PRP+MSC groups (80.6±13.5 vs 84.7±16.2, all respectively, p=0.36). Articular cartilage healing was rated as improved with MSCs following video review of second-look arthroscopy; blinding of this measure is unclear. There are a number of limitations of this study, including the small sample size, short duration of follow-up, and significant improvements on only some of the outcomes. All of the significant
differences in outcomes were modest in magnitude, and as a result, there is uncertainty regarding the clinical significance of the findings.

This group also published a trial comparing treatment with adipose-derived MSCs, fibrin glue, and microfracture to microfracture alone.[12] A total of 80 patients with a single International Cartilage Repair Society grade III/IV symptomatic cartilage defect on the femoral condyle were randomized to receive one of the treatments. The mean follow-up time was 27.4 months. At follow-up, the MSC + fibrin glue + microfracture group had significantly greater improvements in the Knee Injury and Osteoarthritis Outcome Score pain and symptom subscores than the microfracture alone group (P = .034 and .005, respectively). There were no significant differences between groups for the activities of daily living, sports and recreation, or quality of live subscores. Second-look arthroscopies were performed in 57 of the 80 patients, with no significant differences between groups. The lack of blinding in this study limits the conclusions that can be drawn from its results.

The remaining evidence is limited to reports on 3 small retrospective analyses from the same investigators, two for focal osteochondral lesions of the ankle[13,14] and one for post-debridement knee osteoarthritis[15], and a small phase I trial for severe osteoarthritis.[16] Due to methodological limitations, these studies do not permit conclusions about the effectiveness and safety of adipose-derived MSCs. These limitations include small sample size, the lack of randomized treatment allocation, and the lack of prospective comparison of outcomes.

Cartilage Defects: MSCs from Peripheral Blood

A 2013 report described a small randomized controlled trial with autologous peripheral blood MSCs for focal articular cartilage lesions.[17] Fifty patients with grade 3 and 4 lesions of the knee joint underwent arthroscopic subchondral drilling followed by 5 weekly injections of hyaluronic acid (HA). 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 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, HA 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 (p=.022) higher histological scores (by about 10%) for the MSC group (1,066 vs. 957 by independent observers) while blinded evaluation of MRI showed a statistically significant (p=.013) 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: MSCs from Synovial Tissue

Akgun et al. reported a small (n=14) investigator-blinded RCT that compared matrix-induced autologous MSCs from synovial tissue versus matrix-induced autologous chondrocyte implantation (MACI).[18] Both chondrocytes from cartilage and MSCs from synovia were harvested in an arthroscopic procedure, expanded in culture, and then cultured on a collagen membrane for two days. Implantation was performed with the cells facing the subchondral bone. Follow up evaluations were made through 24 months post-procedure. Outcomes on the KOOS subscales and the VAS pain score were statistically better in the MSC group than the MACI group (p < 0.05) at the six month follow up, although it is not clear if the difference observed would be considered clinically significant. Studies with larger samples
sizes and follow-up supported by histological analyses are necessary to determine long-term outcomes of this treatment.

Conclusion

The evidence base on MSCs for repair of cartilage defects is limited to four small randomized studies and a number of small case series in which a variety of methods of MSC preparation were used. All four randomized studies reported an improvement in histological and morphologic outcomes, despite being harvested from different sources and compared against different control treatments. Three of these studies also reported an improvement in functional outcomes, although these varied between studies. In the RCT which found no improvement functional outcomes, peripheral blood stem cells were harvested following stimulation with recombinant human granulocyte colony-stimulating factor. The literature on adipose-derived MSCs includes a phase 1/2 study with cultured MSCs and a small RCT from a separate group in Asia that has been using uncultured MSCs as an adjunctive procedure in clinical practice. Comparisons between patients who have and have not received uncultured adipose-derived MSCs shows modest improvement in health outcomes that are of uncertain clinical significance. Potential for bias from non-blinded use of a novel procedure on subjective outcome measures is a major limitation of these studies. The phase I/II study of cultured MSCs from adipose tissue shows promising results for this technology. Additional studies in larger cohorts with longer follow-up is needed to evaluate the long-term efficacy and safety of the procedure.

