


MEDICAL POLICY		Stem Cell Therapy for Orthopedic Applications	
Effective Date: 2/1/2021		Section: MED	Policy No: 346
 <div style="text-align: right;">2/1/2021</div>		Medical Policy Committee Approved Date: 11/18; 11/19; 1/2021	
Medical Officer	Date		

See Policy CPT/HCPCS CODE section below for any prior authorization requirements

SCOPE:

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:

All lines of business

BENEFIT APPLICATION

Medicaid Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

POLICY CRITERIA

- I. Mesenchymal stem cell therapy (e.g., Regenxx, Stravix®) is considered **investigational and not covered** 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.
- II. Allograft bone products containing viable stem cells, including but not limited to demineralized bone matrix (DBM) with stem cells (e.g., BIO4®, OSTEOCEL® Plus, OSTEOCEL® Pro, OsteoVive™, Trinity Evolution®, Trinity ELITE®, VIA® Form, VIA® Graft, ViviGen®) are considered **investigational and not covered** for all orthopedic applications.

Link to [Policy Summary](#)

BILLING GUIDELINES

There are no specific codes for orthopedic applications of stem cell therapy. The appropriate CPT code for reporting this procedure would be the code for an unlisted procedure of the body area on which the procedure is performed. Therefore, the unlisted codes below may not be all-inclusive.

The additional codes listed on this policy are not appropriate when billed for stem cell therapies for orthopedic applications and are considered investigational per the policy criteria.

CPT/HCPCS CODES

All Lines of Business	
<p>Prior Authorization Required</p> <p>Note: The following codes listed on this policy are not appropriate when billed for stem cell therapies for orthopedic applications and are therefore, considered investigational if used for these applications.</p>	
20939	Bone marrow aspiration for bone grafting, spine surgery only, through separate skin or fascial incision
38205	Blood derived hematopoietic progenitor cell harvesting for transplantation, per collection allogeneic
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
<p>Not Covered</p>	
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
<p>Unlisted Codes</p> <p>All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then it will be denied as not covered.</p>	
20999	Unlisted procedure, musculoskeletal system, general
29999	Unlisted procedure, arthroscopy

DESCRIPTION

Stem cells have the potential to differentiate into the types of cells needed to many different types of tissues. Specifically, mesenchymal stem cells (MSCs) are stem cells that have the ability to differentiate into tissues important for repair of orthopedic injuries, including bone, cartilage, tendon and fat. When signaled to form bone, MSCs differentiate into osteoprogenitor cells and then into bone-forming osteoblast cells. However, like all stem cells, MSCs require requires special microenvironments or conditions to promote their differentiation, such as a particular layer of tissue for cell adherence or specific signals from surrounding cells.

Stem cells used for treatment of various orthopedic indications can be harvested from a variety of tissues, including but not limited to bone marrow, adipose tissue, peripheral blood, synovial or amniotic fluid. Most patients are treated with their own stem cells (autologous stem cells) but cells obtained from unrelated donors (allogeneic stem cells) may also be used. Use of allogeneic stem cells avoids the need for harvesting and processing cells from each patient but increases the risk of an immunological reaction that could destroy native cells or cause tissue rejection.

After harvesting of cells from selected tissue, the cells may either be directly injected into affected tissues, including but not limited to joints or spinal discs. The cells may be injected alone or in combination with materials such as hyaluronic acid (HA) that increase joint lubrication or fibrin glue that promotes localized adherence of the cells to damaged joint. Some protocols involve culturing of stem cells prior to injection to increase the number of cells available for injection. However, this may reduce the pluripotency of the cells, making it less likely for them to mature into the desired cell type.

In addition, once MSCs are cultured, they can be mixed with biomaterials, including but not limited to demineralized bone matrix (DBM) to hold the cells in suspension and provide a matrix for filling defects. MSCs can also be seeded on scaffolds made of biomaterials. These types of products are referred to as allograft bone products or cell-based bone graft substitutes.

