Washington State Health Care Authority

Stem Cell Therapy for Musculoskeletal Conditions

Appendix

February 17, 2020

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Stem Cell Therapy for Musculoskeletal Conditions

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APPENDIX

February 17, 2020

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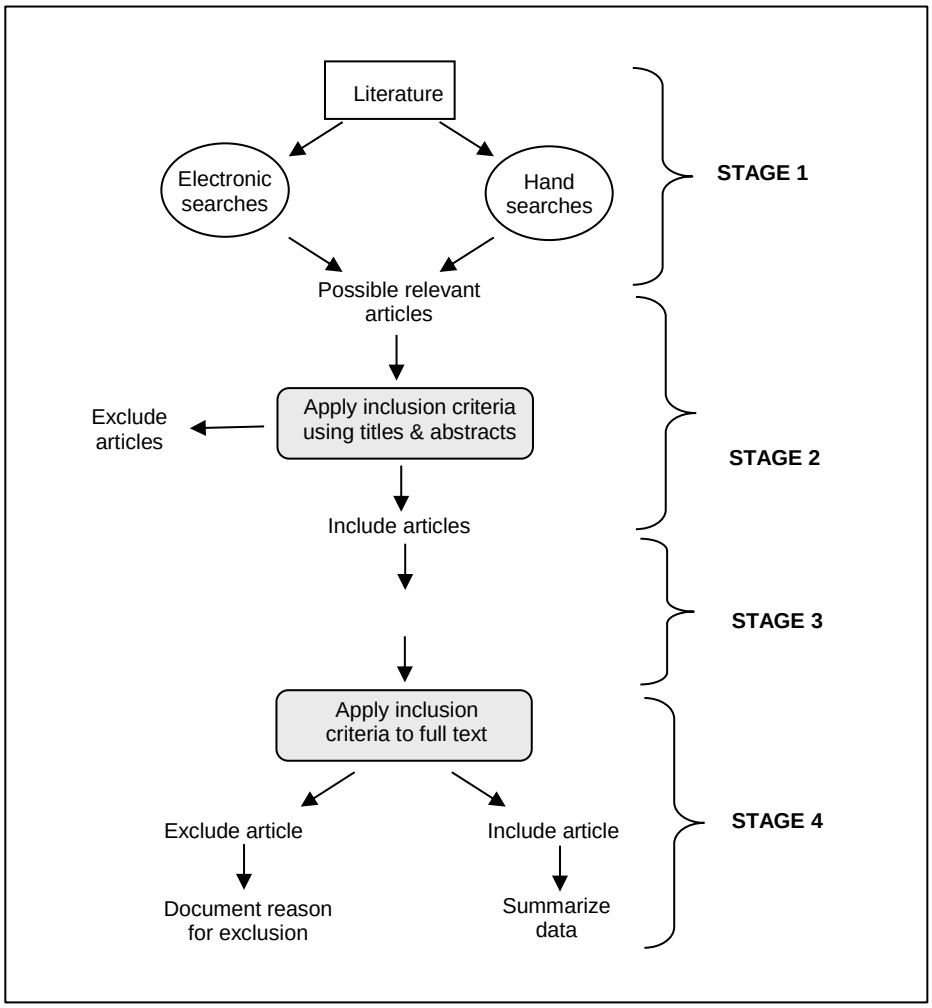
Appendix Tables & Figures

APPENDIX A. Algorithm for Article Selection



APPENDIX B. Search Strategies

Below is the search strategy for PubMed. Parallel strategies were used to search other electronic databases listed below. Keyword searches were conducted in the other listed resources. In addition, hand-searching of included studies was performed.

Appendix Table B1: PubMed Search Strategy and Results Performed on 09/12/19

	Search Strategy	No. of hits
1.	"Stem Cells"[Mesh] OR "Stem Cell Transplantation"[Mesh] OR "Stem Cell Research"[Mesh] OR "Bone Marrow Transplantation"[Mesh] OR "stem cell*"[TIAB] OR progenitor cell*[TIAB] OR stromal cell*[TIAB] OR mesenchymal cell*[TIAB] OR bone marrow[TIAB] OR osteocel[TIAB]	518,139
2.	"Tendons"[Mesh] OR "Tendon Injuries"[Mesh] OR "Tendinopathy"[Mesh] OR "Tennis Elbow"[Mesh] OR "Fasciitis, Plantar"[Mesh] OR "Soft Tissue Injuries"[Mesh] OR "Athletic Injuries"[Mesh] OR "Contusions"[Mesh] OR "Sprains and Strains"[Mesh] OR "Muscle, Skeletal"[Mesh] OR "Cartilage"[Mesh] OR "Ligaments, Articular"[Mesh] OR "Osteoarthritis"[Mesh] OR "Low Back Pain"[Mesh] OR "Neck Pain"[Mesh] OR "Temporomandibular Joint"[Mesh] OR "Temporomandibular Joint Disorders"[Mesh] OR "Carpal Tunnel Syndrome"[Mesh] OR "Shoulder Injuries"[Mesh] OR "Meniscus"[Mesh] OR "Tibial Meniscus Injuries"[Mesh] OR "Pseudarthrosis"[Mesh] OR "Intervertebral Disc Displacement"[Mesh] OR "Failed Back Surgery Syndrome"[Mesh] OR "Sacroiliac Joint"[Mesh] OR "Spinal Stenosis"[Mesh] OR "Spondylolysis"[Mesh] OR "Intervertebral Disc Degeneration"[Mesh] OR "Cumulative Trauma Disorders"[Mesh]	569,508
3.	"soft tissue"[TI] OR muscl*[TI] OR Ligament*[TI] OR Tendon*[TI] OR Tendin*[TI] OR Cartilage[TI] OR Fasci*[TI] OR Sport*[TI] OR Athlet*[TI] OR tear*[TIAB] OR strain*[TIAB] OR sprain*[TIAB] OR damage*[TIAB] OR trauma*[TIAB] OR injur*[TIAB] OR "low back pain"[TIAB] OR "back pain"[TIAB] OR lumbar[TIAB] OR lumbo*[TIAB] OR "neck pain"[TIAB] OR cervical[TIAB] OR osteoarthritis[TIAB] OR muscul*[TI] OR "bulging disc"[TIAB] OR "disc tear"[TIAB] OR "torn disc"[TIAB]	2,899,683
4.	#1 AND (#2 OR #3)	74,366
5.	"Case reports"[ptyp] OR cadaver*[TI] OR "In Vitro Techniques"[Mesh] OR "Models, Animal"[Mesh] OR "Animals, Laboratory"[Mesh] OR "Animal Experimentation"[Mesh] OR animal[TI] OR rat*[TI] OR dog*[TI] OR mouse[TI] OR mice[TI] OR rabbit*[TI] OR pig*[TI] OR sheep[TI] OR monkey*[TI] OR rodent*[TI] OR ovine[TI] OR bovine[TI] OR canine[TI] OR equine[TI] OR murine[TI] OR porcine[TI] OR "Neoplasms"[MeSH] OR neoplasm*[TI] OR tumor[TI] OR metasta*[TI] OR necrosis[Mesh] OR "avascular necrosis"[Mesh	7,873,837
6.	(#4 NOT #5) Filters: Abstract; Humans; English	17,981
7.	"Cost-Benefit Analysis"[Mesh] OR "cost-effective*"[TIAB] OR "cost effective*"[TIAB] OR "cost-utility"[TIAB] OR "cost utility"[TIAB] OR economic[TIAB]	
8.	#4 AND #7	164

Appendix Table B2: EMBASE Search Strategy and Results Performed on 09/12/19

	Search Strategy	No. of hits
1.	'stem cell transplant*':ti,ab,kw	86,064
2.	'allogenic bone marrow transplantation'/exp OR 'allogenic bone marrow transplantation' OR 'autologous bone marrow transplantation'/exp OR 'autologous bone marrow transplantation'	16,787
3.	'stem cell transplantation'/exp OR 'stem cell transplantation'	155,265
4.	'stem cell*':ti,ab,kw	375,407
5.	'stroma cell':ti,ab,kw OR 'mesenchymal stem cell':ti,ab,kw OR 'synthetic bone graft':ti,ab,kw	15,460
6.	'stem cell transplant*'	165,109
7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6	432,177
8.	'musculoskeletal disease'/exp OR 'musculoskeletal disease' OR 'musculoskeletal injury'/exp OR 'musculoskeletal injury' OR 'sport injury'/exp OR 'sport injury' OR 'sacroiliac joint'/exp OR 'sacroiliac joint' OR 'cumulative trauma disorder'/exp OR 'cumulative trauma disorder'	2,332,029
9.	#7 AND #8	32,713
10.	#7 AND #8 AND [humans]/lim AND [english]/lim AND [abstracts]/lim	22,043
11.	'case report':it OR 'conference paper':it OR 'conference abstract':it OR 'conference review':it	4,291,564
12.	'cadaver':ti OR 'animal model'/exp OR 'animal experiment'/exp OR 'animal':ti OR 'neoplasm'/exp OR 'metastasis'/exp OR 'necrosis'/exp OR 'avascular necrosis'/exp	7,683,811
13.	#10 NOT (#11 OR #12)	7,711

Electronic Database Searches

The following databases have also been searched for relevant information:
Cochrane Database of Systematic Reviews
Cochrane Registry of Clinical Trials (CENTRAL)
Database of Reviews of Effectiveness (Cochrane Library)
ClinicalTrials.gov

Additional Economics, Clinical Guideline, and Gray Literature Databases

ECRI Guidelines Trust
AHRQ - Healthcare Cost and Utilization Project
Canadian Agency for Drugs and Technologies in Health
Centers for Medicare and Medicaid Services (CMS)
Food and Drug Administration (FDA)
Google

APPENDIX C. Excluded Articles

Articles excluded as primary studies after full text review, with reason for exclusion.

Appendix Table C1. List of Excluded Articles

	Citation	Reason for exclusion after full-text review
1.	Aghdami N, Liastani MG, Emadedin M, et al. Repeated intra articular injection of bone marrow derived mesenchymal stem cell in knee osteoarthritis: double blind randomized clinical trial. Cytotherapy 2014;16:S14.	Abstract only; does not appear that it has been published as a full length article
2.	Bain B. Bone marrow biopsy morbidity and mortality: 2002 data. Clinical & Laboratory Haematology 2004;26:315-8.	Safety specific to bone marrow biopsy
3.	Bain B. Bone marrow biopsy morbidity: review of 2003. Journal of clinical pathology 2005;58:406-8.	Safety specific to bone marrow biopsy
4.	Bain BJ. Bone marrow biopsy morbidity and mortality. British journal of haematology 2003;121:949-51.	Safety specific to bone marrow biopsy
5.	Bastos R, Mathias M, Andrade R, et al. Intra-articular injections of expanded mesenchymal stem cells with and without addition of platelet-rich plasma are safe and effective for knee osteoarthritis. Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA 2018;26:3342-50.	Comparative study of the addition of PRP with <10 patients per treatment group
6.	Bucher TA, Ebert JR, Smith A, Breidahl W, Fallon M, Wang T, Zheng MH, Janes GC. Autologous tenocyte injection for the treatment of chronic recalcitrant gluteal tendinopathy: a prospective pilot study. Orthopaedic journal of sports medicine. 2017 Feb 21;5(2):2325967116688866.	Excluded intervention; Tenocytes are further differentiated than stem cells
7.	Buda R, Vannini F, Castagnini F, et al. Regenerative treatment in osteochondral lesions of the talus: autologous chondrocyte implantation versus one-step bone marrow derived cells transplantation. International orthopaedics 2015;39:893-900.	Excluded intervention; stem cells as an adjunct to surgery
8.	Centeno C, Markle J, Dodson E, et al. Treatment of lumbar degenerative disc disease-associated radicular pain with culture-expanded autologous mesenchymal stem cells: a pilot study on safety and efficacy. Journal of translational medicine 2017;15:197.	Excluded population; patients with radicular low back pain
9.	Centeno CJ, Al-Sayegh H, Bashir J, Goodyear S, Freeman MD. A dose response analysis of a specific bone marrow concentrate treatment protocol for knee osteoarthritis. BMC musculoskeletal disorders 2015;16:258.	Meets all criteria for inclusion of safety data only, but does not report any safety data.
10.	Centeno CJ, Busse D, Kisiday J, Keohan C, Freeman M, Karli D. Increased knee cartilage volume in degenerative joint disease using percutaneously implanted, autologous mesenchymal stem cells. Pain physician 2008;11:343-53.	Case report (n=1)
11.	Centeno CJ, Freeman MD. Percutaneous injection of autologous, culture-expanded mesenchymal stem cells into carpometacarpal hand joints: a case series with an untreated comparison group. Wiener medizinische Wochenschrift (1946) 2014;164:83-7.	<10 patients per treatment arm (6 vs. 4)
12.	Centeno CJ, Pitts J, Al-Sayegh H, Freeman MD. Anterior cruciate ligament tears treated with percutaneous injection of autologous	The 10 patients reported on in this study are included in larger registry

	Citation	Reason for exclusion after full-text review
	bone marrow nucleated cells: a case series. Journal of pain research 2015;8:437.	study that has been included in the evidence base
13.	Centeno CJ, Schultz JR, Cheever M, et al. Safety and complications reporting update on the re-implantation of culture-expanded mesenchymal stem cells using autologous platelet lysate technique. Current stem cell research & therapy 2011;6:368-78.	Data from patients included in this study are included as part of a larger registry study published subsequent to this publication.
14.	Centeno CJ, Schultz JR, Cheever M, Robinson B, Freeman M, Marasco W. Safety and complications reporting on the re-implantation of culture-expanded mesenchymal stem cells using autologous platelet lysate technique. Current stem cell research & therapy 2010;5:81-93.	Data from patients included in this study are included as part of a larger registry study published subsequent to this publication.
15.	Chahal J, Gómez-Aristizábal A, Shestopaloff K, et al. Bone Marrow Mesenchymal Stromal Cells in Patients with Osteoarthritis Results in Overall Improvement in Pain and Symptoms and Reduces Synovial Inflammation. Stem cells translational medicine 2019.	Dose escalation study with <10 patients per treatment group (n=4 in each group; $1X10^6$, $10X10^6$, $50X10^6$)
16.	Clar C, Cummins E, McIntyre L, et al. Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: Systematic review and economic evaluation. Health Technology Assessment 2005;9:iii-48.	Excluded intervention; stem cells as an adjunct to surgery
17.	Clarke AW, Alyas F, Morris T, Robertson CJ, Bell J, Connell DA. Skin-derived tenocyte-like cells for the treatment of patellar tendinopathy. The American journal of sports medicine 2011;39:614-23.	Excluded intervention; Tenocytes are further differentiated than stem cells
18.	Connell, David, et al. "Treatment of lateral epicondylitis using skin-derived tenocyte-like cells." *British journal of sports medicine* 43.4 (2009): 293-298.	Excluded intervention; Tenocytes are further differentiated than stem cells
19.	Coric D, Pettine K, Sumich A, Boltes MO. Prospective study of disc repair with allogeneic chondrocytes presented at the 2012 Joint Spine Section Meeting. Journal of Neurosurgery: Spine. 2013 Jan 1;18(1):85-95.	Excluded intervention; Chondrocytes are further differentiated than stem cells
20.	Cruz-Sánchez PM, Gámez-Pérez A, Rodríguez-Orta CdlA, et al. Impacto del tratamiento con células madre adultas en la osteoartrosis de la rodilla. Revista Cubana de Hematología, Inmunología y Hemoterapia 2013;29:272-83.	Study published only in Spanish
21.	Darrow M, Shaw B, Schmidt N, Boeger G, Budgett S. Treatment of shoulder osteoarthritis and rotator cuff tears with bone marrow concentrate and whole bone marrow injections. Cogent Medicine 2019;6.	Study comparing different cell preparations; would be included for safety only, but study does not report any safety data
22.	de Windt TS, Vonk LA, Slaper-Cortenbach IC, et al. Allogeneic mesenchymal stem cells stimulate cartilage regeneration and are safe for single-stage cartilage repair in humans upon mixture with recycled autologous chondrons. Stem cells (Dayton, Ohio) 2017;35:256-64.	Excluded intervention; stem cells as an adjunct to surgery
23.	de Windt TS, Vonk LA, Slaper-Cortenbach ICM, Nizak R, van Rijen MHP, Saris DBF. Allogeneic MSCs and Recycled Autologous Chondrons Mixed in a One-Stage Cartilage Cell Transplantion: A First-in-Man Trial in 35 Patients. Stem cells (Dayton, Ohio) 2017;35:1984-93.	Excluded intervention; stem cells as an adjunct to surgery

	Citation	Reason for exclusion after full-text review
24.	Elabd C, Centeno CJ, Schultz JR, Lutz G, Ichim T, Silva FJ. Intra-discal injection of autologous, hypoxic cultured bone marrow-derived mesenchymal stem cells in five patients with chronic lower back pain: a long-term safety and feasibility study. Journal of translational medicine 2016;14:253.	Case series with less than 10 patients (N=5)
25.	Emadedin M, Ghorbani Liastani M, Fazeli R, et al. Long-Term Follow-up of Intra-articular Injection of Autologous Mesenchymal Stem Cells in Patients with Knee, Ankle, or Hip Osteoarthritis. Archives of Iranian medicine 2015;18:336-44.	Reported separately; knee (n=6), ankle (n=6), hip (n=5); would not meet n cut-off for case series; however, long term follow-up = 30 months
26.	Freitag J, Ford J, Bates D, et al. Adipose derived mesenchymal stem cell therapy in the treatment of isolated knee chondral lesions: design of a randomised controlled pilot study comparing arthroscopic microfracture versus arthroscopic microfracture combined with postoperative mesenchymal stem cell injections. BMJ open 2015;5:e009332.	Study protocol; would otherwise be excluded as this study assesses stem cells as an adjunct to surgery
27.	Gellhorn, Alfred C., and Alex Han. "The use of dehydrated human amnion/chorion membrane allograft injection for the treatment of tendinopathy or arthritis: a case series involving 40 patients." *PM&R* 9.12 (2017): 1236-1243.	Excluded intervention; Tenocytes are further differentiated than stem cells
28.	Giannini S, Buda R, Vannini F, Cavallo M, Grigolo B. One-step bone marrow-derived cell transplantation in talar osteochondral lesions. Clin Orthop Relat Res 2009;467:3307-20.	Excluded intervention; stem cells as an adjunct to surgery
29.	Gobbi A, Chaurasia S, Karnatzikos G, Nakamura N. Matrix-Induced Autologous Chondrocyte Implantation versus Multipotent Stem Cells for the Treatment of Large Patellofemoral Chondral Lesions: A Nonrandomized Prospective Trial. Cartilage 2015;6:82-97.	Excluded intervention; stem cells as an adjunct to surgery
30.	Gupta PK, Chullikana A, Rengasamy M, et al. Efficacy and safety of adult human bone marrow-derived, cultured, pooled, allogeneic mesenchymal stromal cells (Stempeucel®): preclinical and clinical trial in osteoarthritis of the knee joint. Arthritis research & therapy 2016;18:301.	Excluded setting; patients hospitalized for the procedure
31.	Hanselman AE, Tidwell JE, Santrock RD. Cryopreserved human amniotic membrane injection for plantar fasciitis: a randomized, controlled, double-blind pilot study. Foot & ankle international 2015;36:151-8.	<10 patients per treatment arm
32.	Hernigou P, Dubory A, Homma Y, Flouzat Lachaniette CH, Chevallier N, Rouard H. Single-stage treatment of infected tibial non-unions and osteomyelitis with bone marrow granulocytes precursors protecting bone graft. International Orthopaedics 2018;42:2443-50. 8	Unclear setting; stem cells as adjunct to surgery
33.	Hernigou P, Homma Y, Flouzat-Lachaniette CH, Poignard A, Chevallier N, Rouard H. Cancer risk is not increased in patients treated for orthopaedic diseases with autologous bone marrow cell concentrate. Journal of Bone and Joint Surgery - Series A 2013;95:2215-21.	Safety specific study; % with each orthopedic condition is unclear - many not conditions not includable