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. Eastlack et al. reported outcomes from a series of 182 patients who were treated with anterior cervical discectomy and fusion using Osteocel Plus in a PEEK cage and anterior plating. At 24 months, 74% of patients (180/249 levels treated) were available for follow-up. These patients had significant improvements in clinical outcomes; 87% of levels achieved solid bridging and 92% of levels had range of motion less than 3°. With 26% loss to follow-up at 24 months and lack of a standard of care control group, interpretation of these results is limited. One retrospective series from 2009 was identified on the use of Trinity MSC bone allograft for revision surgery of the foot and ankle. 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%). However, these outcomes do not permit conclusions because of a lack of a control group for comparison with patients who received stem-cell therapy.

Conclusion

Current evidence is insufficient to determine whether the use of stem cell results in superior outcomes such as higher fusion rates, or lower rates of reoperations and adverse events.

Meniscectomy

In 2014, Vangsness et al. reported an industry-sponsored phase 1/2 randomized, double-blind, multicenter study of cultured allogeneic MSCs (Chondrogen™, Osiris Therapeutics) injected into the knee after partial meniscectomy. The 55 patients were randomized to intra-articular injection of either 50’106 allogeneic MSCs, 150’106 allogeneic MSCs in HA, or HA vehicle control at 7 to 10 days after meniscectomy. The cultured MSCs were derived from bone-marrow aspirates from unrelated donors. At
2-year follow-up, 3 patients in the low-dose MSC group had significantly increased meniscal volume measured by MRI (with an a priori determined threshold of at least 15%) compared to none in the control group and none in the high-dose MSC group. There was no significant difference between the groups in the Lysholm Knee Scale. On subgroup analysis, patients with osteoarthritis who received MSCs had a significantly greater reduction in pain at 2 years compared with patients who received HA alone. This appears to be a post hoc analysis and should be considered preliminary. No serious adverse events were thought to be related to the investigational treatment.

Conclusion

Current evidence for the use of stem cells as an adjunct to meniscectomy is limited to a single preliminary RCT. The outcomes of this study must be validated in large, long-term, randomized controlled trials.

Osteonecrosis

Two randomized comparative trials 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 (CD) alone. At 60 months after surgery, 2 of the 53 hips (3.7%) treated with MSCs continued to have progressive disease and underwent vascularized bone grafting, compared with 10 of 44 hips (23%) in the decompression group who had disease progression and underwent either vascularized bone grafting (n=5) or total hip replacement (n=5). In addition, treatment with MSC improved Harris Hip scores compared to CD and decreased the volume of the necrotic lesion of the hips preoperatively classified at stage IC, IIB, and IIC (P<0.05, respectively; stage IIA, P=0.06, respectively).

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. Blinding of assessments in this small trial was not described. Harris Hip Score (HHS) was significantly improved in the MSC group (scores of 83.65 and 82.42; p<0.05) 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 with the core decompression group (mean of 46.7 weeks). There were no significant differences between the groups in the radiographic assessment or MRI results. The conflicting report of improvement via HHS compared to no observable improvement via MRI, may point to the need for study blinding to control for confounding bias toward treatment.

Conclusion

Two small studies reported improvement in the Harris Hip Score in patients with osteonecrosis of the femoral head treated with core decompression and MSCs, although it was not reported if 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 with 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.

**Clinical Practice Guidelines**

Currently, there are no clinical practice guidelines from US professional societies that address the use of stem cells in orthopedics.

**American Association of Orthopaedic Surgeons (AAOS)**

An informational statement from the 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.[24]

**Summary**

There is not enough research to know if or how well mesenchymal stem cells (MSCs) work to treat people with orthopedic conditions. This does not mean that it does not work, but more research is needed to know. No clinical guidelines based on research recommend MSC treatment for people with orthopedic conditions. Therefore, use of stem cells for orthopedic applications is considered investigational.

**REFERENCES**

8. Wong, KL, Lee, KB, Tai, BC, Law, P, Lee, EH, Hui, JH. Injectable cultured bone marrow-derived mesenchymal stem cells in varus knees with cartilage defects undergoing high tibial


**CROSS REFERENCES**

Autologous Blood-Derived Growth Factors as a Treatment for Wound Healing and Other Conditions, Medicine, Policy No. 77

Progenitor Cell Therapy for the Treatment of Damaged Myocardium Due to Ischemia, Medicine, Policy No. 100

Stem-cell Therapy for Peripheral Arterial Disease, Medicine, Policy No. 141

Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions, Surgery, Policy No. 87

**CODES | NUMBER | DESCRIPTION**

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There are no specific codes for orthopedic applications of stem cell therapy. The appropriate CPT code for reporting this procedure is 20999, or the code for an unlisted procedure of the body area on which the procedure is performed.
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