There are a number of stem-cell containing products that are available to orthopedic applications. Some of examples of these include:

- Mesenchymal stem cell (MSC) therapy:
 - Regenexx® Stem Cell (Regenexx)¹: This procedure uses autologous MSCs from bone marrow concentrate, injected using image guidance, to treat defects/injuries of the knee, hip, shoulder spine, elbow, hand/wrist, and foot-ankle.
 - Stravix® (Osiris Therapeutics, Inc.)²: This product is cryopreserved human placental tissue composed of umbilical amnion and Wharton's jelly that contain MSCs. It is designed to be used as a surgical covering or wrap for various procedures (e.g., tendon repair, Achilles tendon rupture, bunionectomy, hallux rigidus correction, foot amputations, fibromatosis, and arthrodesis).

- Allograft bone products containing viable stem cells:
 - BIO® (Osiris Therapeutics, Inc.)³: This product is referred to as a viable bone matrix containing MSCs to be implanted surgically for orthopedic procedures on the shoulder, elbow, hand/wrist, hip, pelvis, femur, tibia/fibula, or foot/ankle.
 - map3® (RTI Surgical): This product is currently being researched as a cellular allogeneic bone graft composed of cortical-cancellous bone, demineralized bone matrix (DBM), and cryogenically preserved viable MSCs.⁴
 - Osteocele® Plus and Osteocele® Pro (Nuvasive®)⁵: These bone grafts contain allogeneic MSCs and are marketed as bone graft substitutes for use in spinal surgery.
 - OsteoVive™ (Xtant Medical)⁶: This product is a viable cell allograft that contains MSCs derived from the vertebral body region as well as a demineralized bone component. This product is intended for use in bone remodeling.
 - Trinity Evolution® and Trinity ELITE® (Orthofix®)⁷: These cancellous bone allografts contain viable adult MSCs and are intended for the treatment of musculoskeletal defects.
 - VIA® Form and VIA® Graft (Vivex Biomedical)⁸: This is a family of products referred to as “cellular bone matrices” which are viable allogeneic bone allografts with MSC and bone components. These products are intended for use in bone remodeling in a number of applications including spine, upper extremity, foot/ankle, oral/maxillofacial and orthopedic oncology.
 - ViviGen® (DePuy)⁹: This product is a cellular bone matrix is comprised of cryopreserved viable cortical cancellous bone matrix and demineralized bone. ViviGen® is intended for repair or reconstruction of musculoskeletal defects.

REVIEW OF EVIDENCE

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of MSC therapy and allograft bone products containing viable stem cells as treatments for all orthopedic indications. Below is a summary of the available evidence identified through November 2020.

Mesenchymal Stem Cell (MSC) Therapy

Due to the volume of literature on MSC therapy as a treatment for a wide variety of conditions, the evidence review is focused on recent systematic reviews. The use of MSC therapy has been recently evaluated by systematic reviews for the following orthopedic indications:

- Bone healing (non-union or delayed union)¹⁰
- Chondral defects (e.g., ankle, elbow, hip, knee, leg)^{10,11}
- Osteoarthritis and Other Degenerative Conditions:
 - Osteoarthritis of the ankle^{12,13}
 - Osteoarthritis of the carpometacarpal joint^{12,14}
 - Osteoarthritis of the hip¹²
 - Osteoarthritis of the knee^{10,12,14-29}
 - Osteoarthritis of the shoulder¹²
 - Osteonecrosis of the knee¹⁵
 - Osteonecrosis of the hip³⁰⁻³⁷

- Rheumatoid arthritis of the knee¹⁵
- Osteochondral lesions of the:
 - knee^{10,11}
 - talus^{10,14,18}
- Osteochondritis dissecans of the knee¹¹
- Other knee indications (e.g., pain from anterior cruciate ligament or meniscus repair, knee cartilage defects, meniscal tears)^{15,18,38}
- Spinal disc disorders (e.g., lumbar disc disease)^{15,39}
- Tendinopathies:
 - Achilles tendinopathy or tendinosis^{10,40}
 - Lateral epicondylitis^{40,41}
 - Patellar tendinopathy⁴¹
 - Rotator cuff injury^{10,15,40,41}

Systematic reviews were heterogeneous in the methods used to examine primary studies evaluating stem cell therapy, and several concluded the methods of the studies that they reviewed were too heterogeneous for meaningful conclusions. Many reviews included or focused entirely on nonrandomized studies, and many included more than one indication. Reviews that did include RCTs reported that the majority of trials were not blinded, and that randomization methods were questionable. However, in general, the reviews reported differences in treatment protocols related to number of stem cells injected, use of autologous versus allogeneic stem cells, use of freshly-isolated versus cultured stem cells, and use of stem cells from varying sources (e.g., bone marrow, adipose tissue, or peripheral blood). Reviews published on the same indication often included studies with patient cohorts of varied stages/severity of disease. All reviews mentioned the need for larger, better-quality studies with longer-term follow-up. The majority of recent reviews were unable to draw definitive conclusions regarding the efficacy of stem therapy as a treatment for any indication.