	Citation	Reason for exclusion after full-text review
34.	Huh Y, Ji RR, Chen G. Neuroinflammation, bone marrow stem cells, and chronic pain. Frontiers in Immunology 2017;8.	Excluded intervention; stem cells as an adjunct to surgery
35.	Jo CH, Chai JW, Jeong EC, et al. Intra-articular Injection of Mesenchymal Stem Cells for the Treatment of Osteoarthritis of the Knee: A 2-Year Follow-up Study. Am J Sports Med 2017;45:2774-83.	Two year follow-up of the above study
36.	Jo CH, Chai JW, Jeong EC, et al. Intratendinous Injection of Autologous Adipose Tissue-Derived Mesenchymal Stem Cells for the Treatment of Rotator Cuff Disease: A First-In-Human Trial. Stem Cells 2018;36:1441-50.	Dose escalation study with <10 patients per treatment group
37.	Jo CH, Lee YG, Shin WH, et al. Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a proof-of-concept clinical trial. Stem Cells 2014;32:1254-66.	Dose escalation study with <10 patients per treatment group
38.	Jones IA, Wilson M, Togashi R, Han B, Mircheff AK, Thomas Vangsness C. A randomized, controlled study to evaluate the efficacy of intra-articular, autologous adipose tissue injections for the treatment of mild-to-moderate knee osteoarthritis compared to hyaluronic acid: A study protocol. BMC Musculoskeletal Disorders 2018;19.	Study protocol; **would otherwise be included**
39.	Jorgensen C, Noeth U, Facchini A, et al. MSC based therapy for severe osteoarthritis of the knee. A phase 1 dose escalation trial. Osteoarthritis and cartilage 2014;22:S442.	Abstract only; does not appear that it has been published as a full length article
40.	Kamei N, Ochi M, Adachi N, et al. The safety and efficacy of magnetic targeting using autologous mesenchymal stem cells for cartilage repair. Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA 2018;26:3626-35.	n<10; adjunct to surgery
41.	Kasemkijwattana C, Hongeng S, Kesprayura S, Rungsinaporn V, Chaipinyo K, Chansiri K. Autologous bone marrow mesenchymal stem cells implantation for cartilage defects: Two cases report. Journal of the Medical Association of Thailand 2011;94:395-400.	n<10; adjunct to surgery
42.	Kennedy GA, Morton J, Western R, Butler J, Daly J, Durrant S. Impact of stem cell donation modality on normal donor quality of life: A prospective randomized study. Bone marrow transplantation 2003;31:1033-5.	Safety specific to stem cell donation; patients diagnosis unclear
43.	Kim SJ, Song DH, Park JW, Park S, Kim SJ. Effect of bone marrow aspirate concentrate–platelet-rich plasma on tendon-derived stem cells and rotator cuff tendon tear. Cell transplantation 2017;26:867-78.	Same population as Kim 2018 (an included study) with no unique data
44.	Kim YS, Choi YJ, Koh YG. Mesenchymal stem cell implantation in knee osteoarthritis: an assessment of the factors influencing clinical outcomes. The American journal of sports medicine 2015;43:2293-301.	Excluded intervention; stem cells as an adjunct to surgery
45.	Kim YS, Kwon OR, Choi YJ, Suh DS, Heo DB, Koh YG. Comparative Matched-Pair Analysis of the Injection Versus Implantation of Mesenchymal Stem Cells for Knee Osteoarthritis. The American journal of sports medicine 2015;43:2738-46.	Excluded intervention; stem cells as an adjunct to surgery
46.	Kim YS, Lee HJ, Choi YJ, Kim YI, Koh YG. Does an injection of a stromal vascular fraction containing adipose-derived mesenchymal	Excluded intervention; stem cells as an adjunct to surgery

	Citation	Reason for exclusion after full-text review
	stem cells influence the outcomes of marrow stimulation in osteochondral lesions of the talus? A clinical and magnetic resonance imaging study. The American journal of sports medicine 2014;42:2424-34.	
47.	Kroschinsky F, Kittner T, Mauersberger S, et al. Pelvic magnetic resonance imaging after bone marrow harvest--a retrospective study in 50 unrelated marrow donors. Bone marrow transplantation 2005;35:667-73.	Safety specific case series; diagnoses unclear
48.	Kuah D, Sivell S, Longworth T, et al. Safety, tolerability and efficacy of intra-articular Progenza in knee osteoarthritis: a randomized double-blind placebo-controlled single ascending dose study. Journal of translational medicine 2018;16:49.	<10 patients per treatment arm
49.	Lamas JR, García-Fernández C, Tornero-Esteban P, et al. Adverse effects of xenogenic scaffolding in the context of a randomized double-blind placebo-controlled study for repairing full-thickness rotator cuff tears. Trials 2019;20.	Excluded intervention; stem cells as an adjunct to surgery
50.	Lanham NS, Carroll JJ, Cooper MT, Perumal V, Park JS. A Comparison of Outcomes of Particulated Juvenile Articular Cartilage and Bone Marrow Aspirate Concentrate for Articular Cartilage Lesions of the Talus. Foot & ankle specialist 2017;10:315-21.	Excluded intervention; stem cells as an adjunct to surgery
51.	Lee SY, Kim W, Lim C, Chung SG. Treatment of Lateral Epicondylosis by Using Allogeneic Adipose-Derived Mesenchymal Stem Cells: A Pilot Study. Stem cells (Dayton, Ohio) 2015;33:2995-3005.	Dose escalation study with <10 patients per treatment group
52.	Lullove E. A flowable placental tissue matrix allograft in lower extremity injuries: a pilot study. Cureus 2015;7.	Unclear if product contains live stem cells
53.	March L, Hunter D, Ward C, Fedorova T, Chen J. A randomised placebo controlled pilot study of autologous non-expanded adi-pose-derived mesenchymal stem cells in the treatment of knee osteoarthritis. Internal medicine journal 2013;43:4-5.	abstract only; no publications available yet – study was completed in 2013
54.	Matas J, Orrego M, Amenabar D, et al. Umbilical Cord-Derived Mesenchymal Stromal Cells (MSCs) for Knee Osteoarthritis: Repeated MSC Dosing Is Superior to a Single MSC Dose and to Hyaluronic Acid in a Controlled Randomized Phase I/II Trial. Stem cells translational medicine 2019;8:215-24.	<10 patients per treatment arm
55.	Matsumoto T, Okabe T, Ikawa T, et al. Articular cartilage repair with autologous bone marrow mesenchymal cells. Journal of cellular physiology 2010;225:291-5.	Case report (n=2)
56.	Mautner K, Bowers R, Easley K, Fausel Z, Robinson R. Functional Outcomes Following Microfragmented Adipose Tissue Versus Bone Marrow Aspirate Concentrate Injections for Symptomatic Knee Osteoarthritis. Stem cells translational medicine 2019.	Excluded comparator; study compares the source of the cells (Bone Marrow Derived vs. Adipose Derived) – does not report safety outcomes
57.	Mochida J, Sakai D, Nakamura Y, Watanabe T, Yamamoto Y, Kato S. Intervertebral disc repair with activated nucleus pulposus cell transplantation: a three-year, prospective clinical study of its safety. European cells & materials 2015;29:202-12; discussion 12.	Case series with <10 patients (N=9)

	Citation	Reason for exclusion after full-text review
58.	Monckeberg JE, Rafols C, Apablaza F, Gerhard P, Rosales J. Intra-articular administration of peripheral blood stem cells with platelet-rich plasma regenerated articular cartilage and improved clinical outcomes for knee chondral lesions. The Knee 2019;26:824-31.	Excluded intervention; stem cells as an adjunct to surgery
59.	Montoya F, Martínez F, García-Robles M, et al. Clinical and experimental approaches to knee cartilage lesion repair and mesenchymal stem cell chondrocyte differentiation. Biological research 2013;46:441-51.	Excluded intervention; stem cells as an adjunct to surgery
60.	Muiños-López E, Delgado D, Sánchez P, et al. Modulation of synovial fluid-derived mesenchymal stem cells by intra-articular and intraosseous platelet rich plasma administration. Stem Cells International 2016;2016.	Excluded intervention
61.	Murphy MP, Buckley C, Sugrue C, et al. ASCOT: Autologous Bone Marrow Stem Cell Use for Osteoarthritis of the Thumb—First Carpometacarpal Joint. Plastic and Reconstructive Surgery Global Open 2017;5.	Excluded intervention; stem cells as an adjunct to surgery
62.	Nejadnik H, Hui JH, Feng Choong EP, Tai BC, Lee EH. Autologous bone marrow-derived mesenchymal stem cells versus autologous chondrocyte implantation: an observational cohort study. The American journal of sports medicine 2010;38:1110-6.	Excluded intervention; stem cells as an adjunct to surgery
63.	Obaid H, Clarke A, Rosenfeld P, Leach C, Connell D. Skin-derived fibroblasts for the treatment of refractory Achilles tendinosis: preliminary short-term results. JBJS 2012;94:193-200.	Excluded intervention
64.	Pak J, Lee JH, Lee SH. A novel biological approach to treat chondromalacia patellae. PloS one 2013;8:e64569.	Case report (n=2)
65.	Pak J, Lee JH, Lee SH. Regenerative repair of damaged meniscus with autologous adipose tissue-derived stem cells. BioMed research international 2014;2014:436029.	Case report (n=1)
66.	Pak J, Lee JH, Park KS, Jeong BC, Lee SH. Regeneration of cartilage in human knee osteoarthritis with autologous adipose tissue-derived stem cells and autologous extracellular matrix. BioResearch Open Access 2016;5:192-200.	n<10 (N=3)
67.	Pang X, Yang H, Peng B. Human umbilical cord mesenchymal stem cell transplantation for the treatment of chronic discogenic low back pain. Pain physician 2014;17:E525-E30.	N<10 (N=2)
68.	Park YB, Ha CW, Lee CH, Yoon YC, Park YG. Cartilage Regeneration in Osteoarthritic Patients by a Composite of Allogeneic Umbilical Cord Blood-Derived Mesenchymal Stem Cells and Hyaluronate Hydrogel: Results from a Clinical Trial for Safety and Proof-of-Concept with 7 Years of Extended Follow-Up. Stem cells translational medicine 2017;6:613-21.	n<10; adjunct to surgery
69.	Peeters CM, Leijs 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 and cartilage 2013;21:1465-73.	Systematic Review: checked all the relevant studies

	Citation	Reason for exclusion after full-text review
70.	Pers YM, Quentin J, Feirreira R, et al. Injection of Adipose-Derived Stromal Cells in the Knee of Patients with Severe Osteoarthritis has a Systemic Effect and Promotes an Anti-Inflammatory Phenotype of Circulating Immune Cells. Theranostics 2018;8:5519-28.	Secondary publication to Pers 2016; no outcomes of interest
71.	Pers YM, Rackwitz L, Ferreira R, et al. Adipose Mesenchymal Stromal Cell-Based Therapy for Severe Osteoarthritis of the Knee: A Phase I Dose-Escalation Trial. Stem cells translational medicine 2016;5:847-56.	Dose escalation study with <10 patients per treatment group (n=8 in low, mid and high dose groups)
72.	Pulsipher MA, Chitphakdithai P, Logan BR, et al. Acute toxicities of unrelated bone marrow versus peripheral blood stem cell donation: Results of a prospective trial from the National Marrow Donor Program. Blood 2013;121:197-206.	Pull for background
73.	Richardson JB, Wright KT, Wales J, et al. Efficacy and safety of autologous cell therapies for knee cartilage defects (autologous stem cells, chondrocytes or the two): randomized controlled trial design. Regenerative medicine 2017;12:493-501.	Study protocol; study would be excluded, adjunct to surgery
74.	Rios CG, McCarthy MB, Arciero C, Spang JT, Arciero RA, Mazzocca AD. Biologics in shoulder surgery: The role of adult mesenchymal stem cells in tendon repair. Techniques in Orthopaedics 2007;22:2-9.	Narrative review
75.	Roukis TS, Hyer CF, Philbin TM, Berlet GC, Lee TH. Complications associated with autogenous bone marrow aspirate harvest from the lower extremity: an observational cohort study. The Journal of foot and ankle surgery : official publication of the American College of Foot and Ankle Surgeons 2009;48:668-71.	Excluded condition; not musculoskeletal conditions
76.	Russo A, Condello V, Madonna V, Guerriero M, Zorzi C. Autologous and micro-fragmented adipose tissue for the treatment of diffuse degenerative knee osteoarthritis. Journal of Experimental Orthopaedics 2017;4.	Excluded intervention; stem cells as an adjunct to surgery
77.	Russo A, Screpis D, Di Donato SL, Bonetti S, Piovan G, Zorzi C. Autologous micro-fragmented adipose tissue for the treatment of diffuse degenerative knee osteoarthritis: an update at 3 year follow-up. Journal of Experimental Orthopaedics 2018;5.	Excluded intervention; stem cells as an adjunct to surgery
78.	Schiavone Panni A, Vasso M, Braile A, et al. Preliminary results of autologous adipose-derived stem cells in early knee osteoarthritis: identification of a subpopulation with greater response. International orthopaedics 2019;43:7-13.	Excluded intervention; stem cells as an adjunct to surgery
79.	Song Y, Du H, Dai C, et al. Human adipose-derived mesenchymal stem cells for osteoarthritis: a pilot study with long-term follow-up and repeated injections. Regenerative medicine 2018;13:295-307.b	Dose escalation study with <10 patients per treatment group
80.	Spasovski D, Spasovski V, Baščarević Z, et al. Intra-articular injection of autologous adipose-derived mesenchymal stem cells in the treatment of knee osteoarthritis. Journal of Gene Medicine 2018;20.	Case series with less than 10 patients per treatment arm (N=9)
81.	Srinivas P, Kumar PP. Role of PRP and stem cell injections in osteoarthritic patients of knee joint. Journal of evolution of medical and dental sciences J Evolution Med Dent Sci 2015;4:9468-74.	Does not report safety data; would otherwise meet inclusion criteria

	Citation	Reason for exclusion after full-text review
82.	Stroncek DF, Holland PV, Bartch G, et al. Experiences of the first 493 unrelated marrow donors in the National Marrow Donor Program. Blood 1993;81:1940-6.	Pulled for background information only.
83.	Tassi C, Tazzari PL, Bonifazi F, et al. Short- and long-term haematological surveillance of healthy donors of allogeneic peripheral haematopoietic progenitors mobilized with G-CSF: A single institution prospective study. Bone marrow transplantation 2005;36:289-94.	No outcomes of interest
84.	Tran TDX, Wu CM, Dubey NK, et al. Time-and kellgren-lawrence grade-dependent changes in intra-articularly transplanted stromal vascular fraction in osteoarthritic patients. Cells 2019;8.	Excluded intervention; stem cells as an adjunct to surgery
85.	Tschugg A, Diepers M, Simone S, et al. A prospective randomized multicenter phase I/II clinical trial to evaluate safety and efficacy of NOVOCART disk plus autologous disk chondrocyte transplantation in the treatment of nucleotomized and degenerative lumbar disks to avoid secondary disease: safety results of Phase I—a short report. Neurosurgical review 2017;40:155-62.	Adjunct to surgery; comparison of two formulations of the same treatment
86.	Vad V, Barve R, Linnell E, Harrison J. Knee osteoarthritis treated with percutaneous chondral-bone interface optimization: a pilot trial. Surgical Science 2016;7:1.	Excluded intervention
87.	Vyas R, Dudhat D, Navik P, et al. Clinical safety in using unmatched allogeneic umbilical cord blood mononuclear cells transplantations in non-haematopoietic degenerative conditions. Journal of stem cells 2014;9:219-24.	Wrong population; primarily neural degenerative conditions
88.	Wakitani S, Okabe T, Horibe S, et al. Safety of autologous bone marrow-derived mesenchymal stem cell transplantation for cartilage repair in 41 patients with 45 joints followed for up to 11 years and 5 months. Journal of tissue engineering and regenerative medicine 2011;5:146-50.	All patients had surgery
89.	Wang A, Breidahl W, Zheng MH. Autologous Tenocyte Injection for the Treatment of Severe, Chronic Resistant Lateral Epicondylitis. The American journal of sports medicine;41.	Excluded intervention
90.	Wang Y, Shimmin A, Ghosh P, et al. Safety, tolerability, clinical, and joint structural outcomes of a single intra-articular injection of allogeneic mesenchymal precursor cells in patients following anterior cruciate ligament reconstruction: a controlled double-blind randomised trial. Arthritis research & therapy 2017;19:180.	stem cells as an adjunct to surgery
91.	Wei N, Beard S, Delauter S, et al. Guided mesenchymal stem cell layering technique for treatment of osteoarthritis of the knee. Journal of Applied Research 2011;11:44-8.	Excluded intervention; stem cells as an adjunct to surgery
92.	Werber B. Amniotic tissues for the treatment of chronic plantar fasciosis and Achilles tendinosis. Journal of Sports Medicine 2015;2015.	Excluded intervention; unclear as to if product contains stem cells
93.	Zelen CM, Poka A, Andrews J. Prospective, randomized, blinded, comparative study of injectable micronized dehydrated amniotic/chorionic membrane allograft for plantar fasciitis—a feasibility study. Foot & ankle international 2013;34:1332-9.	AmnioFix does not contain live stem cells and is not categorized as a stem cell injection

APPENDIX D. Risk of Bias, Class of Evidence, Strength of Evidence, and QHES Determination

Each included comparative study is rated against pre-set criteria that resulted in a Risk of Bias (RoB) assessment and presented in a table. Definitions of the RoB categories are provided in Table D1, and criteria for determining RoB for primary studies of therapy are listed in the Table D2. Table D3 provides an example of the format used to assess RoB for individual cohort studies of therapy. A "No" indicates that the criterion was not met; an "Unclear" indicates that the criterion could not be determined with the information provided or was not reported by the author. Risk of bias assessments were not conducted for case series; all were considered High risk of bias.

Appendix Table D1. Definition of the risk of bias categories

Risk of Bias	Definition
Low risk of bias	Study adheres to commonly held tenets of high quality design, execution and avoidance of bias
Moderately low risk of bias	Study has potential for some bias; does not meet all criteria for low risk of bias but deficiencies not likely to invalidate results or introduce significant bias
Moderately high risk of bias	Study has flaws in design and/or execution that increase potential for bias that may invalidate study results
High risk of bias	Study has significant potential for bias; does not include design features geared toward minimizing bias and/or does not have a comparison group

Appendix Table D2. Definitions of the different levels of evidence for studies of therapy

Risk of Bias	Studies of Therapy*	
	Study design	**Criteria***
Low risk: Study adheres to commonly held tenets of high quality design, execution and avoidance of bias	Good quality RCT	• Random sequence generation • Statement of allocation concealment • Intent-to-treat analysis • Blind or independent assessment for primary outcome(s) • F/U rate of 80%+ • <10% difference in F/U between groups • Controlling for possible confounding‡
Moderately low risk: Study has potential for some bias; study does not meet all criteria for class I, but deficiencies not likely to invalidate results or introduce significant bias	Moderate quality RCT	• Violation of one or two of the criteria for good quality RCT
	Good quality cohort	• Blind or independent assessment for primary outcome(s) • F/U rate of 80%+ • <10% difference in F/U between groups • Controlling for possible confounding‡
Moderately High risk: Study has significant flaws in design and/or execution that increase potential for bias that may invalidate study results	Poor quality RCT	• Violation of three or more of the criteria for good quality RCT
	Moderate quality cohort	• Violation of any of the criteria for good quality cohort
	Case-control	• Any case-control design
High risk: Study has significant potential for bias; lack of comparison group precludes direct assessment of important outcomes	Poor quality cohort Case series	• Violation of two or more criteria for a good quality cohort • Any case series design

* Additional domains evaluated in studies performing a formal test of interaction for subgroup modification (i.e., HTE) based on recommendations from Oxman and Guyatt[3,4,7]:
  - Is the subgroup variable a characteristic specified at baseline or after randomization? (subgroup hypotheses should be developed a priori)
  - Did the hypothesis precede rather than follow the analysis and include a hypothesized direction that was subsequently confirmed?
  - Was the subgroup hypothesis one of a smaller number tested?