Overall, the body of evidence for any given indication suffers from one or more of the following limitations:

- extremely limited number of randomized controlled trials (RCTs) reporting outcomes for any given indication
- primary studies, including very small numbers of RCTs, were of low- to very-low quality of due to methodological limitations including:
 - small sample size (under 100 patients)
 - insufficient statistical power or lack of a power analysis
 - lack of or incomplete blinding
 - high rate of attrition
 - primary outcomes reported consisted mostly of subjective, patient-reported outcomes
 - differences in the surgeries and co-interventions that accompanied stem cell therapy
 - insufficient statistical analysis of differences between groups
 - inadequate follow-up
 - heterogeneity of:
 - comparator treatment
 - primary outcomes reported

- evaluation of stem cell therapy as a stand-alone treatment or as an adjunct to a variety of treatments
- conflicting or no evidence of short-term improvements in pain and/or function (first few months following treatment) when alternate treatments
- no evidence on long-term outcomes, including function or pain outcomes

Allograft Bone Products Containing Viable Stem Cells

No systematic reviews or randomized controlled trials (RCTs) were identified that evaluated the efficacy of allograft bone products containing viable stem cells for any orthopedic indication. Below is a summary of nonrandomized studies, grouped by product.

OsteoCel and OsteoCel Plus (Nuvasive®)

Only one comparative study was identified that compared OsteoCel to standard allograft for use in anterior cervical discectomy and fusion procedures.⁴² This was a retrospective study (n=114) that reported that radiologic fusion rates at 12-months post-procedure were not significantly different between treatment groups.

Uncontrolled studies have been published that evaluated the use of OsteoCel or OsteoCel Plus in different procedures, including:

- lumbar spinal fusion⁴³
- anterior cervical discectomy and fusion⁴⁴
- minimally invasive instrumented transforaminal lumbar interbody fusion (MITLIF)⁴⁵
- extreme lateral interbody fusion (XLIF)⁴⁶
- foot and ankle fusions⁴⁷

However, the majority of these studies were small in sample size (52 patients or less) and reported short-term follow-up (5-12 months). In addition, half of these studies were retrospective in study design.

ViviGen® (DePuy)

One small (n=21) retrospective case series reported on the use of ViviGen during cervical spinal fusions.⁴⁸ This series included a heterogeneous patient population, as patients included those who either underwent either three- or four-level anterior cervical discectomy and fusion, anterior cervical corpectomy and fusion, or posterior cervical fusion. In addition, only six-month follow up was reported.

map3® Cellular Allogeneic Bone Graft (RTI Surgical)

One small retrospective chart review of 41 patients treated via anterior lumbar interbody fusion (ALIF) with either map3® or recombinant human BMP-2 (rhBMP-2) growth factor reported one-year outcomes.⁴ Both of these treatments were evaluated as potential alternatives to conventional iliac crest autograft. The overall fusion rate was 91% and was similar between groups. Improvements in ODI and

VAS were observed among all patients with no significant difference between groups. There was no significant difference in terms of changes to disc height and lordosis between groups.

Trinity Evolution® and Trinity ELITE® (Orthofix®)

Only one comparative study was identified that compared the Trinity Evolution® to standard allograft for use in patients undergoing single-level anterior cervical discectomy and fusion for symptomatic cervical degenerative disc disease.⁴⁹ This was a small study of 31 patients who underwent the procedure using the Trinity bone allograft and the comparator group was historical matched controls. Self-reported pain and function outcomes, as well as fusion rates, were at 12-months post-procedure. Due to the small number of patients, additional larger studies are needed to determine the efficacy of the product.

One small (n=40) uncontrolled study, published by the same authors, evaluated the Trinity Evolution® for use in patients undergoing two-level anterior cervical discectomy and fusion.⁵⁰ At 12-month follow-up, this study reported improved self-reported pain and function outcomes compared to baseline and high rates of fusion. A lack of a comparator treatment makes the benefit of this product difficult to assess.

Evidence Summary for Allograft Bone Products Containing Viable Stem Cells

Overall, there is a paucity of studies evaluating the efficacy of allograft bone products containing viable stem cells. The overall body of evidence for these products consists mainly of small case series or poorly designed comparative studies. The available studies report relatively short follow-up (six months to two years) and focus primarily on self-reported measures of function and pain. Larger, well-designed comparative studies, preferably randomized trials, reporting longer-term follow-up are required in order to determine if the use of these products is as effective as conventional autografts or allograft products that do not contain stem cells, such as those containing conventional demineralized bone matrix.

CLINICAL PRACTICE GUIDELINES

Department of Veterans Affairs (VA)/Department of Defense (DoD)

In 2020, the VA/DoD published an evidence-based clinical practice guideline for the non-surgical management of hip and knee osteoarthritis. Investigators issued a “weak recommendation” against stem cell injections for the treatment of osteoarthritis of the knee.

American Society of Interventional Pain Physicians (ASIPP)

In 2019, the ASIPP published an evidence-based clinical practice guideline for the responsible, safe, and effective use of biologic therapy in the lumbar spine.⁵¹ Recommendations were graded based on Agency for Healthcare Research and Quality (AHRQ) practice. The guideline notes that MSC and platelet-rich plasma (PRP) injections are the mainstays of regenerative medicine for the lumbar spine. In their review of the evidence, the expert panel identified one high-quality RCT, multiple moderate-quality observational studies, a single-arm meta-analysis, and two systematic reviews regarding MSC therapy. With a qualitative modified approach to the grading of level of evidence, the expert was assessed as

Level III (on a scale of Level I through V). Level III evidence is *fair: evidence obtained from at least one relevant high quality nonrandomized trial or observational study with multiple moderate or low quality observational studies.*

American Academy of Orthopaedic Surgeons (AAOS)

The AAOS published evidence-based clinical practice guidelines on the management of osteoarthritis of the hip (2017) and the knee (2013).^{52,53} The association conducted evidence reviews of stem cell therapy versus other comparators for these indications, but did not identify enough high-quality evidence to formally address the treatment in their recommendations.

CENTERS FOR MEDICARE & MEDICAID

As of 11/29/2020, the Centers for Medicare & Medicaid (CMS) has published guidance for stem cell transplantation (National Coverage Determination (NCD) for Stem Cell Transplantation, 110.23).⁵⁴ However, this NCD does not specifically address stem cell therapy for musculoskeletal indications, and states:

“All other indications for stem cell transplantation not otherwise noted as covered or non-covered remain at local Medicare Administrative Contractor discretion.”

Neither Noridian nor Wisconsin Physicians Service has published guidance on stem cell therapies for orthopedic applications.

POLICY SUMMARY

There is insufficient evidence that the use of stem therapy, whether used alone or in conjunction with other biomaterials such as allograft bone product, is effective or consistently improves health outcomes for any orthopedic indication, including but not limited to degenerative and non-degenerative conditions of the hips or knees, spinal disc disorders, and tendinopathies. Interpreting results and drawing conclusions about treatment efficacy is difficult due to heterogeneity in stem cell therapy treatment protocol, including variability in the number of stem cells injected, use of freshly-isolated versus cultured stem cells, use of additional biomaterial, and use of stem cells from varying sources (e.g., bone marrow, adipose tissue, or peripheral blood). This limitation is consistently reported for the use of stem cell therapy for all orthopedic indications. Other major limitations of stem cell therapy observed across all indications include a lack of large, well-designed randomized controlled trials, and inconsistency in terms of whether or not stem cell therapy has a beneficial long-term effect. In addition, no clinical practice guidelines were identified that support the use of stem cell therapy as a treatment for any orthopedic indication.

INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed

annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

REGULATORY STATUS

Food and Drug Administration (FDA)

The FDA regulates “human cells or tissues intended for implantation, transplantation, infusion, or transfer into a human recipient” through the human cells, tissues, or cellular- or tissue-based products (HCT/P) process. The HCT/P process is in accordance with U.S. FDA requirements defined under 21 CFR Section 1271.3 regulations.⁵⁵ Products under HCT/P regulation do not require 510(k) clearance or premarket approval. However, the manufacturer must meet specific FDA regulations for the collection, processing, and selling of HCT/Ps.