† Outcome assessment is independent of healthcare personnel judgment. Reliable data are data such as mortality or re-operation.

‡ Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

Appendix Table D3: Assessment of RoB for individual studies of therapy

Methodological Principle	Author 1, 2014	Author 2, 2012	Author 3, 2010
Study design			
Randomized controlled trial	■	■	■
Prospective cohort study			
Retrospective cohort study			
Case-control			
Case-series			
Random sequence generation*	Yes	No	Yes
Concealed allocation*	Unclear‡	No	Yes
Intention to treat*	Yes	Yes	Yes
Independent or blind assessment	No§	Yes	Yes
Complete follow-up of ≥80%	Yes**	Yes	Yes
<10% difference in follow-up between groups	Yes	No	Yes
Controlling for possible confounding†	Yes	Yes	Yes
Risk of Bias	Moderately Low	Moderately High	Low

*Applies to randomized controlled trials only.
†Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.
‡Authors state that allocation occurred via envelopes prepared by a study coordinator; however, they did not specify that the envelopes were opaque so the study did not receive credit for this criterion.
§An independent critical events committee adjudicated all clinical end points in a blinded fashion for the initial two thirds of events. However, there was a delay in adjudicating the final one third of events which were adjudicated without blinding.
**For primary outcome at 12 months (end of study) 89% follow-up, criterion met; for primary outcome at additional 24 months follow up was 73%, criterion not met for 24 months.

Procedures for determining adherence to Risk of Bias for Registry Studies

Table D4 describes Aggregate Analytics' methodology for determining whether or not a registry study has met the specific individual criterion used to assign the risk of bias. Table D5 provides an example of the format used to assess RoB for individual registry studies of treatment. A "No" indicates that the criterion was not met; an "Unclear" indicates that the criterion could not be determined with the information provided or was not reported by the author.

Appendix Table D4. Definitions of the different levels of evidence for registry studies of therapy

Risk of Bias	Study design	Criteria
Moderately low risk: Study has potential for some bias; does not meet all criteria for class I but deficiencies not likely to invalidate results or introduce significant bias	Good quality registry study/cohort study	• Designed specifically for conditions evaluated • Includes prospective data only • Validation of completeness and quality of data • Patients followed long enough for outcomes to occur • Independent outcome assessment* • Complete follow-up of ≥ 80% • Controlling for possible confounding† • Accounting for time at risk‡
Moderately high risk: Study has flaws in design and/or execution that increase potential for bias that may invalidate study results	Moderate quality registry study/cohort	• Prospective data from registry designed specifically for conditions evaluated with violation of 2 of the rest of the criteria in level II
High risk: Study has significant potential for bias; does not include design features geared toward minimizing bias and/or does not have a comparison group	Poor quality registry study/cohort	• Prospective data from registry designed specifically for conditions evaluated with violation of 3 or more of the rest of the criteria in level II • Retrospective data or data from a registry not designed specifically for conditions evaluated

Appendix Table D5: Assessment of RoB for individual registry studies

Methodological principle	Australia Registry	Swedish Registry	UK Registry
Designed specifically for conditions evaluated	Yes	Yes	No
Includes prospective data only	Yes	Yes	Unclear
Validation of completeness and quality of data	Yes	No	No
Patients followed long enough for outcomes to occur	Yes	Yes	Yes
Independent outcome assessment*	Yes	Yes	Yes
Complete follow-up of ≥ 80%	Yes	No	No
Controlling for possible confounding†	Yes	Yes	No
Accounting for time at risk‡	Yes	Yes	Yes
Risk of Bias	**Mod Low**	**Mod High**	**High**

* Outcome assessment is independent of healthcare personnel judgment. Some examples include patient reported outcomes, death, and reoperation.

† Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

‡ Equal follow-up times or for unequal follow-up times, accounting for time at risk.

Risk of Bias for Diagnostic Test Studies – Accuracy/Validity Studies

Table D6 and Figure D1 outline Aggregate Analytics' methodology for evaluating the quality of evidence for diagnostic studies of accuracy/validity and criteria used to determine the Risk of Bias (RoB). The

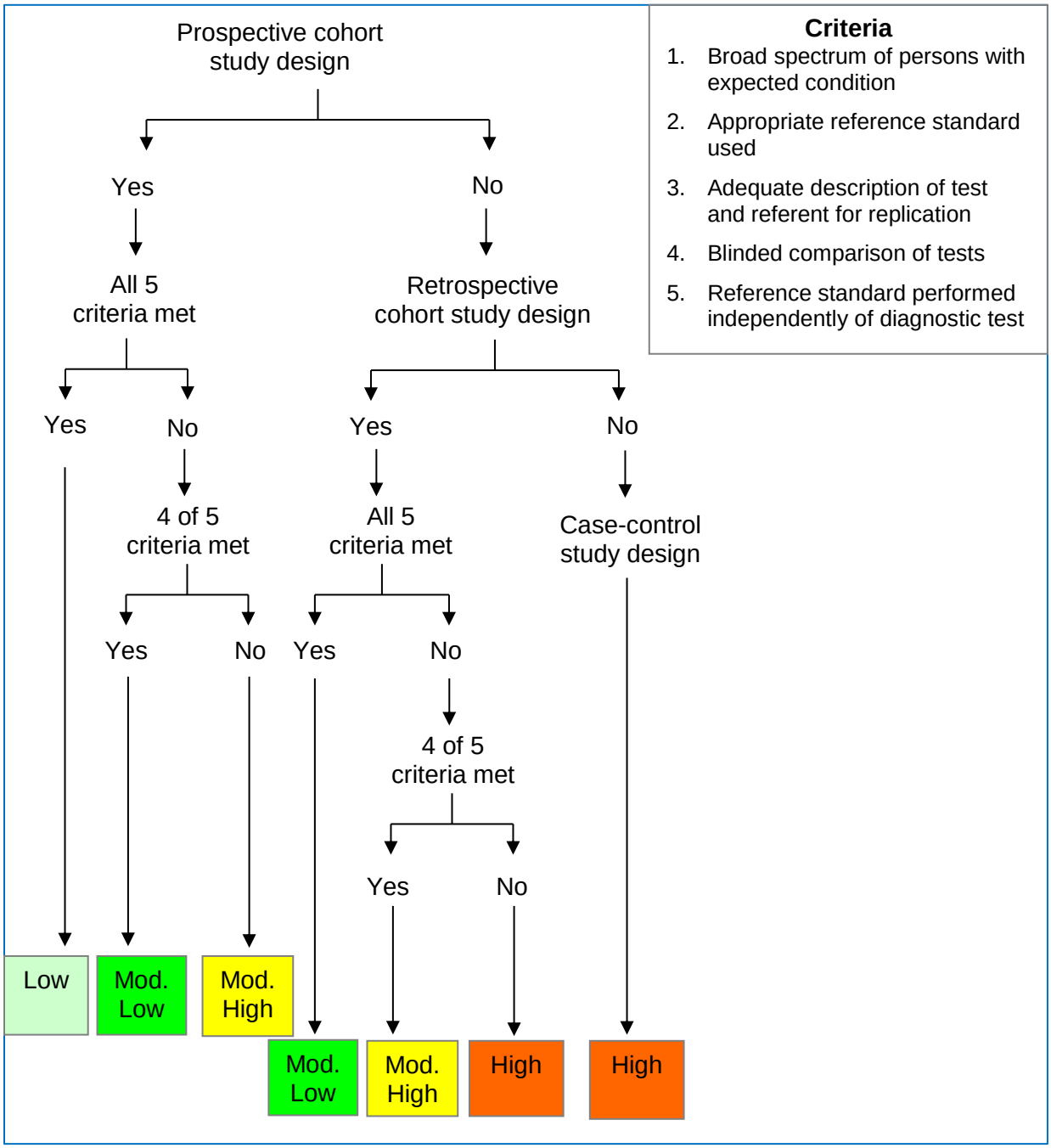
procedure that follows describes specific considerations used to determine whether or not the various criteria were met. This method takes into account the primary sources of bias for such studies.

Each included study was evaluated independently by two investigators based on the criteria below and a RoB assigned to each article, initially at the abstract level and confirmed when the full articles were reviewed. Discrepancies in RoB determination were resolved by discussion until consensus was achieved. Table D7 provides an example of the format used to assess RoB for individual studies of diagnostic test evaluation.

Appendix Table D6. Definitions of the different levels of evidence for diagnostic test accuracy/validity studies

RoB	Study type	Criteria
Low	Good quality prospective study	Broad spectrum of persons with the expected condition Appropriate reference standard used Adequate description of test and reference for replication Blinded comparison of tests with appropriate reference standard Reference standard performed independently of diagnostic test
Moderately Low	Moderate quality prospective study	Violation of any one of the criteria for a good quality prospective study
	Good quality retrospective study	Broad spectrum of persons with the expected condition Appropriate reference standard used Adequate description of test and reference for replication Blinded comparison of tests with appropriate reference standard Reference standard performed independently of diagnostic test
Moderately High	Poor quality prospective study	Violation of any two or more of the criteria for a good quality prospective study
	Moderate quality retrospective study	Violation of any one of the criteria for a good quality retrospective study
High	Poor quality retrospective study	Violation of any two or more of the criteria for a good quality retrospective study
	Case-Control Study	

Figure D1. Level of Evidence Algorithm – Accuracy/Validity Studies



Procedures for determining adherence to Risk of Bias criteria for Diagnostic Test Studies – Accuracy/Validity Studies

The following describes the method for determining whether or not a given study has met the specific individual criterion used to assign the RoB. Table D6 provides a template for indicating whether the individual criterion is met or not. A "No" indicates that the criterion was not met; an "Unclear" indicates that the criterion could not be determined with the information provided or was not reported by the author.

Determine if the study is **prospective or retrospective.**

Accuracy of diagnostic tests is best assessed using a prospective study of consecutive series of patients from a relevant patient population (i.e. study designed for prospective collection of data using specific protocols). Ideally, a consecutive series of patients or random selection from the relevant patient population should be prospectively studied. Retrospective collection of data or evaluation of patients who have had the diagnostic test and reference test previously may be more subject to bias.

If it is cannot be determined whether a prospective or retrospective approach was taken, no credit will be given for this criterion having been met.

Was a **broad spectrum of persons with the suspected condition** used to evaluate the diagnostic test and reference standard?

The study population must be comprised of those with a broad spectrum of suspected disease who are likely to have the test now or in the future. A broad spectrum would include patients with mild as well as more severe cases, those presenting early as well as late and those whose differential diagnosis may be commonly confused with the condition of interest. Subjects from specialty referral sources may be more likely to have a specific abnormality/condition than those presenting to a general family practice clinic. Overestimation of diagnostic accuracy may occur if a population with known disease is compared with a group of normal individuals instead of those from the relevant patient population.

Studies providing a description of the demographic and clinical characteristics of subjects were given credit as appropriate for the type of disease under investigation.

Was an **appropriate reference standard** used to compare the diagnostic test being evaluated?

Ideal reference standards are termed "gold" standards and in theory, provide the "truth" about the presence or absence of a condition or disease. Such standards provide a basis for comparing the accuracy of other tests and allow for the calculation of characteristics such as sensitivity, specificity and predictive values.

In most instances, the reference standard does not perfectly classify individuals with respect to the presence or absences of disease, but may reflect the current "best" reference and/or one that can be practically applied. It should be "likely" to classify patients according to disease status. A reference measure can be performed at the time of the testing. It may be an anatomical, physiological or pathological state or measure or a specific outcome at a later date.

The reference standard should be reproducible and the description of both the referent standard and the test should be explicit enough for replication, validation and generalization.

Are the **details of the test and the reference/gold standard sufficient to allow study replication**?

Are the technical features of the test and protocols used to collect information about test results, any measurements performed, planes of section evaluated, diagnostic criteria used, etc. sufficient that other investigators could duplicate the conditions and reproduce the findings in a similar population?

Was there **blinded comparison of the tests with the appropriate reference standard**?

Interpretation of the reference standard must be done without prior knowledge of the test results and the test must be interpreted without knowledge of the results of the reference test. This is necessary to avoid bias. It must be clear from the text that tests were interpreted without knowledge of the results of the other. A statement that blinding was done (for either test, preferably both) was necessary for credit.

Was the **reference standard performed independently of the diagnostic test**?

The reference standard must have been applied objectively or blindly to all patients without the results of test influencing use of the reference. If the "test" affects the reference (or referral to the reference test) or is part of the reference standard, this does not constitute independent performance of the test.

Appendix Table D7. Assessment of RoB for individual studies of diagnostic test evaluation

METHODOLOGICAL PRINCIPLE	Author 1 (1999)	Author 2 (2002)	Author 3 (2004)	Author 4 (2005)
Study Design				
Prospective cohort design			■	
Retrospective cohort design	■	■		■
Case-control design				
Broad spectrum of patients with expected condition	Yes	Yes	Unclear	Yes
Appropriate reference standard used	Yes	Yes	No	No
Adequate description of test and reference for replication	Unclear	No	No	No
Blinded comparison with appropriate reference	Yes	No	Yes	No
Reference standard performed independently of test	Yes	Yes	Yes	Yes
Risk of Bias	**Mod. Low**	**Mod. High**	**Mod. High**	**High**

* "No" indicates that the criterion was not met; "Unclear" indicates that the criterion could not be determined with the information provided or was not reported by the author.

Risk of Bias for Diagnostic Test Studies – Reliability Studies

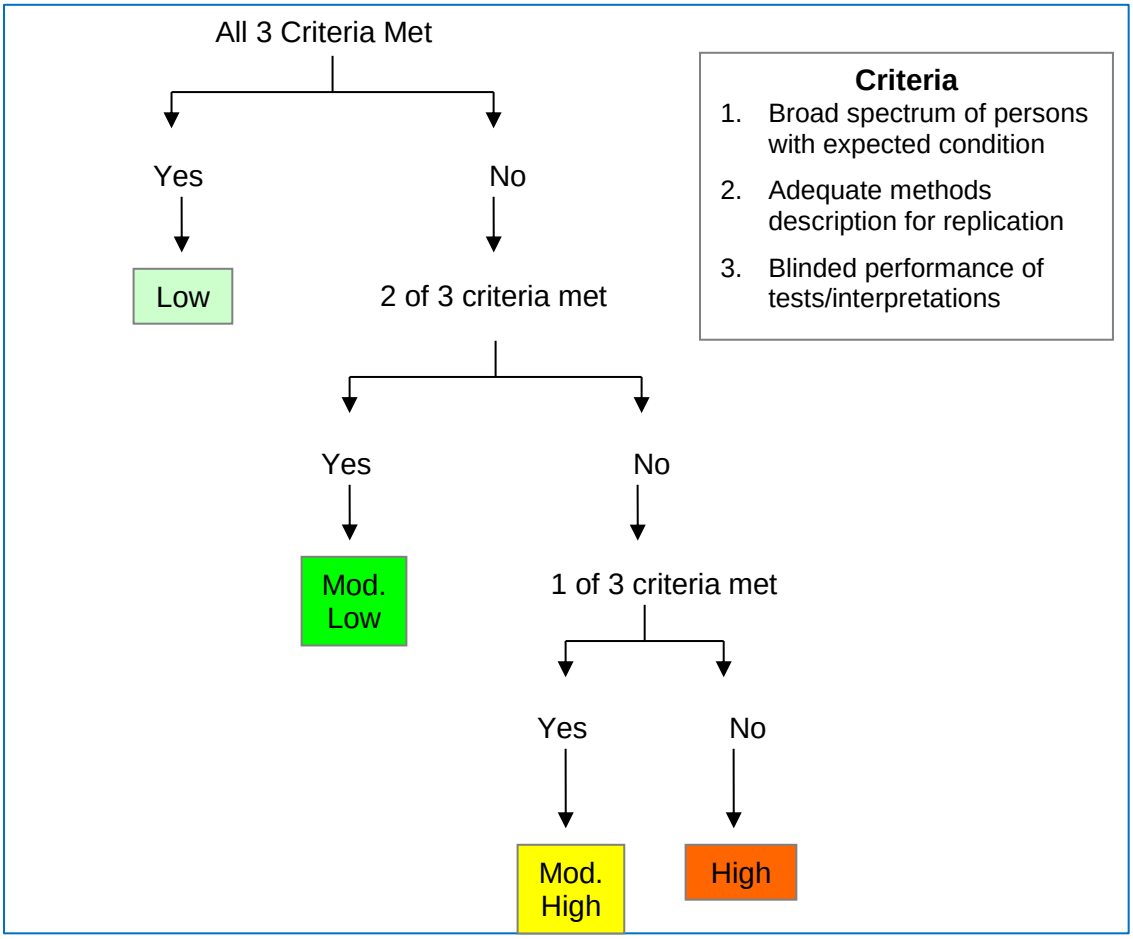
Methods for assessing the quality of evidence for reliability studies have not been well reported in the literature. Aggregate Analytics' determination of quality for such is based on epidemiologic methods for evaluating validity and reliability.

Table D8 and Figure D2 describe the method for determining whether or not a given study has met the specific individual criterion used to assign the Risk of Bias (RoB). Table D9 provides a template for indicating whether the individual criterion is met or not. A "No" indicates that the criterion was not met; an "Unclear" indicates that the criterion could not be determined with the information provided or was not reported by the author.

Appendix Table D8. Definitions of the different levels of evidence for reliability studies

RoB	Study type	Criteria
Low	Good quality study	Broad spectrum of persons with the expected condition Adequate description of methods for replication Blinded performance of tests, measurements or interpretation Second test/interpretation performed independently of the first
Moderately Low	Moderate quality	Violation of any one of the criteria for a good quality study
Moderately High	Poor quality study	Violation of any two of the criteria
High	Very poor quality study	Violation of all three of the criteria

Figure D2. Level of Evidence Algorithm – Reliability studies



Procedures for determining adherence to Risk of Bias criteria for Reliability studies
For these studies, the first performance or interpretation of the text is usually considered the "reference" and the second performance or interpretation the "test". Typical reliability studies are done using the same method (e.g., supine MRI) and include test-retest, inter- and intra-rater reliability. Statistical analysis is based on whether the same method or different methods are compared, the types of variables measured and the goal of the study. In general, the degree (%) of concordance does not account for the role of chance agreement and is not a good index of reliability.[7] Different types of *kappa* (κ) or statistical correlation are frequently used to evaluate the role of chance.

Determination of the RoB involves evaluation of the following questions:

Was a **broad spectrum of persons with the suspected condition** used to determine reliability?

The study population must be comprised of those with a broad spectrum of suspected disease who are likely to have the test now or in the future. Since differences in gender, age, body habitus and other characteristics may influence measurements and the ability to reproduce the results, the range of patients used for reliability studies is important. Ideally a random sample of patients from the relevant clinical population would be used but may not be feasible, depending on the study. A broad spectrum would include patients with mild as well as more severe cases, those presenting early as well as late and

those whose differential diagnosis may be commonly confused with the condition of interest. Reproducibility studies in a population with known disease may give different results compared with studies on a group of normal individuals and may not give an accurate picture of overall reproducibility. (If the goal of the study is to evaluate the potential for differential measurement error or bias, the separate analyses on "normal" and "diseased" populations should be done to evaluate the extent of such bias. If it is a test-retest design, the test administrations should be on the same population. If it is an inter- or inter-rater reliability study the object (e.g., radiographs) should be the same for each reading/interpretation, (e.g., the same patients' radiographs are read twice).