Donated mesenchymal stem cells from various tissues and human bone products used for bone allografts containing stem cells are not subject to FDA clearance or approval.

Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

MEDICAL POLICY CROSS REFERENCES

- Stem Cell Transplantation (All Lines of Business Except Medicare), MED441
- Stem Cell Transplantation (Medicare Only), MED440
- Prolotherapy, MED311

REFERENCES

1. Regenexx Website. Updated: 2018. <https://www.regenexx.com/regenexx-procedures-family/the-regenexx-procedure-explained/>. Accessed 11/29/2020.
2. Osiris Therapeutics, Inc. Website. Graftix® cryopreserved placental membrane. Updated: 2018. <http://www.osiris.com/stravix/>. Accessed 11/29/2020.

3. Osiris Therapeutics, Inc. Website. BIO4® Viable Bone Matrix. Updated: 2018. <http://www.osiris.com/bio4/>. Accessed 11/29/2020.
4. Lee DD, Kim JY. A comparison of radiographic and clinical outcomes of anterior lumbar interbody fusion performed with either a cellular bone allograft containing multipotent adult progenitor cells or recombinant human bone morphogenetic protein-2. *J Orthop Surg Res*. 2017;12(1):126. <https://www.ncbi.nlm.nih.gov/pubmed/28841904>.
5. Nuvasive® website. OsteoCel® Patient Education Brochure. Updated:2017. <https://www.nuvasive.com/wp-content/uploads/2017/03/OsteoCel-Patient-Education-Brochure-US.pdf>. Accessed 11/29/2020.
6. Xtant Medical Website. OsteoVive™ Viable Cell Allograft brochure. . <https://xtantmedical.com/app/uploads/2016/09/OSTEOVIVE-Sell-Sheet.pdf>. Accessed 09/26/2018.
7. Orthofix® Website. Trinity Evolution® and Trinity ELITE product information. Updated: 2018. <http://web.orthofix.com/Products/Pages/Biologics.aspx>. Accessed 11/29/2020.
8. Vivex Biomedical Website. VIA® Cellular Bone Matrices product page. Updated 2018. <https://vivex.com/products/via/>. Accessed 11/29/2020.
9. DePuySynthes website. ViviGen® Cellular Bone Matrix product information. Updated: 06/28/2018. www.jnjmedicaldevices.com/en-US/product/vivigen-cellular-bone-matrix. Accessed 11/30/2020.
10. Gianakos AL, Sun L, Patel JN, Adams DM, Liporace FA. Clinical application of concentrated bone marrow aspirate in orthopaedics: A systematic review. *World J Orthop*. 2017;8(6):491-506. <https://www.ncbi.nlm.nih.gov/pubmed/28660142>.
11. Peeters CM, Leijts MJ, Reijman M, van Osch GJ, Bos PK. Safety of intra-articular cell-therapy with culture-expanded stem cells in humans: a systematic literature review. *Osteoarthritis Cartilage*. 2013;21(10):1465-1473. <https://www.ncbi.nlm.nih.gov/pubmed/23831631>.
12. Jevotovsky DS, Alfonso AR, Einhorn TA, Chiu ES. Osteoarthritis and stem cell therapy in humans: a systematic review. *Osteoarthritis Cartilage*. 2018;26(6):711-729. <https://www.ncbi.nlm.nih.gov/pubmed/29544858>.
13. Vannabouathong C, Del Fabbro G, Sales B, et al. Intra-articular Injections in the Treatment of Symptoms from Ankle Arthritis: A Systematic Review. *Foot Ankle Int*. 2018;1071100718779375. <https://www.ncbi.nlm.nih.gov/pubmed/29909689>.
14. Borakati A, Mafi R, Mafi P, Khan WS. A Systematic Review And Meta-Analysis of Clinical Trials of Mesenchymal Stem Cell Therapy for Cartilage Repair. *Curr Stem Cell Res Ther*. 2018;13(3):215-225. <https://www.ncbi.nlm.nih.gov/pubmed/28914207>.
15. Hayes Inc. Comparative Effectiveness Review. Stem Cell Therapy for Joint Pain. <https://evidence.hayesinc.com/report/dir.stemcelljoint4381>. Published 2018 (updated 2020). Accessed 11/29/2020.
16. Cui GH, Wang YY, Li CJ, Shi CH, Wang WS. Efficacy of mesenchymal stem cells in treating patients with osteoarthritis of the knee: A meta-analysis. *Exp Ther Med*. 2016;12(5):3390-3400. <https://www.ncbi.nlm.nih.gov/pubmed/27882169>.
17. Yubo M, Yanyan L, Li L, Tao S, Bo L, Lin C. Clinical efficacy and safety of mesenchymal stem cell transplantation for osteoarthritis treatment: A meta-analysis. *PLoS One*. 2017;12(4):e0175449. <https://www.ncbi.nlm.nih.gov/pubmed/28448518>.
18. Xu S, Liu H, Xie Y, Sang L, Liu J, Chen B. Effect of mesenchymal stromal cells for articular cartilage degeneration treatment: a meta-analysis. *Cytotherapy*. 2015;17(10):1342-1352. <https://www.ncbi.nlm.nih.gov/pubmed/26122717>.

19. Xia P, Wang X, Lin Q, Li X. Efficacy of mesenchymal stem cells injection for the management of knee osteoarthritis: a systematic review and meta-analysis. *Int Orthop*. 2015;39(12):2363-2372. <https://www.ncbi.nlm.nih.gov/pubmed/25944079>.
20. Pas HI, Winters M, Haisma HJ, Koenis MJ, Tol JL, Moen MH. Stem cell injections in knee osteoarthritis: a systematic review of the literature. *Br J Sports Med*. 2017;51(15):1125-1133. <https://www.ncbi.nlm.nih.gov/pubmed/28258177>.
21. Zhao L, Kaye AD, Abd-Elsayed A. Stem Cells for the Treatment of Knee Osteoarthritis: A Comprehensive Review. *Pain Physician*. 2018;21(3):229-242. <https://www.ncbi.nlm.nih.gov/pubmed/29871367>.
22. Iijima H, Isho T, Kuroki H, Takahashi M, Aoyama T. Effectiveness of mesenchymal stem cells for treating patients with knee osteoarthritis: a meta-analysis toward the establishment of effective regenerative rehabilitation. *NPJ Regenerative medicine*. 2018;3:15. <https://www.ncbi.nlm.nih.gov/pubmed/30245848>.
23. Xing D, Wang Q, Yang Z, et al. Mesenchymal stem cells injections for knee osteoarthritis: a systematic overview. *Rheumatology international*. 2018;38(8):1399-1411. <https://www.ncbi.nlm.nih.gov/pubmed/29273938>.
24. Kim SH, Ha CW, Park YB, Nam E, Lee JE, Lee HJ. Intra-articular injection of mesenchymal stem cells for clinical outcomes and cartilage repair in osteoarthritis of the knee: a meta-analysis of randomized controlled trials. *Arch Orthop Trauma Surg*. 2019;139(7):971-980. <https://www.ncbi.nlm.nih.gov/pubmed/30756165>.
25. Delanois RE, Etcheson JI, Sodhi N, et al. Biologic Therapies for the Treatment of Knee Osteoarthritis. *J Arthroplasty*. 2019;34(4):801-813. <https://www.ncbi.nlm.nih.gov/pubmed/30612835>.
26. Dai W, Leng X, Wang J, et al. Intra-articular Mesenchymal Stromal Cell Injections Are No Different From Placebo in the Treatment of Knee Osteoarthritis: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Arthroscopy*. 2020
27. Kim SH, Djaja YP, Park YB, Park JG, Ko YB, Ha CW. Intra-articular Injection of Culture-Expanded Mesenchymal Stem Cells Without Adjuvant Surgery in Knee Osteoarthritis: A Systematic Review and Meta-analysis. *Am J Sports Med*. 2020;48(11):2839-2849
28. Prodromos C, Finkle S, Rumschlag T, Lotus J. Autologous Mesenchymal Stem Cell Treatment is Consistently Effective for the Treatment of Knee Osteoarthritis: The Results of a Systematic Review of Treatment and Comparison to a Placebo Group. *Medicines (Basel)*. 2020;7(8)
29. Song Y, Zhang J, Xu H, et al. Mesenchymal stem cells in knee osteoarthritis treatment: A systematic review and meta-analysis. *J Orthop Translat*. 2020;24:121-130
30. Hayes Inc. Autologous Stem Cell Therapy for Treatment of Avascular Necrosis of the Hip. <https://evidence.hayesinc.com/report/dir.autologous3254>. Published 2015 (updated 2019). Accessed 11/29/2020.
31. Lau RL, Perruccio AV, Evans HM, Mahomed SR, Mahomed NN, Gandhi R. Stem cell therapy for the treatment of early stage avascular necrosis of the femoral head: a systematic review. *BMC Musculoskelet Disord*. 2014;15:156. <https://www.ncbi.nlm.nih.gov/pubmed/24886648>.
32. Li X, Xu X, Wu W. Comparison of bone marrow mesenchymal stem cells and core decompression in treatment of osteonecrosis of the femoral head: a meta-analysis. *Int J Clin Exp Pathol*. 2014;7(8):5024-5030. <https://www.ncbi.nlm.nih.gov/pubmed/25197374>.
33. Papakostidis C, Tosounidis TH, Jones E, Giannoudis PV. The role of "cell therapy" in osteonecrosis of the femoral head. A systematic review of the literature and meta-analysis of 7 studies. *Acta Orthop*. 2016;87(1):72-78. <https://www.ncbi.nlm.nih.gov/pubmed/26220203>.