Are the **details of the methods sufficient to allow study replication**?

Is the description of the methods, i.e. the protocols used to collect information, measurements taken, planes of section, diagnostic criteria used, etc. sufficient that other investigators could duplicate the conditions and reproduce the findings in a similar population? Are the methods used for each part of the replication consistent?

Was there **blinded/independent performance of the repeat test administrations or interpretations**?

The second administration of the test or second interpretation of results should be done without influence of the first test/interpretation. This is necessary to avoid bias. It must be clear from the text that both tests were interpreted without knowledge of the results of the other. Examples of when the administration would not be considered blinded or independent could include:
Interpretation of the second test is to be done without prior knowledge of the test results or the first interpretation.

The timing of the second test administration or reading/interpretation of the results is not done such that sufficient time has elapsed between them to avoid influence of the first test/interpretation on the results of the second. In the case of re-administration of the test, the timing should not be so far apart that the stage/period of disease is different from the first administration.

Appendix Table D9. Assessment of risk of bias (RoB) for reliability studies

Methodological Principle	Author 1 (1999)	Author 2 (2002)	Author 3 (2004)	Author 4 (2005)
Broad spectrum of patients with expected condition	Yes	Yes	Unclear	No
Adequate description of methods for replication	Yes	Yes	No	No
Blinded/independent comparison of tests/interpretations	Yes	No	Yes	Unclear
Risk of Bias	**Low**	**Mod. Low**	**Mod. High**	**High**

Determination of Overall Strength (Quality) of Evidence
The strength of evidence for the overall body of evidence for all *critical health outcomes* was assessed by one researcher following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation) as outlined by the Agency for Healthcare Research and Quality (AHRQ)[1,6,8].

The strength of evidence was based on the highest quality evidence available for a given *primary* outcome. In determining the strength of body of evidence regarding a given *primary* outcome, the following domains were considered:

- **Risk of bias:** the extent to which the included studies have protection against bias.
- **Consistency:** the degree to which the included studies report results are similar in terms of range and variability.
- **Directness:** describes whether the evidence is directly related to patient health outcomes.
- **Precision:** describes the level of certainty surrounding the effect estimates.
- **Publication bias:** is considered when there is concern of selective publishing.

All AHRQ "required" and "additional" domains (risk of bias, consistency, directness, precision, and if possible, publication bias) were assessed. Bodies of evidence consisting of RCTs were initially considered as High strength of evidence (SoE), while those that comprised nonrandomized studies began as Low strength of evidence. The strength of evidence could be downgraded based on the limitations described above. There could also be situations where the *nonrandomized* studies could be upgraded, including the presence of plausible unmeasured confounding and bias that would decrease an observed effect or increase an effect if none was observed, presence of a dose-response relationship, and large magnitude of effect (strength of association) *if no downgrades for domains above*. Publication and reporting bias are difficult to assess. Publication bias is particularly difficult to assess with fewer than 10 RCTs (AHRQ methods guide). When publication bias was unknown in all studies and this domain is often eliminated from the strength of evidence tables for our reports. The final strength of evidence for each **primary** outcome was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows:

High— Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.

Moderate— Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are probably stable but some doubt remains.

Low— Limited confidence that effect size estimates lie close to the true effect for this outcome; important or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or that the estimate is close to the true effect.

Insufficient— We have no evidence, are unable to estimate an effect or have no confidence in the effect estimate for this outcome; OR no available evidence or the body of evidence has unacceptable deficiencies precluding judgment.

Similar methods for determining the overall quality (strength) of evidence related to economic studies have not been reported, thus the overall strength of evidence for outcomes reported in Key Question 4 was not assessed.

Appendix Table D10. Example methodology outline for determining overall strength of evidence (SoE):

All AHRQ "required" and "additional" domains* are assessed. Only those that influence the baseline grade are listed in table below.

Baseline strength: HIGH = RCTs. LOW = observational, cohort studies, administrative data studies.

DOWNGRADE: Risk of bias for the individual article evaluations (1 or 2); Inconsistency** of results (1 or 2); Indirectness of evidence (1 or 2); Imprecision of effect estimates (1 or 2); Sub-group analyses not stated *a priori* and no test for interaction (2)

UPGRADE (non-randomized studies): Large magnitude of effect (1 or 2); Dose response gradient (1) done for observational studies ***if no downgrade for domains above***

Outcome	Strength of Evidence	Conclusions & Comments	Baseline SOE	DOWNGRADE	UPGRADE
Outcome	**HIGH**	Summary of findings	**HIGH** RCTs	**NO** consistent, direct, and precise estimates	**NO**
Outcome	**MODERATE**	Summary of findings	**LOW** Cohort studies	**NO** consistent, direct, and precise estimates; high quality (moderately low ROB)	**YES** Large effect
Outcome	**LOW**	Summary of findings	**HIGH** RCTs	**YES (2)** Inconsistent Indirect	**NO**

*Required domains: risk of bias, consistency, directness, precision. Plausible confounding that would decrease observed effect is accounted for in our baseline risk of bias assessment through individual article evaluation. Additional domains: dose-response, strength of association, publication bias.

**Single study = "consistency unknown", may or may not be downgraded

Assessment of Economic Studies

Full formal economic analyses evaluate both costs and clinical outcomes of two or more alternative interventions. The four primary types are cost minimization analysis (CMA), cost-utility analysis (CUA), cost-effectiveness analysis (CEA), and cost-benefit analyses (CBA). Each employs different methodologies, potentially complicating critical appraisal, but some common criteria can be assessed across studies.

No standard, universally accepted method of critical appraisal of economic analyses is currently in use. A number of checklists [Canadian, BMJ, AMA] are available to facilitate critique of such studies. The Quality of Health Economic Studies (QHES) instrument developed by Ofman, et al.[7] QHES embodies the primary components relevant for critical appraisal of economic studies. It also incorporates a weighted scoring process and which was used as one factor to assess included economic studies. This tool has not yet undergone extensive evaluation for broader use but provides a valuable starting point for critique.

In addition to assessment of criteria in the QHES, other factors are important in critical appraisal of studies from an epidemiologic perspective to assist in evaluation of generalizability and potential sources of study bias.

Such factors include:

- Are the interventions applied to similar populations (e.g., with respect to age, gender, medical conditions, etc.)? To what extent are the populations for each intervention comparable and are differences considered or accounted for? To what extent are population characteristics consistent with "real world" applications of the comparators?
- Are the sample sizes adequate so as to provide a reasonable representation of individuals to whom the technology would be applied?
- What types of studies form the basis for the data used in the analyses? Data (e.g., complication rates) from randomized controlled trials or well-conducted, methodologically rigorous cohort studies for data collection are generally of highest quality compared with case series or studies with historical cohorts.
- Were the interventions applied in a comparable manner (e.g., similar protocols, follow-up procedures, evaluation of outcomes, etc.)?
- How were the data and/or patients selected or sampled (e.g., a random selection of claims for the intervention from a given year/source or all claims)? What specific inclusion/exclusion criteria or processes were used?
- Were the outcomes and consequences of the interventions being compared comparable for each? (e.g., were all of the relevant consequences/complications for each intervention considered or do they primarily reflect those for one intervention?

An outline of suggested standards for reporting stem cell studies based on Murray and Chu[2,5] can be found below.

Appendix Table D11. Example of methodology for assessing reporting standards for studies of stem cell therapy

Reporting Standards*	Author Year		
Study Reporting			
Randomized controlled trial - CONSORT	Yes		
Observational study - STROBE			
SR with/without meta-analysis - PRISMA			
Patient demographics	limited		
Patient comorbidities	No		
Patient medications (anti-inflammatory)	Yes		
Diagnosis/injury (chronicity, relevant grading)	Yes		
Previous interventions	Excluded		
Cell source, harvesting , time to processing*	Minimal		
Cell processing specified*	Limited		
Cell culture detailed*	N/A		
MSC characteristics*	No		
Delivery*	minimal		
Post-intervention care (PT, immobilization, etc.)	Yes		
Criteria met			

* Studies must report sufficient detail to allow for evaluation and replication of methods

- Harvesting: anatomical source, equipment, reagents, storage media and environment and
- Processing: digestion methods(solutions, concentrations, volumes, duration, agitation, temperature, identification of commercial system; methods for purification and assurance of purity;
- MSC source, details of cellular composition, immunophenotype (tested in vitro), viability
- Site of delivery, suspension volume, details of media used as delivery vehicles, and if co-delivered with carriers, growth factors or scaffold

APPENDIX E. Study Quality: Risk of Bias evaluation

Appendix Table E1. Risk of Bias Assessment: Knee OA trials comparing autologous, *non-culture-expanded* BM-derived stem cells versus controls* in different patients

Methodological Principle	Centeno 2018	Goncars 2017	Ruane 2019	Tucker 2019
Study design				
Randomized controlled trial	■	■	■	■
Prospective cohort study				
Retrospective cohort study				
Case-control				
Case-series				
Random sequence generation†	Yes	Unclear	Unclear	Unclear
Concealed allocation†	Unclear	No	No	Unclear
Intention to treat†	Unclear	Yes	Yes	Yes
Independent or blind assessment	No	No	No	Yes
Complete follow-up of ≥80%	Unclear	Yes	Yes	Yes
<10% difference in follow-up between groups	Unclear	Yes	No	Yes
Controlling for possible confounding‡	Unclear	Unclear	Yes	Unclear
Risk of Bias	**Moderately High**	**Moderately High**	**Moderately High**	**Moderately High**

Unclear indicates that the study had insufficient detail to determine whether criteria were met
*Centeno = Exercise control group; Goncars = Hyaluronic acid (HA) control group
†Applies only to randomized controlled trials.
‡Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

Investigator Notes:

Centeno 2018:

- **Concealed allocation**: only says that "enrollment randomization envelopes [were kept] blinded until time of enrollment by study coordinator" but does specify process by which that was carried out.
- **ITT**: Point of randomization unclear; appears to have been when consent provided, rationale for physician exclusion of patients not clear (see below); unclear how withdrawals during treatment were analyzed by 3 months; all exercise group crossed over at 3 months.
- **Independent/blind assessment**: primary outcomes were patient-reported and patients were not blinded to treatments (stem cells vs. exercise)
- **Follow-up**: patients crossed over after 3 months; data on attrition not provided; withdrawals appeared to be AFTER randomization based on text – CONSORT diagram does not indicate where randomization was done and is inconsistent with text.
    - If randomization occurred and time of consent, it appears that 7 individuals were withdrawn (4 voluntarily, 3 by physician no rationale provided)
    - 14 total appear to have withdrawn after randomization, 4 voluntarily, 7 by investigator (for having additional therapies and an additional 3 who had TKA) based on results text
    - If 7 withdrawn at time of consent and an addition 14 withdrew after treatment delivered, follow-up is 34/55 or 62%
    - N's for outcomes at follow-up times NR
- **Confounding**: only limited patient demographics provided; baseline scores for outcome measures not presented except via figure (cannot determine if LEAS and SF-12 physical are comparable at baseline)
- **Funding**: Industry

Goncars 2017:

- **Randomization, Concealed allocation**: No information/statement provided regarding either criteria; Only states that enrolled pts were randomized 1:1
- **Independent/blind assessment**: primary outcomes were patient-reported and patients were not blinded to treatments (stem cells vs. HA); no mention of assessors/assessor blinding either
- **Confounding**: No Table 1 outlining baseline characteristics; no statement that groups were found to be/not to be comparable at baseline; Figure 1 includes age, sex and K-grade only for both groups – difference in age (53.4 vs. 58.6 years) and sex (54% vs. 36% male) relevance unclear (KL grade comparable b/w groups) due to small sample sizes. Baseline outcomes data not reported.
- **Funding**: NR

Ruane:

- **Randomization, Concealed allocation**: Unclear how randomization was performed; protocol states that "the randomization allocation schedule will be developed by the research team member performing the statistical analyses and will not be shared with the remainder of the research team" but does not provided specifics; unclear if criteria described meets concealed allocation
- **Independent/blind assessment**: patient reported outcomes and it does not appear that the patients were blinded per the following statement: "The primary investigator (i.e., the physician providing the treatment) will not be blinded to group allocation as knowledge of group allocation will be essential to deliver two distinctly different treatment procedures and to provide the participant with an explanation of the clinical procedure prior to initiating the treatment."
- **F/U**: 84% (27/32); 76% (13/17) BMC vs. 93% (14/15)
- **Confounding**: Difference in baseline demographics and previous procedures; however protocol states that the statiscal methods employed would control for baseline imbalances.

Tucker:

- **Randomization, Concealed allocation**: Unclear how randomization was performed; protocol states that "Access to the randomization code will be strictly controlled and only the processing technician, who will not be involved in safety or efficacy evaluation, will know to which group the subject is randomized on the day of the surgery"; unclear if criteria described meets concealed allocation
- **Confounding**: List of baseline demographics not robust; no mention of controlling in the protocol

Appendix Table E2. Risk of Bias Assessment: Knee OA trials comparing autologous, *non-culture-expanded* BM-derived stem cells versus placebo in knees in the same patient.

Methodological Principle	Shapiro 2017/2018
Study design	
Randomized controlled trial	■
Prospective cohort study	
Retrospective cohort study	
Case-control	
Case-series	
Random sequence generation*	Yes
Concealed allocation*	No
Intention to treat*	N/A
Accounting for repeated measures (knees in same patient)	Yes (paired Wilcoxon signed rank test)
Independent or blind assessment	Yes
Complete follow-up of ≥80%	Yes
<10% difference in follow-up between groups	N/A
Controlling for possible confounding†	N/A
Risk of Bias	**Moderately High**

Unclear indicates that the study had insufficient detail to determine whether criteria were met
*Applies only to randomized controlled trials.
†Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

Investigator Notes:
Shapiro 2017/2018

- **Concealed allocation:** No statement of concealment
- **Confounding:**: Demographics, patient characteristics, OA severity, prior surgery NR by treatment group; comorbidities NR; baseline outcomes score values appear comparable
- **Funding**: Private research institution (not industry)

Appendix Table E3. Risk of Bias Assessment: Knee OA trials comparing autologous, *culture-expanded stem cells* versus controls*

Methodological Principle	Emadedin 2018	Freitag 2019	Lamo-Espinosa 2016, 2018	Lee 2019	Lu 2019
Study design					
Randomized controlled trial	■	■	■	■	■
Prospective cohort study					
Retrospective cohort study					
Case-control					
Case-series					
Random sequence generation†	Yes	Yes	Yes	Unclear	Yes
Concealed allocation†	Yes	Unclear	Yes	No	Yes
Intention to treat†	No	No	Yes	Yes	Yes
Independent or blind assessment	Yes	No	No	Yes	Yes
Complete follow-up of ≥80%	Yes	Yes	Yes	Yes	Yes
<10% difference in follow-up between groups	No	Yes‡	No§	Yes	Yes
Controlling for possible confounding**	Unclear	No	Unclear	Yes	No
Risk of Bias	**Moderately High**	**Moderately High**	**Moderately High**	**Moderately Low**	**Moderately Low**

Unclear indicates that the study had insufficient detail to determine whether criteria were met
***Emadedin**: bone marrow-derived (BM) mesenchymal stems cells (MSCs) vs. placebo; **Freitag**: Adipose-derived (AD) MSCs vs. usual care; **Lamo-Espinosa**: BM-MSCs vs. hyaluronic acid (HA); **Lee**: AD-MSCs vs. placebo; **Lu**: AD multipotent progenitor cells (MPCs) vs. HA.
†Applies only to randomized controlled trials.
‡Differential loss-to-follow-up is based on the final three treatment groups.
§Based on comparison between the two intervention groups vs. the control group (differences between the two intervention groups were considered for RoB assessment as that comparison is not the focus of the review)
**Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

Investigator Notes:

Emadedin 2018

- **ITT**: 2 patients randomized to MSC did not received the treatment and no explanation provided.
- **Follow-up:** overall: 88% (43/49); b/w groups: 79% (19/24) vs. 96% (24/25)

- **Confounding:** Kellgren-Lawrence (KL) grades somewhat different between groups (fewer MSC [68%] vs. placebo [83%] had KL grade 3 and more had grade 4 [21% vs. 13%] but sample sizes were small; baseline scores not reported for outcomes, only change scores given
- **Funding**: Non-profit organization

Freitag 2019

- **ITT:** A third treatment group (5 injections of 40 x 10^6 AD-MSCs) was intended but discontinued due to "observed and reproducible moderate adverse events in a concurrently run study with the same treatment protocol (documented as increasing self-limiting pain with sequential injections at monthly intervals)." Participants that were already randomized to this treatment group and who had not yet started treatment were re-randomized to another trial group. Authors do not provided information regarding how many patients were initially randomized to this third group or the number of patients who had started treatment and therefore were excluded vs. number of patients who had not yet commenced therapy and were re-randomized; and there is no accounting for those patients that were excluded after randomization.
- **Independent/blind assessment**: primary outcomes were patient-reported and patients were not blinded to treatments (stem cells vs. conservative care)
- **Concealed allocation**: No information/statement provided
- **Follow-up**: b/w group diff; 95% vs. 100% when injection groups combined; when considered separately the rates are 90% (1 inj.) vs. 100% (2 inj.) vs. 100% (control).
- **Confounding:** limited information on patient characteristics and sample size is very small; statistical difference between groups in BMI (both treatment groups obese while control group overweight, p=0.02); unclear if baseline KOOS symptom and ADL scores were significantly different between groups at baseline; KOOS Sport, QOL appear to be different at baseline (NOTE: all based on figures – supplemental table #3 indicates only KOOS symptom was statistically significantly different)
- **Funding**: Industry

Lamo-Espinosa 2016, 2018

- **Independent/blind assessment**: primary outcomes were patient-reported and patients were not blinded to treatments (stem cells vs. HA)
- **Follow-up**: 94% (30/32); 100% (low-dose; 10/10) vs. 100% (high dose; 10/10) vs. 84% (control; 10/12).
- **Confounding**: sample sizes are small; relevance of differences between groups at baseline is unclear; authors state that the groups showed uneven distribution according to the KL scale but without statistical significance; other characteristics appeared to be statistically similar though there were differences: time since OA diagnosis 3 to 4 years longer in high dose group; only 4 males in low-dose group; baseline WOMAC function and overall and WORMS may differ between groups; baseline VAS scores appear to be comparable based on figures
- **Funding**: Government (Spain)

Lee 2019

- **Randomization**: No description of methods used; only state that patients were "randomized".
- **Concealed allocation**: No description of methods used; only says that "patients were blindly assigned to [groups]" but does specify process.
- **Follow-up**: 87% (47/53); 88% (23/26) vs. 89% (24/27)
- **Confounding**: baseline variables seem similar between groups, but sample size is all and SDs are very large
- **Funding**: Industry

Lu 2019

- **Confounding**: age was statistically different between groups and not controlled for; NS differences in other baseline variables, however for baseline measures, SD's are large indicating substantial variability; % who had prior treatment and concomitant diagnoses were not statistically different; sample size is small.
- **Funding**: Industry & Government

Appendix Table E4. Risk of Bias Assessment: Knee OA trials comparing allogenic, *culture-expanded* stem cells versus controls*

Methodological Principle	Khalifeh Soltani 2019	Vega 2015
Study design		
Randomized controlled trial	■	■
Prospective cohort study		
Retrospective cohort study		
Case-control		
Case-series		
Random sequence generation†	Yes	Yes
Concealed allocation†	Unclear	Yes
Intention to treat†	Yes	Yes
Independent or blind assessment	Yes	Unclear
Complete follow-up of ≥80%	Yes	Unclear
<10% difference in follow-up between groups	Yes	Unclear
Controlling for possible confounding‡	No	Unclear
Risk of Bias	**Moderately Low**	**Moderately High**

Unclear indicates that the study had insufficient detail to determine whether criteria were met
***Khalifeh Soltani**: placenta-derived mesenchymal stem cells (MSCs) vs. placebo; **Vega**: bone marrow-derived MSCs vs. hyaluronic acid.
†Applies only to randomized controlled trials.
‡Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

Investigator Notes:

Khalifeh Soltani

- **Concealed allocation**: no indication/statement of how or if this was done.
- **Confounding**: baseline QOL-BI (p=0.001) and ROM (p=0.007) differed statistically b/w groups; ADL seem different; small sample size
- **Funding:** Private research institution (not industry)

Vega 2015

- **ITT:** benefit of the doubt given as it appears based on numbers in results tables that all patients were analyzed according to the group they were randomized to.
- **Independent/blind assessment:** authors state that participants, providers, and radiologists were blinded AFTER group assignment; unclear what this means.
- **Follow-up**: no consort diagram and no description of how many patients were eligible, how many enrolled, how many randomized and received treatment and therefore follow-up cannot be calculated; also further indication of loss-to-follow-up not provided by authors.
- **Controlling**: baseline variables provided in table 2 appear fairly similar b/w groups (KL grade; previous surgeries; more controls had steroids, more MSCs had PRP?); however, some differences in the baseline outcome measures scores (e.g., VAS 10 points higher in control group) – small sample size makes relevance unclear.
- **Funding:** Government (Spain)

Appendix Table E5. Risk of Bias Assessment: Knee OA nonrandomized cohort study evaluating autologous, non-culture-expanded bone marrow-aspirate concentrate stem cells

	Autologous, non-culture-expanded BM-MSCs	Allogenic (amniotic fluid) stem cells
Methodological Principle	**Garay-Mendoza 2018**	**Bhattacharya 2011**
Study design		
Randomized controlled trial		
Prospective cohort study	■	
Retrospective cohort study		
Case-control		
Case-series		
Random sequence generation*	N/A	N/A
Concealed allocation*	N/A	N/A
Intention to treat*	N/A	N/A
Independent or blind assessment	No	Unclear
Complete follow-up of ≥80%	Yes	Yes
<10% difference in follow-up between groups	Yes	Yes
Controlling for possible confounding†	Unclear	Unclear
Risk of Bias	**High**	**High**

Unclear indicates that the study had insufficient detail to determine whether criteria were met
BM-MSC = bone marrow-derived mesenchymal stem cells.
*Applies only to randomized controlled trials.
†Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

Garay-Mendoza 2018:

- **Independent/blind assessment**: primary outcomes were patient-reported and patients were not blinded to treatments (stem cells vs. acetominophen)
- **Controlling**: authors do not provide a robust set of baseline data; they do not present the KL grades but only state that they were similar between groups.

Appendix Table E6. Risk of Bias Assessment: Partial rotator cuff tear cohort comparing autologous, non-*culture-expanded* stem cells versus PT

Methodological Principle	Kim 2018
Study design	
Randomized controlled trial	
Prospective cohort study	■
Retrospective cohort study	
Case-control	
Case-series	
Random sequence generation†	N/A
Concealed allocation†	N/A
Intention to treat†	N/A
Independent or blind assessment	No
Complete follow-up of ≥80%	Yes
<10% difference in follow-up between groups	Yes
Controlling for possible confounding‡	No
Risk of Bias	**Moderately High**

*Unclear indicates that the study had insufficient detail to determine whether criteria were met
†Applies only to randomized controlled trials.
‡Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed

Appendix Table E7. Risk of Bias for RCTs of Intervertebral Disc Repair

Methodological Principle	Noriega 2017
Study design	
Randomized controlled trial	■
Prospective Cohort Study	
Retrospective Cohort Study	
Prospective Case Series	
Retrospective Case Series	
Random sequence generation*	Yes
Concealed allocation*	Yes
Intention-to-treat*	Unclear
Independent/blind assessment	No (patient-reported) §
Complete follow-up of ≥80%	Unclear**
<10% difference in follow-up between groups	Yes
Controlling for possible confounding†	Unclear††
Risk of Bias	**Moderately High**

*Applies only to randomized controlled trials
†Groups must be comparable on baseline characteristics or evidence of control for confounding present
§ Authors state that patients and assessors were "blinded after assignment", thus patient-reported outcomes do not appear to have been blinded, although radiographic measures were blinded.
** Authors do provide enough information on the screening process or number of eligible patients to adequately determine

follow-up or if ITT was followed.
†† Group population characteristics were not reported separately. No table of baseline demographics by group provided.

Appendix Table E8. Risk of Bias for RCTs of Tendinopathies

Methodological Principle	Usuelli 2018
Study design	
Randomized controlled trial	■
Prospective cohort study	
Retrospective cohort study	
Case-control	
Case-series	
Random sequence generation*	Unclear
Concealed allocation*	Yes
Intention to treat*	Yes
Independent or blind assessment	Yes (assessor) No (patients
Complete follow-up of ≥80%	Yes
<10% difference in follow-up between groups	Yes
Controlling for possible confounding†	No
Risk of Bias	**Moderately high**

Unclear indicates that the study had insufficient detail to determine whether criteria were met
*Applies only to randomized controlled trials.
†Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

- 67% of the AD-SVF group vs. 35% of the PRP group were male; the AD-SVF group were slightly older; more patients in the SVF group (7/21) vs. the PRP group (5/23) had bilateral treatment.
- Authors report that radiologists and assessors were blinded but make no statement that patients were blinded to treatment allocation and adipose tissue appears to have been harvested only from patients assigned to the SVF group. For patient reported outcomes (e.g. VAS pain), there is a potential for bias.

Appendix Table E9. Methodological quality of registry studies assessing stem cell therapies.

Methodological principle	Centeno 2014 (Hip OA)§ Centeno 2015 (Shoulder OA/Rotator Cuff Tear)§ Centeno 2018 (ACL Tear)§ Centeno 2014 (Knee OA)§ Centeno 2016 (safety specific – mixed conditions)§
Study comparing treatment options?	No (case series)
Designed specifically for condition evaluated	No
Includes prospective data only	Unclear
Validation of completeness and quality of data	Unclear
Patients followed long enough for outcomes to occur	Yes (short-term) No (long-term)
Independent outcome assessment*	Yes
Complete follow-up of ≥ 80%	No
Controlling for possible confounding†	No
Accounting for time at risk‡	Unclear/not comparative study
Risk of Bias	**High**

* Outcome assessment is independent of healthcare personnel judgment. Some examples include patient reported outcomes, death, and reoperation.
† Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.
‡ Equal follow-up times or for unequal follow-up times, accounting for time at risk.
§This HTA has included 5 registry studies from the same author group as part of its evidence base. The evaluation above applies to all studies using this registry.

APPENDIX F. Data Abstraction of Included Studies

Appendix Table F1: Study characteristics and demographics for comparative studies evaluating the use of stem cell therapies for knee osteoarthritis

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
Tucker 2019 N=39 USA RCT (ongoing – partially published results; data are from clinical trials.gov) ROB	Inclusion: 1. Grade II or Grade III osteoarthritis using Kellgren-Lawrence grading scale (K-L Grade) as diagnosed using weight bearing X-ray, physician review, and/or pre-op MRI. 2. Study Subjects must have failed a minimum of at least two conservative therapies, spanning a period of at least 3 months, including (i) oral pain medications, (ii) physical therapy, (iii) corticosteroid injection of the knee, (iv) viscosupplementation injection of the knee. 3. Study Subjects must be willing to voluntarily give written Informed Consent to participate in the study and sign the Health Insurance Portability and Accountability Act (HIPAA) authorization before any study procedures are performed. 4. Males and females 40-75 years old. 5. Subjects will be in good health (ASA Class I-II) with a BMI < 35.	Low dose SVF Injection (n=13) **Cell Type**: nucleated SVF **Cell Source**: Adipose tissue from abdominal and thigh **Cell Preparation**: SVF Procedure Pack for fat processing **Cell Expansion**: No **Cell Concentration**: 15 x 10^6 (range 12.5 x 10^6 to 17.2 x 10^6) **Cell Delivery**: Ultrasound guided intra-articular injection **Anesthetic use:** Lidocaine **Number of injections**: 1 High dose SVF injection (n=13) Same as above except cell dose = 30 x 10^6 (range 27.5 x 10^6 to 32.5 x 10^6) Placebo (4 mL lactated Ringer's) injection (n=13) Post-tx Protocol (across all treatment groups) crutches and asked to be non-weight bearing on the injected	*Low dose SVF vs. High dose SVF vs. Placebo* **Mean age**: 60.5 vs. 59.5 vs. 57.1 years **% Male**: 31% vs. 54% vs. 46% **Ethnicity** Hispanic/Latino: 8% vs. 15% vs. 23% Not Hispanic/Latino: 92% vs. 85% vs. 77% (All patients were white except one patient in the placebo group who was black/African American) **KL OA Grade** II: 31% (4/13) vs. 31% (4/13) vs. 31% (4/13) III: 69% (9/13) vs. 69% (9/13) vs. 69% (9/13)	6 months 12 months	• Western Ontario and McMaster Universities Osteoarthritis (WOMAC) (0-100, higher=greater disability) • Adverse Events	**Funding**: NR **COI**: NR

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
	6. Subjects must have continued pain in the knee despite conservative therapies for at least 63 months. 7. Subjects with unilateral disease must present with a knee pain score ≥6 and ≤16 using the short-form WOMAC pain (A1 subscale, 20 total points). 8. Subjects with bilateral disease will only be treated in one knee. The treated knee must have K-L grade II or III with a pain score ≥6 and ≤16 using the short-form WOMAC pain (A1 subscale, 20 total points) and the contralateral knee has a K-L grade of I or II with a pain score <6 using the short-form WOMAC pain (A1 subscale, 20 total points). 9. Subjects must speak, read and understand English. 10. Subjects must be reasonably able to return for multiple follow-up visits. <u>Exclusion</u>: 1. Subjects whose knee pain is caused by, (i) diffuse edema, (ii) displaced meniscus tear, (iii) lesion greater than 1 cm in any	knee for two (2) days. The patient will be encouraged and allowed to bend and flex the knee as long as non-weight bearing conditions are maintained.				

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
	direction, or (iv) osteo chondritis desicans. 2. Subjects who have had surgery of either knee within 6 months prior to the screening visit. 3. Subjects who have had a major injury to the targeted knee within 12 months prior to enrolling in the study. 4. Subjects who have had an injection in either knee in the prior 3 months, including corticosteroids, viscosupplementation or platelet rich plasma (PRP). 5. Subjects who have gout, rheumatoid arthritis, lupus arthropathy, psoriatic arthritis, avascular necrosis, severe bone deformity, infection of the knee joint, fibromyalgia, pes anserine bursitis, or neurogenic or vascular claudication. 6. Subjects who have symptomatic OA of the hips, spine, or ankle that would interfere with the evaluation of the treated knee. 7. Subjects that are unwilling to stop taking prescription or over the counter pain medication 7 days prior to any visit					

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
	8. Subjects that are allergic to lidocaine, epinephrine or valium 9. Subjects with a history of bleeding disorders, anticoagulation therapy that cannot be stopped as follows prior to injection Thrombolytics and anti-platelet medication including but not limited to Coumadin (warfarin) for 3 days, Plavix (colpidogrel) for 3 days, ASA/NSAIDs/fish oil supplements for 7 days, Xeralta® (rivaroxaban) for 24 hours. 10. Subjects with systemic immunosuppressant use within six (6) weeks from screening and subjects with HIV/viral hepatitis. 11. Subjects with chondrocalcinosis, Paget's disease and Villonodular synovitis 12. Subjects that use any form of tobacco 13. Women that are pregnant or planning to become pregnant during the study. 14. Subjects on long term use of oral steroids 15. History of any chemotherapy or radiation					

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
	therapy of the targeted/treatment leg or adipose harvest site. 16. Subjects currently on worker's compensation					
Ruane 2019 (data are from clinicaltrials.gov) N=32 USA RCT ROB	<u>Inclusion</u>: 1) Male and female patients 40 to 70 years old 2) Diagnosed with KOA based on the American College of Rheumatology criteria including symptomatic reports and radiographic findings 3) Kellgren-Lawrence grade 1-3 based on a radiograph within 6 months of presentation to the clinic 4) Symptomatic evidence of tibiofemoral osteoarthritis for ≥6 months 5) Average numeric pain rating of 4 – 8 on a scale of zero to 10 (defined as moderate level) over the past week <u>Exclusion</u>: 1) Grade 4 KOA according to the Kellgren-Lawrence scale 2) History of intraarticular viscosupplementation or steroid injection in the target knee in the past 6 months at the time of the baseline visit or	<u>BMAC + PRP Injection (n=17)</u> **Cell Type**: BMAC **Cell Source**: Bone near the hip (volume = 60 mL) **Cell Preparation**: NR **Cell Expansion**: No **Cell Concentration**: NR **Cell Delivery**: Ultrasound guided intraarticular injection (~5-6 mL of concentrate was injected) **Anesthetic use:** No **Number of injections**: 1 **PRP injection**: 60mL of venous blood will be withdrawn from either arm. Approximately 4-5 ml of platelet-rich plasma will be introduced under ultrasound guidance to the subject's target knee by the study physician. <u>Gel-One® Hyaluronate Injection (n=15)</u> Gel-One® is a hyaluronate gel used in the treatment	*BMAC + PRP vs. Gel-One®* **Mean age**: 58 vs. 59 years **% Male**: 53% vs. 67% **Mean BMI**: 29.2 vs. 29.2 **KL OA Grade** I: 29% (5/17) vs. 13% (2/15) II: 35% (6/17) vs. 53% (8/15) III: 35% (6/17) vs. 33% (5/15) **Previous surgery on target knee**: 65% (11/17) vs. 47% (7/17) **Previous PT on Target Knee**: 77% (13/17) vs. 40% (6/15)	<u>F/U</u> 3 months 6 months 12 months <u>% Followed</u> 94% (30/32)	• Knee Injury and Osteoarthritis Outcome Score (KOOS) (0-100; higher=best possible score) • Numerical Pain Rating Scale score (NPRS) (0-10; higher=increased pain) • PROMIS Global Health Physical Score (score of 50 = average patient)	**Funding**: Not-for-profit healthcare system **COI**: All Principal Investigators are employed by the organization sponsoring the study.

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
	intraarticular injection planned during the trial 3) History of arthroscopic surgery in the target knee in the past 12 months at the time of presentation to the clinic or planned surgery during the trial period (e.g., scheduled for/awaiting arthroscopy or a knee replacement procedure) 4) Bilateral KOA (unless the contralateral knee involvement is limited to radiographic osteoarthritis and not symptomatic) 5) Ipsilateral (same side) or contralateral (opposite side) symptomatic osteoarthritis of hip or ankle 6) Clinically apparent tense effusion or other acute inflammation of the target knee at the time of presentation to the clinic 7) Active infection of either lower extremity such as cellulitis or any skin disease or infection in the area where BMAC is aspirated, blood is drawn, or an injection is given 8) History of diagnosis of any of the following: 1) septic osteoarthritis of any joint, 2) inflammatory arthropathy such	of knee osteoarthritis by injection into the knee joint (intra-articular). Gel-One® hyaluronate injection: Patients will receive a single injection of Gel-One® (3 ml syringe of Gel-One® - 1% solution [10 mg/mL], 30mg total hyaluronan) into the target knee. Injections will be performed by the study physician under real-time dynamic ultrasound guidance.				

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
	as rheumatoid arthritis, gout, pseudogout, lupus, crystalline arthropathy, chondrocalcinosis and other rheumatology diagnoses 9) Cruciate/collateral knee ligament instability, ligament laxity, or meniscal instability of the target knee 10) Significant alignment deformity such as varus/valgus of the target knee in the judgment of the investigator 11) Currently pregnant, nursing, or planning to become pregnant during the trial period 12) Previous or known allergic reaction or hypersensitivity to heparin; sodium citrate; hyaluronan products or specifically Gel-One®; cinnamon; bird products such as feathers, eggs, or poultry; avian proteins 13) Not suitable for BMAC tissue allograft injection per physician (e.g., blood dyscrasia) 14) Unable to be prescribed stable dose of NSAIDs and/or tramadol based on medical history as ad lib use of OTC analgesics will be allowed in both groups after treatment 15) Current cigarette smoker					

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
	16) Unable to give informed consent 17) Non-English speaking					
Vega 2015 N=30 Spain RCT Moderately High	Inclusion: 1. Grade II-IV osteoarthritis, identified by two different observers, according to the Kellgren-Lawrence grading scale 2. Chronic knee pain of mechanical origin 3. Absence of local or general infection 4. Hematological and biochemical analyses with no significant alterations that contraindicate intervention 5. Patient is able to understand the nature of the study 6. Informed written consent provided by the patient 7. Unresponsive to conventional treatments (physical and medical) for at least 6 months before recruitment Exclusion: 1. Age >75 or <18 years, or legally dependent 2. Signs of infection or positive serology for HIV, hepatitis, or syphilis	Allogeneic expanded BM-MSCs (n=15) **Cell Type**: Allogenic MSCs (3 donors) **Cell Source**: Bone marrow harvested from iliac crest **Cell Preparation**: BM volume = 103 ± 8 mL; number of mononuclear cells obtained = 1.1 ± $0.5x10^9$; viability > 98% **Cell Expansion**: Yes (Mean expansion time: 22 ± 2 days) **Cell Concentration**: $40x10^6$ cells/knee suspended in Ringer-lactate at $5x10^6$ cells/mL **Cell Delivery**: Medial parapatellar injection **Anesthetic use:** NR **Number of injections**: 1 HA injection (n=15) 60 mg in 3 mL; Durolane Co-interventions (across all tx groups) NR	*BM-MSCs vs. HA* **Mean age**: 57 vs. 57 years **% Male**: 33% vs. 40% **OA grade** II: 47% (7/15) vs. 40% (6/15) III: 33% (5/15) vs. 40% (6/15) IV: 20% (3/15) vs. 20% (3/15) **Laterality** Left: 13% (2/15) vs. 33% (5/15) Right: 87% (13/15) vs. 66% (10/15) (all patients were treated unilaterally) **Previous treatments** • Medial meniscus surgery: 33% (5/15) vs. 53% (8/15) • Lateral meniscus surgery: 13% (2/15) vs. 13% (2/15) • Quadriceps re-tensioning: 7% (1/15) vs. 0% (0/15)	F/U 1 week 3 months 6 months 12 months % Followed 100% (30/30)	• Pain visual analogue scale (VAS) (0-100, higher=increased pain) • Western Ontario and McMaster Universities Osteoarthritis (WOMAC) (0-100, higher=greater disability) • Lequesne algofunctional indices (0-100, higher=greater disability) • Short form-12 life quality questionnaire (SF-12) (0-100, higher=increased QOL) • Adverse events	**Funding**: Government **COI**: None reported