34. Piuzzi NS, Chahla J, Jiandong H, et al. Analysis of cell therapies used in clinical trials for the treatment of osteonecrosis of the femoral head: a systematic review of the literature. *The Journal of arthroplasty*. 2017;32(8):2612-2618.<http://www.drpascualmd.com/pdf/joa-2017-analysis-cell-therapy-onfh.pdf>.
35. Piuzzi NS, Chahla J, Schrock JB, et al. Evidence for the use of cell-based therapy for the treatment of osteonecrosis of the femoral head: a systematic review of the literature. *The Journal of arthroplasty*. 2017;32(5):1698-1708
36. Xu S, Zhang L, Jin H, et al. Autologous Stem Cells Combined Core Decompression for Treatment of Avascular Necrosis of the Femoral Head: A Systematic Meta-Analysis. *Biomed Res Int*. 2017;2017:6136205.<https://www.ncbi.nlm.nih.gov/pubmed/28840126>.
37. Yuan HF, Zhang J, Guo CA, Yan ZQ. Clinical outcomes of osteonecrosis of the femoral head after autologous bone marrow stem cell implantation: a meta-analysis of seven case-control studies. *Clinics (Sao Paulo)*. 2016;71(2):110-113.<https://www.ncbi.nlm.nih.gov/pubmed/26934241>.
38. Chew E, Prakash R, Khan W. Mesenchymal stem cells in human meniscal regeneration: A systematic review. *Ann Med Surg (Lond)*. 2017;24:3-7.<https://www.ncbi.nlm.nih.gov/pubmed/29062478>.
39. Wu T, Song HX, Dong Y, Li JH. Cell-Based Therapies for Lumbar Discogenic Low Back Pain: Systematic Review and Single-Arm Meta-analysis. *Spine (Phila Pa 1976)*. 2018;43(1):49-57.<https://www.ncbi.nlm.nih.gov/pubmed/26953666>.
40. Imam MA, Holton J, Horriat S, et al. A systematic review of the concept and clinical applications of bone marrow aspirate concentrate in tendon pathology. *SICOT J*. 2017;3:58.<https://www.ncbi.nlm.nih.gov/pubmed/28990575>.
41. Pas H, Moen MH, Haisma HJ, Winters M. No evidence for the use of stem cell therapy for tendon disorders: a systematic review. *Br J Sports Med*. 2017;51(13):996-1002.<https://www.ncbi.nlm.nih.gov/pubmed/28077355>.
42. McAnany SJ, Ahn J, Elboghdady IM, et al. Mesenchymal stem cell allograft as a fusion adjunct in one- and two-level anterior cervical discectomy and fusion: a matched cohort analysis. *Spine J*. 2016;16(2):163-167.<https://www.ncbi.nlm.nih.gov/pubmed/25725368>.
43. Kerr EJ, 3rd, Jawahar A, Wooten T, Kay S, Cavanaugh DA, Nunley PD. The use of osteoconductive stem-cells allograft in lumbar interbody fusion procedures: an alternative to recombinant human bone morphogenetic protein. *J Surg Orthop Adv*. 2011;20(3):193-197.<https://www.ncbi.nlm.nih.gov/pubmed/22214145>.
44. Eastlack RK, Garfin SR, Brown CR, Meyer SC. Osteocel Plus cellular allograft in anterior cervical discectomy and fusion: evaluation of clinical and radiographic outcomes from a prospective multicenter study. *Spine (Phila Pa 1976)*. 2014;39(22):E1331-1337.<https://www.ncbi.nlm.nih.gov/pubmed/25188591>.
45. Ammerman JM, Libricz J, Ammerman MD. The role of Osteocel Plus as a fusion substrate in minimally invasive instrumented transforaminal lumbar interbody fusion. *Clin Neurol Neurosurg*. 2013;115(7):991-994.<https://www.ncbi.nlm.nih.gov/pubmed/23182179>.
46. Tohmeh AG, Watson B, Tohmeh M, Zielinski XJ. Allograft cellular bone matrix in extreme lateral interbody fusion: preliminary radiographic and clinical outcomes. *ScientificWorldJournal*. 2012;2012:263637.<https://www.ncbi.nlm.nih.gov/pubmed/23251099>.
47. Hollawell SM. Allograft cellular bone matrix as an alternative to autograft in hindfoot and ankle fusion procedures. *J Foot Ankle Surg*. 2012;51(2):222-225.<https://www.ncbi.nlm.nih.gov/pubmed/22036146>.