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
	3. Congenital or acquired diseases leading to significant knee deformities that may interfere with cell application or the interpretation of results 4. Obesity with a body mass index >30 (calculated as mass in kg/height in m2) 5. Pregnancy or breast-feeding 6. Neoplasia 7. Immunosuppression 8. Intra-articular injection of any drug during the previous 3 months 9. Participation in another clinical trial or treatment with another investigational product within 30 days prior to inclusion in the study. 10. Other conditions that may, according to medical criteria, discourage participation in the study	Post-treatment protocol (across all tx groups) NR	• ACL surgery: 0% (0/15) vs. 7% (1/15) • Infiltration w/ corticosteroids: 20% (3/15) vs. 7% (1/20) • Hyaluronic acid: 33% (5/15) vs. 27% (4/15) • PRP: 13% (2/15) vs. 20% (3/15)			
Goncars 2017 N=56 Latvia RCT Moderately High	Inclusion: 1. Degenerative osteoarthritis of the knee 2. Grade 2–3 Kallgren–Lawrence classification 3. At least 6 months of persisting OA symptoms 4. Voluntarily agreed to participate and signed informed consent form Exclusion:	Autologous bone marrow mononuclear cells (BM-MNC) (n=28) **Cell Type**: Autologous BM mononuclear cells **Cell Source**: Bone marrow harvested from iliac crest **Cell Preparation**: BM volume = up to 45 ml; diluted with sterile 0.9% NaCl; filtrated through	*BM-MNC vs. HA* **Mean ± SD age**: 53.44 ± 15 vs. 58.55 ± 13 years **% male:** 53% vs. 34% **OA grade** II: 32% (9/28) vs. 25% (7/28) III: 68% (19/28) vs. 75% (21/28)	F/U 1 month 3 months 6 months 12 months % Followed 100% (56/56)	• Knee Society Function Score (KSS-function) (0-100, higher=increased function) • Knee Society Knee Score (KSS-knee score) (0-100, higher=ROM and decreased pain)	**Funding**: NR **COI**: None

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
	1. Age over 75 2. Oncologic diseases. Severe kidney, lungs or liver function disorder 3. Hematologic diseases including anemia and thrombocytopenia. First type diabetes mellitus. 4. Severe effusion, contracture and axial deformities in the knee joint 5. Septic arthritis or skin disorders 6. Use of NSAID medication for more than 1 week during observations period. 7. Previous injection in target knee within 2 months before and during observation period 8. Use of corticosteroids and immunosuppressive agents	70mm cell strainer; BM mononuclear cells isolated and enriched **Cell Expansion**: No **Cell Concentration, mean**: 38.64 ± 33.7x10^6 (range 8.3x10^6 to 158.79x10^6) **Cell Delivery**: Intra-articular injection **Anesthetic Use**: None **Number of injections**: 1 <u>HA injection (n=28)</u> Three intra-articular injections with an interval of one week, starting at the week 1 and finishing at the week 3 <u>Co-interventions (across all tx groups)</u> Short-term (<1 months) use of pain reliever drugs during the evaluation period of 12 months was accepted. The use of the glucosamine, the chondroitin sulfate, the avocado and the soybean oil over the counter drugs was not specially recommended or restricted. The patients maintained previous habit	**Laterality**: Unilateral treatment		• Knee Osteoarthritis Outcome Score (KOOS) (0-100, higher=no symptoms)	

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
		of the use of symptomatic slow-acting drugs for OA. <u>Post-treatment protocol (all patients)</u> After 1 hour of bed rest the patients were released home and recommended to avoid excessive physical activity				
Lamo-Espinosa 2016, 2018 30 Spain RCT Moderately High	<u>Inclusion</u>: Males and females aged 50–80, diagnosis of knee OA according to American College of Rheumatology criteria, visual analogue scale joint pain ≥2.5, Kellgren–Lawrence radiological classification scale ≥2, body mass index between 20 and 35 kg/m, and availability to be followed during the study period <u>Exclusion</u>: Previous diagnosis of polyarticular disease, severe mechanical extra-articular deformation (>15° *varus*/15° *valgus*), systemic autoimmune rheumatic disease, arthroscopy or intraarticular infiltration in the last 6 months, chronic treatment with	<u>Low-dose expanded autologous BM-MSCs + HA injection (n=10)</u> **Cell Type**: Autologous MSCs **Cell Source**: Bone marrow harvested from iliac crest **Cell Preparation**: BM volume = 100 ml; Expansion time = 10-15 days **Cell Expansion**: Yes **Cell Concentration**: $10x10^6$ MSCs cultured in 1.5 ml Ringers lactate **Cell Delivery**: Lateral patellar intra-articular injection without radiographic guidance 3-4 weeks after BM biopsy **Anesthetic Use**: NR **Number of injections**: 1 BM-MSC injection + 1 HA injection (4 ml)	*Low-dose BM-MSCs + HA vs. High-dose BM-MSCs + HA vs. HA alone* **Median age**: 65.9 vs. 57.8 vs. 60.3 **% Male**: 40% vs. 80% vs. 70% **Median BMI**: 27.1 vs. 28.5 vs. 29.6 **Median duration of OA diagnosis**: 9 vs. 10 vs. 6 years **OA grade** II: 10% (1/10) vs. 30% (3/10) vs. 40% (4/10) III: 20% (2/10) vs. 30% (3/10) vs. 20% (2/10) IV: 70% (7/10) vs. 40% (4/10) vs. 40% (4/10)	<u>F/U</u> 3 months 6 months 12 months 48 months <u>% Followed</u> At 12 months: 100% (30/30) At 48 months: 83% (25/30)	• Visual Analouge Scale – Pain (VAS-pain) (0-10, higher scores=increased pain) • Western Ontario and McMaster Universities Osteoarthritis (WOMAC) (0-100, higher=greater disability) -Pain (0-20) -Stiffness (0-8) -Function (0-68) • Complications and AEs	**Funding**: Government **COI**: None

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
	immunosuppressive or anticoagulant drugs, corticosteroids treatment in the 3 last months, nonsteroidal anti-inflammatory drugs therapy in the last 15 days, bilateral knee OA requiring treatment in both knees, poorly controlled diabetes mellitus, blood dyscrasias, and allergy to HA or bird proteins	<u>High-dose expanded autologous BM-MSCs + HA injection (n=10)</u> All the same as above with the exception of… **Cell Concentration**: $100x10^6$ MSCs cultured in 3 ml Ringers lactate <u>HA injection (n=10)</u> Single intra-articular injection of 60 mg HA (Hyalone®) in a final volume of 4 ml <u>Co-interventions (across all tx groups)</u> NR <u>Post-treatment protocol (across all tx groups)</u> NR	**Laterality**: Unilateral treatment			
Lu 2019 52 China RCT Moderately Low	<u>Inclusion</u>: Between 18 and 70 years old, with a definite diagnosis of knee OA according to the American College of Rheumatology Clinical classification criteria for knee osteoarthritis and accompanied by pain in knee joint, and were below grade 4 by Kellgren Lawrence criteria.	<u>Re-Join® expanded autologous adipose-derived mesenchymal progenitor cells (haMPC) (n=26)</u> **Cell Type**: Mesenchymal progenitor cells **Cell Source**: Abdominal adipose tissue **Cell Preparation**: **Cell Expansion**: Yes **Cell Concentration**: $5×10^7$ (around 2.5 ml)	*Rejoin® vs. HA* **Mean age ± SD**: 55 ± 9 vs. 60 ± 6, p=0.0375 **% Male**: 12% vs. 12% **Mean BMI**: 24.3 vs. 24.3 Mean symptom duration: 53.6 vs. 63.8 months	<u>F/U</u> 1 week 6 months 12 months <u>% Followed</u> 90% (47/52)	• Western Ontario and McMaster Universities Osteoarthritis (WOMAC) (0-100, higher=greater disability) -Pain (0-20) -Stiffness (0-8) -Function (0-68) • Visual Analogue Scale – Pain (VAS-	**Funding**: Industry & Government **COI**: Chengxiang Dai, Suke Li, and Li Zhang are current employees and stock option holders of the Cellular biomedicine Group (Nasdaq: CBMG). The other authors declare that they have no competing interests.

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
	Exclusion: (1) History of allergy or allergic constitution; (2) concomitant severe infection, malignant tumor, coagulation disorder, or uncontrolled or unmanageable systemic diseases; (3) presence of other types of arthritis except OA; (4) intra-articular injection of HA or corticosteroid in the preceding 2 months; and (5) pregnant or breast-feeding women.	**Cell Delivery**: **Anesthetic Use**: **Number of injections**: 2 haMPC injections at weeks 0 and 3, 2 sham injections at weeks 1 and 2 HA injection (n=26) • ARTZ Dispo; 25 mg/2.5 mL (ARTZ is a 1% sodium hyaluronic acid) • One injection per week for 4 consecutive weeks (week 0, 1, 2, and 3) Co-interventions (across all tx groups) NR Post-treatment protocol (across all tx groups) Patients were advised to rest for 24 hours following each injection.	**OA Grade – Left** I: 4% (1/26) vs. 8% (2/26) II: 35% (9/26) vs. 31% (8/26) III: 62% (16/26) vs. 62% (16/26) **OA Grade – Right** I: 4% (1/26) vs. 8% (2/26) II: 35% (9/26) vs. 31% (8/26) III: 62% (16/26) vs. 62% (16/26) **Laterality**: Bilateral treatment **Previous treatment**: 73% (19/26) vs. 54% (14/26) **Concomitant diseases**: 8% (2/26) vs. 23% (6/26)		pain) (0-10, higher scores=increased pain) • Short form-36 life quality questionnaire (SF-36) (0-100, higher=increased QOL) • AEs and SAEs	
Emadedin 2018 47 Iran RCT Moderately High	Inclusion: 1. Age 18 to 65 years 2. Kellgren and Lawrence grades 2, 3and 4 OA diagnosed using X-ray 3. No severe joint involvement for grade 4 OA 4. Angle of parenthesis feet not >20° 5. WOMAC pain score >25	Autologous culture expanded BM-MSCs (n=19) **Cell Type**: MSCs **Cell Source**: Bone marrow from the iliac crest **Cell Preparation**: BM volume = ~50 mL, BM aspirate was added to 50 ml phosphate buffer saline, then loaded onto a	*BM-MSCs vs. Placebo* **Mean age**: 51.7 vs. 54.7 years **% Male**: 63.2% vs. 62.5% **Mean duration of disease**: 12.5 vs. 13.5 years	F/U 1 week 3 months 6 months % Followed 91.5% (43/47) [Those lost to follow-up (n=4) were not	• Western Ontario and McMaster Universities Osteoarthritis (WOMAC) (0-100, higher=greater disability) -Pain (0-20) -Stiffness (0-8) -Function (0-68)	**Funding**: Non-profit organization **COI**: NR

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
	Exclusion: 1. Malignancy 2. Organ failure 3. Uncontrolled chronic disease other than OA 4. Allergic reaction to anesthesia 5. Positive viral markers for Human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV) and Human T-cell leukemia virus type 1 (HTLV-1/2). 6. Allergic reaction to components of study treatment and/or study implantation procedure 7. Pregnancy or lactation	Lymphodex and centrifuged at 1500 g for 20 minutes. Mononuclear cells were washed with PBS and plated at 10^6 cells/cm2 in 150-cm^2 culture flask in 15 ml alpha modifed eagle medium supplemented with 100 IU penicillin and 100 IU streptomycin and 10% hyclon bovine serum. Patients received MSC injection as soon as the cells were prepared. **Cell Expansion**: Yes **Cell Concentration**: 40x10^6 MSCs in 5ml saline supplemented with 2% human serum albumin **Cell Delivery**: Intra-articular injection **Anesthetic Use**: NR **Number of injections**: 1 Placebo (saline) injection (n=24) For the placebo group, MSCs were frozen and the same amount of saline was injected instead. The placebo saline injection was also supplemented with 2% human serum albumin.	**BMI**: 30.2 vs. 31.5 kg/m^5 **K-L OA grade** II: 10.5% (2/19) vs. 4.2% (1/24) III: 68.4% (13/19) vs, 83.3% (20/24) IV: 21.1% (4/19) vs. 12.5% (3/19) **Laterality**: Unilateral treatment	included in the analysis]	• Visual Analogue Scale – Pain (VAS-pain) (0-100, higher scores=increased pain)	

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
		Co-interventions (across all tx groups): NR Post-treatment protocol (across all tx groups): NR				
Khalifeh Soltani 2019 20 Iran RCT Moderately Low	Inclusion: NR Exclusion: Age <35 or >75 years Any acute or chronic infection Visible knee deformity (varus >10°; valgus >20°) Pregnant or lactating women Any sort of neoplasia BMI >35 Conditions along with impaired immune system Any inflammation in the joints or secondary OA Intra-articular injections during the last 3 mo History of knee surgery Kidney malfunction (creatinine >2.0 mg/dL) Liver malfunction (bilirubin >2.0 mg/dL; AST and ALT >100 IU/L) Uncontrolled diabetes mellitus	Placenta-derived MSCs (n=10) **Cell Type**: MSCs **Cell Source**: Placenta donors form full-term healthy mothers who had normal vaginal delivery without complication **Cell Preparation**: Placenta (3-4 grams) was rinsed and minced into minute pieces, then washed 3 times with 9% sodium chloride solution. Tissue was then incubated with 1mg/mL GMP-grade collagenase NB6 at 37°C for 3 hours, with shaking every 30 min. Then, 9% sodium chloride solution was added and the mixture was shaken and centrifuged. The supernatant was discarded and the cell pellet was cultivated in MSC complete medium containing Dulbecco's Modified Eagle's Medium	*Placenta MSCs vs. Placebo* **Mean age**: 57.5 vs. 55.8 years **% Male**: 10% vs. 10% **BMI**: 29.6 vs. 28.9 **Laterality**: Unilateral treatment	F/U 2 weeks 2 months 6 months % Followed 100% (20/20)	• Visual Analogue Scale – Pain (VAS-pain) (0-10, higher scores=increased pain • Knee Osteoarthritis Outcome Score (KOOS) (0-100, higher=no symptoms)	**Funding**: Private research institution (not industry) **COI**: None

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
		+ 10% pharmaceutical grade Australian-origin fetal bovine serum. **Cell Expansion**: Yes **Cell Concentration**: 10 mL; 0.5-0.6x10^8 **Cell Delivery**: intra-articular injection **Anesthetic Use**: NR **Number of injections**: 1 Placebo (saline) injection (n=10) 10 mL of normal saline Co-interventions (across all tx groups): NR Post-treatment protocol (across all tx groups): The patients' routine activities of daily living were continued early after intervention and only heavy activities or prolonged walking were restricted for 1-week post-injection.				
Lee 2019 24 South Korea	Inclusion: 1) Patients must consent in writing to participate in the study by signing and dating an informed consent document approved by IRB indicating that	Autologous adipose tissue-derived mesenchymal stem cells (JointStem®) (n=12) **Cell Type**: MSCs **Cell Source**: obtained by lipoaspiration from	*Auto-A-MSCs vs. Placebo* **Mean Age**: 62.2 vs. 63.2	F/U 3 months 6 months % Followed 100% (24/24)	• Western Ontario and McMaster Universities Osteoarthritis (WOMAC) (0-100,	**Funding**: Industry **COI**: W.S.L., W.J., and K.I.K. reported receiving research grants from

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
RCT Moderately Low	the patient has been informed of all pertinent aspects of the study prior to completing any of the screening procedures 2) Male or female at age 18-75 3) Healthy patients with no major history of illness 4) Patents must have a diagnosis of osteoarthritis by radiographic criteria of Kellgren and Lawrence grade 2-4 5) Patients must have had more than Grade 4 (0~10 point numeric scale) pain at least for 12 weeks <u>Exclusion</u>: 1) Patients with measures twice or more than normal in lab test or with any condition that principle investigator considers clinically important. 2) Pregnant women or lactating mothers. 3) Patients who have received any anti-inflammatory drugs including herb-drug within 14 days prior to the investigational drug injection. Patients with a known, current substance abuse (Ex: alcohol, illegal drugs, etc.) or urine-tested positively for those substances within one year prior to this study.	abdominal subcutaneous fat **Cell Preparation**: ~20 mL of adipose tissue was collected, digested with collagenase (1 mg/mL) under gentle agitation for 60 minutes at 37 degrees C. The digested tissues were filtered through a 100-mm nylon sieve to remove cellular debris and were centrifuged to obtain a pellet. The pellet was resuspended in Dulbecco's modified Eagle's medium (Invitrogen, USA)-based media containing 0.2 mM ascorbic acid and 10% fetal bovine serum. The cell suspension was recentrifuged. The supernatant was removed and the pellet was collected. **Cell Expansion**: Yes (4–5 days in Keratinocyte-SFM-based media containing 0.2 mM ascorbic acid, 0.09 mM calcium, 5 ng/mL recombinant epidermal growth factor, and 5% fetal bovine serum until 90% confluency	**% Male**: 25% vs. 25% **Mean BMI**: 25.3 vs. 25.4 **KL OA Grade** II: 50% (6/12) vs. 41.7% (5/12) III: 50% (6/12) vs. 50% (6/12) IV: 0% (0/12) vs. 8.3% (1/12) **Mean Cartilage Defect, mm^2**: 312.4 vs. 389.9 **Laterality**: Unilateral treatment		higher=greater disability) • Visual Analogue Scale – Pain (VAS-pain) (0-100, higher scores=increased pain • Knee Osteoarthritis Outcome Score (KOOS) (0-100, higher=no symptoms) • Adverse Events	R-Bio Co., Ltd. The other authors indicated no potential conflicts of interest.

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
	4) Patients who received any drug by intra-articular injection for treatment within 2 months prior to this enrollment. 5) Patients with other disease (no matter the length of time) including systemic or Rheumatoidal or inflammatory cartilage disease, crystalline disease (gout or pseudogout), hemochromatosis, inflammatory joint disease, femoral head necrosis, Paget disease in the joint of femur or tibia, or related knee joint disease, ochronosis, hemophilia arthropathy, joint infections, joint sarcoidosis, villonodular synovitis, or solitary synovial chondromatosis 6) Patients with positive human immunodeficiency (HIV), hepatitis B (HBV) or hepatitis C (HCV) at screening indicative of current of pass infection. 7) Patients with serious condition which can affect this study such as cardiovascular diseases, renal diseases, liver diseases, endocrine diseases, cancer or diabetes. 8) Patients with Body Mass Index (BMI) > 30.	**Cell Concentration**: 1×10^8 cells **Cell Delivery**: Intra-articular injection under ultrasound guidance **Anesthetic Use**: NR **Number of injections**: 1 <u>Placebo (saline) injection (n=12)</u> 1 injection of 3 mL of saline (NaCl 9 mg/mL) <u>Co-interventions (across all tx groups)</u> All pain medications were discontinued except the rescue analgesic (acetaminophen at a dose of 4,000 mg or less per day). Other analgesics were not permitted, and any medications that patients were taking were recorded. If the participant had an osteoarthritis medication, the drug was discontinued for 2 weeks as a wash-out period. <u>Post-treatment protocol (across all tx groups)</u> No specific physical limitation was				

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
	9) Patients who had participated in other clinical trials within 12 weeks prior to this study. 10) Patients who the principal investigator considers inappropriate for the clinical trial due to any other reasons than those listed above	recommended from the day after the injection**.**				
Shapiro 2017, 2018 25 (50 knees) USA RCT Moderately High	<u>Inclusion</u>: longstanding bilateral knee pain from mild to moderate bilateral osteoarthritis despite conventional treatments such as activity modification, weight loss, physical therapy, analgesics, nonsteroidal anti-inflammatory drugs, or injection therapy for at least 6 weeks <u>Exclusion</u>: 1. Clinically abnormal hematology, serum chemistry, or screening laboratory results as reviewed by the Principal Investigator Use of anti-inflammatory medications (prescription or over-the-counter), including herbal therapies, within 14 days of baseline visit	<u>Autologous BMAC (n=25 knees)</u> **Cell Type**: BM derived MCSc **Cell Source**: Iliac crest **Cell Preparation**: 5 to 10 mL BM was aspirated until approximately 26 mL of BM from 3 sites on each iliac crest was harvested for a total of 52 mL **Cell Expansion**: No **Cell Concentration**: The concentration process yielded a BMAC product containing a median of 34,400 MSCs with 97% cellular viability and 4.62 million HSCs. 5 mL of treatment cells + 10 mL of previously separated platelet-poor BM plasma to increase the volume of injectate was used.	*All patients* **Median age (range):** 60 (42 to 68) years **% Male**: 28% **Median BMI**: 27.1 **% White:** 80% **Prior knee surgery:** 44% (11/25) - On BMAC-treated knee: 75% (9/11) On placebo-treated knee: 25% (3/11) (One patient had undergone prior bilateral knee surgery.) **Laterality**: Patients had bilateral knee OA and each knee was randomized *BMAC vs. Placebo* **KL OA Grade, % knees (n/N)**	<u>F/U</u> 1 week 3 months 6 months 12 months <u>% Followed</u> 100% (25/25)	• Osteoarthritis Research Society International Intermittent and Constant Osteoarthritis Pain questionaire (ICOAP)	**Funding**: Private **COI**: M.I.O. holds stock in and is an unpaid consultant for Accelalox Inc and is a paid consultant for Zimmer.

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
	2. Use of anti-rheumatic disease medication (including methotrexate or other antimetabolites) within the 3 months prior to study entry 3. Injections to the treated knee within 3 months prior to study entry 4. Pregnant or currently breast-feeding 5. Systemic, rheumatic, or inflammatory disease of the knee or chondrocalcinosis, hemochromatosis, inflammatory arthritis, arthropathy of the knee associated with juxta-articular Paget's disease of the femur or tibia, ochronosis, hemophilic arthropathy, infectious arthritis, Charcot's knee joint, villonodular synovitis, and synovial chondromatosis 6. Ongoing infectious disease, including HIV and hepatitis 7. Clinically significant cardiovascular, renal, hepatic, endocrine disease, cancer, or diabetes 8. Participation in a study of an experimental drug or	**Cell Delivery**: intra-articular injection through a superolateral approach under continuous ultrasound guidance. **Anesthetic Use**: NR **Number of injections**: 1 <u>Placebo (saline) injection (n=25 knees)</u> 1 intra-articular injection of 15 mL of sterile saline <u>Co-interventions (across all tx groups)</u> Both knees were aspirated before the injection. <u>Post-treatment protocol (across all tx groups)</u> NR	I: 8% (2/25) vs. 8% (2/25) II: 44% (11/25) vs. 64% (16/25) III: 48% (12/25) vs. 28% (7/25)			

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
	medical device within 30 days of study entry 9. Severe degenerative change (Kellgren-Lawrence 4 radiographs, or significant malalignment)					
Freitag 2019 30 Australia RCT Moderately High	Inclusion: 1. Radiological diagnosis of osteoarthritis using the American College of Rheumatology criteria 2. Radiological grading of Grade II–III osteoarthritis (OA) of the knee as determined by a qualified radiologist using the Kellgren and Lawrence system 3. Medial or lateral compartment OA as determined above 4. Conservative OA treatment already undertaken defined as: analgesia/anti-inflammatory medication, supplements approved by the treating clinician (e.g., glucosamine sulphate), an attempted exercise program prescribed by a physiotherapist or medical practitioner for at least 8 weeks, weight loss and nutritional management as prescribed by a dietitian or medical practitioner for at least 8 weeks, and biomechanical	Autologous-Addipose-MSCs-1 (n=10) **Cell Type**: MSCs **Cell Source**: Abdominal adipose tissue **Cell Preparation**: the subcutaneous fat was infiltrated with up to 300 ml of tumescent fluid (30 ml of 2% lidocaine, 1 ml of 1:1000 adrenaline and 1 ml of 8.4% bicarbonate suspended in a normal saline solution to a total 1000 ml). Then, up to 60ml of adipose tissue and tumescent fluid was aspirated. Lipoaspirate was separated into stromal vascular fraction using enzymatic digestion and centrifugation and later cell culturing performed under hypoxic conditions within standard growth media containing 10% fetal bovine serum. Cultured until 80% confluency.	*MSCs-1 vs. MSCs-2 vs. UC* **Mean age**: 54.6 vs. 54.7 vs. 51.6 **% Male**: 70% vs. 40% vs. 50% **Mean BMI (kg/m^2)**: 31.6 vs. 30.4 vs. 25.2, p=0.023	F/U 1 month 3 months 6 months 12 months % Followed 100% (30/30)	• Numeric Pain Rating Scale (NPRS) (0 to 10, higher=greater pain) • Western Ontario and McMaster Universities Osteoarthritis (WOMAC) (0-100, higher=no disability)* • Knee Osteoarthritis Outcome Score (KOOS) (0-100, higher=no symptoms) • Adverse Events	**Funding**: Industry **COI**: J Freitag, D Bates, L Huguenin, A Tenen are clinic partners within Melbourne Stem Cell Centre. J Freitag, D Bates, R Boyd, K Shah, L Huguenin, A Tenen are associated with Magellan Stem Cells and are part of its Medical and Scientific Advisory Committee. This proposed study was funded jointly by both Magellan Stem Cells and Melbourne Stem Cell Centre. Members of their Medical and Scientific Advisory board have been involved in the study conception and design and are listed as co-authors of this paper. The authors received no payment for their involvement in the study. Interpretation of results,

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
	management including bracing if appropriate as prescribed by a physiotherapist, podiatrist or medical practitioner. 5. A minimum pain score of 5 on an 11-point numerical rating scale 6. Single knee osteoarthritis 7. <5◦ varus or valgus knee deformity as measured by the long mechanical axis of the knee on x-ray 8. Sufficient English skills to complete the questionnaires required for the study, as well as to understand the instructions given by the study doctors. <u>Exclusion</u>: 1. Pregnancy 2. Breast feeding 3. Have other causes of their knee symptoms suspected to be due to serious pathology such as tumors or referral from the hip or lumbar spine. 4. Bleeding disorder – i.e., hemophilia 5. MRI confirmed displaced meniscal tear 6. MRI confirmed Grade IV chondral loss	**Cell Expansion**: Yes. **Cell Concentration**: $100x10^6$ cells (mean cell count = 103.9 million; mean viability = 95.4%) **Cell Delivery**: ultrasound guided intra-articular injection using superolateral patella approach **Anesthetic Use**: Yes (2 ml of 1% lidocaine) **Number of injections**: 1 <u>Autologous-Addipose-MSCs-2 (n=10)</u> Same as above, except patients received a second stem cell injection 6 months after the first. <u>Conservative Usual Care (n=10)</u> Consisting of simple analgesia, weight management and exercise. Participants were not prescribed a trial-specific conservative program. (baseline injection mean cell count = 95.1 million, baseline injection mean viability = 93%; 6 month injection mean cell count =				and subsequent submission and publication decisions have been made independent of the sponsors.

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
	7. Previous meniscectomy/significant partial meniscectomy or other knee related surgery within the last 12 months 8. Previous intra-articular injectable therapies within the last 6 months 9. History of cancer 10. History of atypical chronic pain syndrome – i.e., chronic regional pain 11. History of systemic illness or significant organ impairment/failure (i.e., renal failure) 12. History of allergy to any substances used within the treatments 13. Plans at the time of enrollment to undergo surgery in the following 12 months. This criterion is aimed at avoiding co-interventions that may confound the results of the study. While involvement in the project will not strictly prevent participants from undertaking such interventions if required, we will exclude volunteers who already have such procedures scheduled	102.6 million, 6 months injection mean viability = 92.9% Co-interventions (across all tx groups): NR Post-treatment protocol (across all tx groups) Participants in the treatment groups were provided with post injection analgesia as required. They were advised to remain non-weight bearing with the use of crutches for 4 weeks. Education regarding range of motion and quadriceps activation exercises was provided. Participants in the two injection group were not required to be non-weight bearing after the second injection at 6 months.				

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
Centeno 2018 48 USA RCT Moderately High	Inclusion: 1. Men or women aged 18–70 2. Diagnosis of knee OA 3. Kellgren–Lawrence (KL) classification of grade II or III OA severity Exclusion: 1. BMI > 30 2. Knee flexion < 110º 3. Knee varus > 12º 4. Knee valgus > 15º 5. Instability as demonstrated by > 2 mm translation upon physical examination 6. Knee flexion contracture greater than 15º 7. History of ACL reconstruction or evidence of complete or partial ACL disruption 8. Knee Society Score < 65 9. History of septic arthritis within the last 5 years 10. History of knee surgery within the last 6 months 11. Currently experiencing low back pain with radiculopathy 12. History of immunosuppressive disease or chemotherapy in last 5 years 13. History of systemic neurological disease 14. Positive HIV serology or chronic hepatitis	Prolotherapy + Autologous BMAC + PRP + PL + steroids + PT (n=26) **Cell Type**: BM-MCSs **Cell Source**: 6 sites on the posterior superior iliac crest. **Cell Preparation**: BM volume = 60–90 cc. BM was processed by hand in a biologic safety cabinet to isolate the buffy coat to create BMC from which the total nucleated cell count was calculated. Concurrently, ~100 cc of venous blood was drawn and concentrated into two portions of leukocyte poor PRP by centrifuging the blood and extracting the plasma and buffy coat layers. One portion of PRP was set aside for injection and the other portion underwent further processing into platelet lysate via a freeze-thawing method. **Cell Expansion**: No **Cell Concentration**: NR **Cell Delivery**: Using fluoroscopy, needle placement into the intra-	*Prolotherapy + BMAC + PRP + PL + steroids + PT vs. Exercise* **Mean age**: 54 vs. 57 years **Mean BMI**: 26 vs. 26 lbs/in^2 **KL OA grade** II: 42% vs. 45% III: 58% vs. 55%	F/U 1.5 months 3 months 6 months 12 months 24 months % Followed 70.8% (34/48)	• Knee Society Function Score (KSS-function) (0-100, higher=increased function) • Knee Society Knee Score (KSS-knee score) (0-100, higher=ROM and decreased pain) • Short form-12 life quality questionnaire (SF-12) (0-100, higher=increased QOL) • Pain visual analogue scale (VAS) (0-100, higher=increased pain) • Lower Extremity Activity Scale (LEAS) (1-18, lower=greater disability)	**Funding**: Industry **COI**: CC is a shareholder and CMO of Regenexx, LLC. MS, ED, IS, CW, MH, TI, and MF have no competing interests to declare.

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
		articular space of the knee was confirmed by injecting a small amount of contrast. A 5–7 cc injectate solution consisting of ~75% by volume of BMC, 12.5% by volume PRP, and 12.5% by volume PL was percutaneously injected, specifically targeting the sites of greatest chondral loss. Two to four days after the BMC injection, the patient underwent an additional blood draw, from which approximately 3 cc solution of 25% by volume five times concentrated over baseline leukocyte poor PRP, 25% by volume of PL, 25% by volume of compounded 400 ng/ml dose of hydrocortisone, and 25% by volume of a 40 µg/ml dose of doxycycline, which was delivered via a percutaneous, ultrasound guided, intra-articular injection. **Anesthetic Use**: NR **Number of injections**: 1 injection of BMAC, PRP, and PL + 1 injection 2 to 4				

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
		days later of PRP, PL, hydrocortisone, and doxycycline **Co-interventions**: 2 to 4 days prior to the BMAC injection, patients received an injection of hyperosmolar dextrose (2–5 cc of 12.5% dextrose and 0.125% ropivacaine in normal saline) <u>Home Exercise Therapy Program (n=22)</u> A physical therapist provided a home exercise program in an initial visit and an upgraded program at a 6-week follow-up visit. All programs followed the same basic principles of therapeutic exercise including functional strengthening, resistance training and monitor alignment for core, pelvis and entire lower extremity, as well as balance/neuro-muscular training, and aerobic activity. If ROM was an issue, manual therapy and mobility was included.				

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
		Patients in the exercise group were offered the opportunity to cross over to the treatment group after 3 months of exercise therapy, as a method to aid in study recruitment and retention. <u>Co-interventions (across all tx groups)</u> SEE ABOVE for information regarding Prolotherapy received by the BMAC group. No other co-interventions across groups were reported. <u>Post-treatment protocol (across all tx groups)</u> Patients receiving BMAC were instructed to wear a brace while weight bearing for 4 weeks and avoid any activities that caused more than 2/10 pain throughout rehabilitation. -Days 0-3: restricted ambulation - Day 3 to week 6: deep water walking/jogging for 30 to 45 minutes 3 to 5 times/week. Stationary bike and then elliptical, as well as core training,				

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
		nonresistance hip and knee strengthening were added as pain allowed. - Weeks 6-12: Patients could start walking for exercise, add resistance exercises/weight, hills, hiking, and low to moderate impact activity. Patients addressed weakness, ligament laxity and ROM deficits in physical therapy. Weeks 12 to 26: no restrictions, unless pain exceeded 2/10				
Bhattacharya 2011 52 Prospective Comparative Cohort ROB India	Inclusion: NR Exclusion: Association of neurodegenerative diseases such as Parkinsonism, malignancy, dementia of varying etiology and other chronic disease burdens.	Amniotic fluid (n=26) **Cell Type**: Progenitor cells isolated from the amniotic fluid (pregnancy-associated progenitor cells) **Cell Source**: Amniotic fluid taken from consenting mothers carrying pregnancy, who were undergoing hysterotomy and ligation as a family planning measure. **Cell Preparation**: NR **Cell Expansion**: NR **Cell Concentration**: 10 mL amniotic fluid per knee	*Amniotic fluid vs. Triamcinolone Acetonide* **Mean age**: 49 vs. 51.3 **% Male**: 46% vs. 53.8% **Mean BMI**: NR **Proportion of patients treated bilaterally, % (n/N):** 69.2% (36/52)	F/U Baseline 1 month 2 months 3 months 4 months 5 months 6 months 9 months 12 months 18 months 24 months % Followed 100%	• Pain visual analogue scale (VAS) (0-100, higher=increased pain) • Distance walked in 1 minute (WD) (in meters) • Locally modified and local (Bengali) language-translated Modified Health Assessment Questionnaire (HAQ) (1-11) (Higher=worse pain)	**Funding**: Government **COI**: NR

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
		Cell Delivery: Intra-articular injection **Anesthetic Use**: NR **Number of injections**: 1 Intraarticular long-acting steroid injection (Triamcinolone Acetonide) (n=26) Co-interventions (across all tx groups): NR Post-treatment protocol (across all tx groups): At completion of the study, patients that received cell therapy were offered steroid therapy if they voluntarily requested the procedure, and vice versa.			• Clinical assessment of nine parameters (subjective and objective improvement) • Patient satisfaction	
Garay-Mendoza 2018 61 Prospective Comparative Cohort ROB Mexico	Inclusion: Individuals of both genders aged over 30 years and with a confirmed diagnosis of knee OA made by clinical and radiological evaluation, with unilateral affection, and at least 6 months of progression. They were classified as OA grades II and III according to the Kellgren and Lawrence	Autologous BM-derived MSCs (n=30) **Cell Type**: BM-MSCs **Cell Source**: BM from iliac crest **Cell Preparation**: Before BM aspiration, patients received 600 µg per day of granulocyte colony stimulating factor for 3 consecutive days. A BM volume of 75 mL from each	*BM-MSCs vs. Acetaminophen* **Mean age**: 59.32 vs. 55.67 **% Male**: 23% vs. 29% **Mean BMI**: 29.48 vs. 31.61 kg/m^2	F/U 1 week 1 month 6 months % Followed 84% (51/61)	• Pain Visual Analog Scale (VAS-pain) (0-10, higher=worse pain) • Western Ontario and McMaster Universities Osteoarthritis (WOMAC) (0-100, higher=greater disability)	**Funding**: NR **COI**: None

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
	radiological classification system. Exclusion: Patients with systemic arthritis, a knee infection or surgery in the last 6 months, an intra-articular injection in the past 3 months, or neurodegenerative, autoimmune, malignant or traumatic lesions (joint fracture, meniscal or ligament injury)	iliac crest was aspirated. BM was centrifuged at 26009 g for 15 min at 6°C and returned to the flow cabinet. Plasma was removed with a 16-gauge needle 2 mm above the buffy coat and discarded. **Cell Expansion**: No **Cell Concentration**: Mean number of BM total nucleated cells: $302.02x10^7$ (range, $155x10^7$ to $469.23x10^7$) Mean number of BM mononuclear cells was $67.33x10^7$ (range, $31.52x10^7$ to $114.02x10^7$) **Cell Delivery**: Intra-articular injection **Anesthetic Use**: Yes - 3 mL of 1% xylocaine and with the patient under sedation with intravenous midazolam at 0.1 mg/kg. **Number of injections**: 1 Oral acetaminophen (n=31) 500 mg every 8 hours for 6 months Co-interventions (across all tx groups): NR				

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
		Post-treatment protocol (across all tx groups): NR				
Centeno 2014 840 procedures on 681 patients USA Registry study ROB	Inclusion: Registry data for all patients who underwent a BMC procedure for knee OA from April 2010 to December 2013 were included in the study. Only patients who had responded to the outcome and complications questionnaires at 1 month and 3, 6, and 12 months following the procedure were included. There were 17 outpatient facilities that contributed patients to the registry, although the majority of cases (67.9%) were performed at a single center at which the primary author (CJC) is affiliated. Registry Information: Data are from a private knee registry, which is an ongoing prospective survey system that was designed to follow up specific treatment protocols. The program used (ClinCapture) includes an automated emailing system to send patients clinical outcome questionnaires at a	Autologous BMC + PRP +PL (n=616 treated knees on 518 patients) **Cell Type**: MSCs **Cell Source**: BM from the posterior iliac crest (6 to 8 sites) **Cell Preparation**: 10–15 cc of BM aspirate was withdrawn. 1,000 units of heparin per 1cc of whole bone marrow aspirate drawn into syringe. Then BM was processed to isolate the buffy coat through centrifugation, producing 1–3 cc of BMC injectate. At the same time, 60ccs of heparinized IV venous blood was drawn to be used for isolating PRP and PL. **Cell Expansion**: No **Cell Concentration**: NR **Cell Delivery**: fluoroscopy or ultrasound guided intra-articular injection **Anesthetic Use**: NR **Number of injections**: **Other**: If a meniscus tear was detected on MRI, the patient's meniscus was also	*BMC+PRP+PL vs. BMC+PRP+PL+Fat graft* **Mean age**: 54.3 vs. 59.9, p<0.001 **% Male**: 64.5% vs. 53.1%, p=0.003 **Mean BMI**: 26.5 vs. 27, p=0.039 **KL OA Grade†** -I: 48.5% vs. 41.6% -II: 30.2% vs. 34.9% -III/IV: 21.3% vs. 23.5% **% White**: 89.3% vs. 88.8% **Laterality** -Unilateral: 68.2% vs. 45.5% -Bilateral: 31.8% vs. 54.5% P<0.001	Mean F/U of last available reported outcome, % (n/N) • Improvement rating scale: 10.4 vs. 10.7 months • LEFS: 6.2 vs. 5.7 months • NPS: 7 vs. 6.7 months Survey response rates by outcome reported, % (n/N) • Improvement rating scale: 66.2% (408/616 procedures) vs. 74.1% (166/224 procedures) • LEFS: 33.3% vs. 40.6% • NPS: 35.7% vs. 46.0%	• A subjective improvement rating scale (−100% to 100%, where 100%=fully improved • Lower extremity functional score (LEFS) (0-80, higher=increased function) • Numeric pain scale (NPS) (0-10, higher=increased pain) • Adverse events	**Funding**: NR **COI**: Dr. Christopher Centeno is a shareholder and director of Regenerative Sciences, LLC.