48. Divi SN, Mikhael MM. Use of Allogenic Mesenchymal Cellular Bone Matrix in Anterior and Posterior Cervical Spinal Fusion: A Case Series of 21 Patients. *Asian Spine J.* 2017;11(3):454-462. <https://www.ncbi.nlm.nih.gov/pubmed/28670414>.
49. Vanichkachorn J, Peppers T, Bullard D, Stanley SK, Linovitz RJ, Ryaby JT. A prospective clinical and radiographic 12-month outcome study of patients undergoing single-level anterior cervical discectomy and fusion for symptomatic cervical degenerative disc disease utilizing a novel viable allogeneic, cancellous, bone matrix (trinity evolution) with a comparison to historical controls. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society.* 2016;25(7):2233-2238. <https://www.ncbi.nlm.nih.gov/pubmed/26849141>.
50. Peppers TA, Bullard DE, Vanichkachorn JS, et al. Prospective clinical and radiographic evaluation of an allogeneic bone matrix containing stem cells (Trinity Evolution(R) Viable Cellular Bone Matrix) in patients undergoing two-level anterior cervical discectomy and fusion. *J Orthop Surg Res.* 2017;12(1):67. <https://www.ncbi.nlm.nih.gov/pubmed/28446192>.
51. Navani A, Manchikanti L, Albers SL, et al. Responsible, Safe, and Effective Use of Biologics in the Management of Low Back Pain: American Society of Interventional Pain Physicians (ASIPP) Guidelines. *Pain Physician.* 2019;22(1S):S1-S74. <https://www.ncbi.nlm.nih.gov/pubmed/30717500>.
52. American Academy of Orthopaedic Surgeons (AAOS). Management Of Osteoarthritis Of The Hip. Evidence-Based Clinical Practice Guideline. Adopted: 03/13/2017. https://www.aaos.org/uploadedFiles/PreProduction/Quality/Guidelines_and_Reviews/OA%20Hip%20CPG_1.5.18.pdf. Accessed 11/29/2020.
53. American Academy of Orthopaedic Surgeons (AAOS). Treatment of Osteoarthritis of the Knee (2nd edition)(Non-Arthroplasty). Evidence-Based Guideline. Adopted: 05/18/2018. <https://www.aaos.org/quality/quality-programs/lower-extremity-programs/osteoarthritis-of-the-knee/>. Accessed 11/29/2020.
54. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Stem Cell Transplantation (110.23). <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=366>. Published 2016. Accessed 11/29/2020.
55. U.S. Food & Drug Administration. CFR - Code of Federal Regulations Title 21. Chapter I , Subchapter L, Part 1271 - HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS. Updated: 09/25/2018. <https://www.ecfr.gov/cgi-bin/text-idx?SID=64664be8edce70ee11cd7d18fcb48887&mc=true&node=pt21.8.1271&rgn=div5#sp21.8.1271.a>. Accessed 11/29/2020.