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
	predetermined posttreatment frequency. The data was collected prospectively and analyzed retrospectively.	injected. Based on medical need, infrequent additional platelet rich plasma injections may have been provided by the treating physician. <u>Autologous BMC + PRP + PL + Adipose graft (lipoaspirate) (n=224 treated knees on 163 patients)</u> Same as above with the addition of the following: ~5–15 cc of lipoaspirate from the superior buttocks or lateral thigh was then drawn into a 60 cc syringe containing heparin. The lipoaspirate was minimally processed via low speed centrifugation or by allowing the layers to settle over several hours and the top oil layer was drawn off. The tissue, at a volume of 5–10 cc, was then injected into the articular space. <u>Co-interventions (across all tx groups)</u>: **Proportion of patients receiving additional PRP**				

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
		injections: 12.5% (77/616) vs. 11.2% (25/163) <u>Post-treatment protocol (across all tx groups)</u>: A posttreatment off-loader brace was commonly prescribed for the most involved compartment with the patient being given instructions to wear the brace with all weight bearing activity for 6 weeks. For patella-femoral compartment dominant OA patients, a patellar stabilizer brace was used. Patients were discharged with instructions to be lightweight bearing for several days if there was significant post-op pain but then to return to full weight bearing as soon as feasible. Post-op activity sheets were provided to the patient, which described a gradual return to full activities over 6 weeks. The patients were encouraged to participate in physical therapy, but this was not required nor controlled.				

AE = adverse events; BM = bone marrow; BMAC = bone marrow aspirate concentrate; BMC = bone marrow concentrate; BMI = body mass index; BM-MNCs = bone marrow mononuclear cells; BM-MSCs = bone marrow derived mesenchymal stem/stromal cells; COI = conflict of interest; F/U = follow-up; HA = hyaluronic acid; haMPC = human autologous adipose-derived mesenchymal progenitor cells; HAQ = health assessment questionnaire; HIV = human immunodeficiency virus; ICOAP = Osteoarthritis Research Society International Intermittent and Constant Osteoarthritis Pain; K-L = Kellgren=Lawrence; KOA = knee osteoarthritis; KOOS = knee injury and osteoarthritis outcome score; KSS = knee society score; LEAS = lower extremity activity scale; LEFS = lower extremity functional score; MRI = magnetic resonance imaging; MSCs = mesenchymal stem/stromal cells; NPRS = numeric pain rating scale; NPS = numerical pain score; NR = not reported; NSAID = non-steroid anti-inflammatory drug; OA = osteoarthritis; OTC = over the counter; PL = platelet lysate; PRP = platelet rich plasma; PT = physical therapy; QOL = quality of life; RCT = randomized controlled trial; ROB = risk of bias; ROM = range of motion; SAE = severe adverse events; SD = standard deviation; SF-12 = short form 12 question health related quality of life questionnaire; SF-36 = short form 36 question health related quality of life questionnaire; SVF = stromal vascular fraction; tx = treatment; VAS = visual analogue scale; WD = walking distance; WOMAC = Western Ontario and McMaster Universities Osteoarthritis

* In this trial the WOMAC score is presented as an inverse percentage to be more easily compared with the KOOS subscales where 100 indicates no symptoms.

† Radiographic data sufficient for OA severity classification were available for 646 out of 840 knees in both groups (76.9%)

Appendix Table F2: Data abstraction for comparative studies evaluating the use of stem cell therapies for knee osteoarthritis

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
Tucker 2019 N=39 USA RCT (ongoing – partially published results; data are from clinicaltrials.gov) ROB	*Low dose SVF vs. High dose SVF vs. Placebo* **Percentage of change in WOMAC score from baseline (IQR)**: • Baseline: NR • 6 month Δ: 52% (29% to 88%) vs. 84% (19% to 91%) vs. 25% (-25% to 58%) -Low dose vs. placebo: p=0.023 -High dose vs. placebo: p=0.043	NR	NR	*Low dose SVF vs. High dose SVF vs. Placebo* TKA (withdrawal from trial) 0% (0/13) vs. 8% (1/13) vs. 0% (0/13); timing a specific reasons NR	*Low dose SVF vs. High dose SVF vs. Placebo* **All-cause mortality, % (n/N)**: 0% (0/13) vs. 0% (0/13) vs. 0% (0/13) **Serious Adverse Events, % (n/N)**: 0% (0/13) vs. 0% (0/13) vs. 0% (0/13) **Non-serious adverse events, % (n/N)** • Possible infections: 7.7% (1/13) vs. 7.7% (1/13) vs. 0% (0-13) • Swelling: 0% (0/13) vs. 7.7% (1/13) vs. 0% (0/13)
Ruane 2019 N=32 USA RCT ROB	*BMAC + PRP vs. Gel-One®* **KOOS-symptoms, Mean ± SD or Mean (95% CI)** • Baseline: 66.54 ± 16.01 vs. 68.80 ± 15.69 • 3 months Δ: 14.00 (4.38 to 23.63) vs. 10.47 (3.48 to 17.45) • 6 months Δ: 14.26 (4.70 to 23.81) vs. 12.41 (5.45 to 19.37)	*BMAC + PRP vs. Gel-One®* **KOOS-pain, Mean ± SD or Mean (95% CI)** • Baseline: 60.82 ± 15.05 vs. 63.33 ± 17.72 • 3 months Δ: 16.71 (6.71 to 26.71) vs. 10.93 (5.15 to 16.71) • 6 months Δ: 20.03 (10.71 to 29.36) vs. 12.52 (3.16 to 21.89)	NR	*BMAC + PRP vs. Gel-One®* **KOOS-QOL, Mean ± SD or Mean (95% CI)** • Baseline: 36.18 ± 18.50 vs. 38.47 ± 15.94 • 3 months Δ: 21.02 (9.03 to 33.01) vs. 21.27 (11.10 to 31.43) • 6 months Δ: 4.97 (14.51 to 35.42) vs. 24.18 (10.99 to 37.36)	*BMAC + PRP vs. Gel-One®* **All-cause mortality, % (n/N)**: 0% (0/17) vs. 0% (0/15) **Serious Adverse Events, % (n/N)**: 0% (0/17) vs. 0% (0/15) **Non-serious adverse events, % (n/N)**

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
	• 12 months Δ: 18.01 (10.29 to 25.72) vs. 8.20 (0.33 to 16.73) **KOOS-ADL, Mean ± SD or Mean (95% CI)** • Baseline: 68.59 ± 17.98 vs. 70.13 (18.34) • 3 months Δ: 15.35 (5.10 to 25.59) vs. 12.47 (5.97 to 18.96) • 6 months Δ: 8.13 (9.00 to 27.25) vs. 14.94 (5.98 to 23.90) • 12 months Δ: 19.10 (9.52 to 28.68) vs. 11.87 (2.05 to 21.68) **KOOS-sport, Mean ± SD or Mean (95% CI)** • Baseline: 31.47 ± 23.57 vs. 39.67 ± 21.59 • 3 months Δ: 29.46 (13.02 to 45.91) vs. 30.07 (18.71 to 41.43) • 6 months Δ: 34.89 (19.90 to 49.88) vs. 31.62 (16.41 to 46.82) • 12 months Δ: 39.07 (22.00 to 56.13) vs. 26.05 (13.16 to 38.93)	• 12 months Δ: 23.48 (14.85 to 32.12) vs. 12.67 (2.62 to 22.71) **NPRS, Mean ± SD or Mean (95% CI)** • Baseline: 4.59 ± 1.84 vs. 4.20 ± 1.70 • 3 months Δ: -1.92 • (-3.27 to -0.57) vs. -1.87 (-2.76 to -0.97) • 6 months Δ: -2.45 (-3.60 to -1.28) vs. -1.77 (-2.55 to -0.99) • 12 months Δ: -3.13 (-3.96 to -2.29) vs. -1.56 (-2.59 to -0.53)		• 12 months Δ: 27.44 (17.61 to 37.27) vs. 21.46 (8.33 to 34.60) **PROMIS Global Health Mental Score, Mean ± SD or Mean (95% CI)** • Baseline: 51.88 ± 5.02 vs. 51.90 ± 9.36 • 3 months Δ: -2.18 (-3.87 to -0.48) vs. -0.65 (-5.13 to 5.83) • 6 months Δ: -0.01 (-3.25 to 3.23) vs. 2.24 (-0.54 to 5.03) • 12 months Δ: 0.07 (-2.64 to 2.77) vs. 3.01 (-0.40 to 6.42) Received additional treatment (not specified) 12% (2/17) vs. 7% (1/15); patients were considered lost to follow-up	Nausea and vomiting: 6% (1/17) vs. 0% (0/15)

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
	PROMIS Global Health Physical Score, Mean ± SD or Mean (95% CI) • Baseline: 44.62 ± 7.61 vs. 48.23 ± 7.99 • 3 months Δ: 4.62 (0.84 to 8.41) vs. 0.59 (-3.76 to 4.94) • 6 months Δ: 6.76 (3.63 to 9.89) vs. 3.50 (0.16 to 6.83) • 12 months Δ: 4.77 (1.99 to 7.54) vs. 3.26 (-0.36 to 6.88)				
Vega 2015 N=30 (n = 15 vs. 15) Spain RCT Moderately High	*Allogenic MSCs vs. HA* **WOMAC-general*, Mean ± SE** • Baseline: 41 ± 3 vs. 45 ± 3 • 1 week: 35 ± 4 vs. 44 ± 4 • 3 months: 33 ± 5 vs. 41 ± 6 • 6 months: 28 ± 4 vs. 40 ± 4 • 12 months: 28 ± 5 vs. 41 ± 6 **Lequesne*, Mean ± SE** • Baseline: 39 ± 4 vs. 45 ± 4 • 1 week: 36 ± 4 vs. 44 ± 4 • 3 months: 36 ± 4 vs. 40 ± 4 • 6 months: 25 ± 4 vs. 40 ± 4	*Allogenic MSCs vs. HA* **VAS-pain*, Mean ± SE** • Baseline: 54 ± 7 vs. 64 ± 7 • 1 week: 50 ± 5 vs. 62 ± 7 • 3 months: 42 ± 6 vs. 57 ± 6 • 6 months: 34 ± 6 vs. 52 ± 7 • 12 months: 33 ± 6 vs. 51 ± 8 **WOMAC-pain*, Mean ± SE** • Baseline: 46 ± 4 vs. 50 ± 4 • 1 week: 39 ± 7 vs. 47 ± 4 • 3 months: 36 ± 4 vs. 46 ± 5	NR	*Allogenic MSCs vs. HA* **SF-12 PCS, Mean ± SE** • Baseline: 40 ± 9 vs. 35 ± 8 • 1 week: 40 ± 10 vs. 37 ± 9 • 3 months: 43 ± 11 vs. 39 ± 8 • 6 months: 44 ± 10 vs. 39 ± 8 • 12 months: 45 ± 11 vs. 40 ± 8 **SF-12 MCS, Mean ± SE** • Baseline: 54 ± 10 vs. 49 ± 9 • 1 week: 52 ± 10 vs. 50 ± 11	*Allogenic MSCs vs. HA* **Minor Adverse Events** • Postimplantation pain and/or synovial fluid effusion with articular swelling at days 1-7 (deemed expected and study-related; treated with ibuprofen; endurance < 1 week): 53% (8/15) vs. 60% (9/15) • Osteoarticular pain and/or inflammation (knee, shoulder, hip, ankle, lumbar) (deemed unexpected and not study-related): 47% (7/15) vs. 33% (5/15)

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
	• 12 months: 30 ± 3 vs. 42 ± 5	• 6 months: 33 ± 4 vs. 44 ± 5 • 12 months: 30 ± 4 vs. 44 ± 6		• 3 months: 50 ± 10 vs. 47 ± 10 • 6 months: 54 ± 12 vs. 48 ± 10 • 12 months: 51 ± 12 vs. 47 ± 11	• Other†: 53% (8/15) vs. 73% (11/15) **Serious Adverse Events** None reported
Goncars 2017 N=56 (n= 28 vs. 28) Latvia RCT Moderately High	*Autologous BM-MNC vs. HA* **KSS-function, Mean** • 12 month Δ: 38.32 vs. 17.5 **KOOS-Total, Mean** • 12 month Δ: 18.25 vs. 12.59; p=NS **KOOS-ADL, Mean** • 12 month Δ: 21.36 vs. 19.09; p=NS **KOOS-sport, Mean** • 12 month Δ: 19.00 vs. 5.97; p=NS	*Autologous BM-MNC vs. HA* **KOOS-pain, Mean ± SD‡** • Baseline: 54.09 ± 17 vs. 50.18 ± 21, p>0.05 • 1 month: 85.25 ± 9 vs. 72.39 ± 13, p>0.05 • 3 months: 79.68 ± 15 vs. 71.05 ± 20, p>0.05 • 6 months: 78.5 ± 15 vs. 61.55 ± 23, p<0.05 • 12 months: 79.53 ± 18 vs. 61.55 ± 22, p<0.05 • 12 month Δ: 25.44 vs. 11.37 **KOOS-symptoms, Mean** • 12 month Δ: 5.07 vs. 12.62; p=NS **Associations between the mononuclear cell count and KOOS-symptom score, Mean§**	NR	*Autologous BM-MNC vs. HA* **KOOS-QOL, Mean change from baseline** • 12 months: 28.83 vs. 18.90; p=NS **KSS-knee score, Mean change from baseline** • 12 months: 25.42 vs. 10.73; p=NS	No adverse effects after the BM-MNC injection were observed. The patients reported the procedure of iliac crest puncture as painless and no complications in the donor sites were observed. The knee joint pain or swelling caused by puncture reduced during an hour and no additional treatment was needed.

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
		Above average cell count vs. below average cell count (BM-MNC group only) • Baseline: 64 vs. 51, p>0.05 • 3 months: 72 vs. 71, p>0.05 • 6 months: 80 vs. 66, p>0.0.5 • 12 months: 82 vs. 70, p<0.05 **Associations between the mononuclear cell count and KOOS-pain score, Mean** *Above average cell count vs. below average cell count (BM-MNC group only)* • Baseline: 51 vs. 50, p>0.05 • 3 months: 81 vs. 76, p>0.05 • 6 months: 81 vs. 74, p>0.05 • 12 months: 88 vs. 59, p<0.05			
Lamo-Espinosa 2016, 2018 N=30 (n = 10 vs. 10 vs. 10) Spain	*Low-dose MCSs + HA vs. High-dose MCSs + HA vs. HA alone*	*Low-dose MCSs + HA vs. High-dose MCSs + HA vs. HA alone* **VAS-pain, Median (IQR)**	NR	*Low-dose MCSs + HA vs. High-dose MCSs + HA vs. HA alone*	*Low-dose MCSs + HA vs. High-dose MCSs + HA vs. HA alone*

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
RCT Moderately High	**WOMAC-total, Median (IQR)** • Baseline: 37 (32, 42) vs. 28 (16, 34) vs. 29 (19, 38) • 3 months: 25.5 (11, 37) vs. 13 (11, 26) vs. 12 (11, 14) • 6 months: 24 (13, 31) vs. 20 (13, 23) vs. 10 (4, 20) • 12 months: 21.5 (15, 26) vs. 16.5 (12, 19) vs. 13.5 (8, 33) • 48 months: 17 (13, 25.5) vs. 16.5 (8, 23) vs. 27 (17, 30) [Low-dose vs. HA, p =0.04] • 12 month Δ: -14 (-27, 4) vs. -14 (-15, -8) vs. -6.5 (-19, -4)** • 48 month Δ: −18 (−27.5, 8.5) vs. −10 (−21.5, −3) vs. 4 (−11, 10)** **WOMAC-function, Median (IQR)** • Baseline: 26.5 (23, 32) vs. 19 (12, 25) vs. 21 (13, 24) • 3 months: 17.5 (8, 26) vs. 10 (7, 18) vs. 9 (7, 11) • 6 months: 18 (10, 23) vs. 14.5 (8, 17) vs. 7.5 (2, 13)	• Baseline: 7 (5, 8) vs. 6 (4, 8) vs. 5 (3, 7) • 3 months: 4 (2, 6) vs. 3 (1, 4) vs. 3 (2, 5) • 6 months: 3 (1, 5) vs. 2 (0, 3) vs. 5 (2, 8) • 12 months: 2 (1, 3) vs. 2 (0, 4) vs. 4 (3, 5) • 48 months: 2 (2, 5) vs. 3 (3, 4) vs. 7 (6, 7) [Low-dose vs HA, p=0.01; High-dose vs HA, p=0.004) **WOMAC-pain, Median (IQR)** • Baseline: 7.5 (5, 9) vs. 4.5 (4, 5) vs. 5.5 (5, 6) • 3 months: 3.5 (3, 7) vs. 3 (2, 5) vs. 3 (1, 3) • 6 months: 3.5 (3, 7) 3.5 (2, 5) vs. 2.5 (1, 5) • 12 months: 3.5 (3, 5) 2.5 (2, 4) vs. 2 (1, 6) • 48 months: NR		**WOMAC-stiffness, Median (IQR)** • Baseline: 4 (2, 5) vs. 2.5 (2, 4) vs. 2 (1, 3) • 3 months: 2 (0, 4) vs. 2 (1, 2) vs. 2 (1, 2) • 6 months: 1.5 (1, 3) vs. 2 (1, 3) vs. 0.5 (0, 2) • 12 months: 2 (1, 2) vs. 2 (1, 2) vs. 2 (1, 2) • 48 months: NR **Received TKA** 10% (1/10) vs. 0% (0/10) vs. 20% (2/10); timing unclear **Additional PRP injections** 0% (0/10) vs. 0% (0/10) vs. 20% (2/10); timing unclear	• No serious adverse events or complications derived from the procedures or treatments were noted. • Articular pain requiring anti-inflammatory treatment during the first 24 hours after treatment: 30% (3/10) vs. 60% (6/10) vs. 10% (1/10) [no treatment group-dependent differences were detected in the dose of required anti-inflammatory drug or in the time that passed until recovery]

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	• 12 months: 17 (10, 20) vs. 11 (9, 14) vs. 9.5 (5, 23) • 48 months: NR				
Lu 2019†† N=52 (n = 26 vs. 26) China RCT Moderately Low	*Re-Join® haMPC vs. HA* **WOMAC-total, Mean ± SD** • Baseline: 33.77 ± 19.99 vs. 32.15 ± 18.07, p=0.9343 • 6 months: 23.81 ± 17.82 vs. 26.48 ± 17.47, p=0.5913 • 12 months: 22.04 ± 18.12 vs. 26.28 ± 16.71, p=0.2417 • 6 month Δ: –9.96 ± 9.97 vs. –6.32 ± 7.96, p= 0.1480 • 12 month Δ: –10.33 ± 11.18 vs. –6.52 ± 7.25, p=0.1189 **Mean improvement rate of WOMAC score compared with baseline, %** • 6 months: 31.65% vs. 20.23%, p=0.2197 • 12 months: 28.52% vs. 20.74%, p=0.2177	*Re-Join® haMPC vs. HA* **WOMAC-pain, Mean ± SD** • Baseline: 7.69 ± 4.08 vs. 7.23 ± 3.68, p=0.6701 • 6 months: 5.08 ± 3.10 vs. 5.88 ± 3.57, p=0.3948 • 12 months: 4.75 ± 3.44) vs. 5.92 ± 3.38, p=0.1774 • 6 month Δ: –2.62 ± 2.21 vs. –1.48 ± 1.53, p=0.0278 • 12 month Δ: –2.63 ± 2.36 vs. –1.44 ± 1.85, p=0.0323 **VAS-pain Left Knee, Mean ± SD** • Baseline: 5.27 ± 2.27 vs. 4.92 ± 2.56, p=0.6078 • 6 months: 2.85 ± 2.65 vs. 4.17 ± 2.55, p=0.0486 • 12 months: 2.83 ± 2.68 vs. 4.29 ± 2.35, p=0.0190 **VAS-pain Right Knee, Mean ± SD**	NR	*Re-Join® haMPC vs. HA* **WOMAC-stiffness, Mean ± SD** • Baseline: 2.42 ± 1.94 vs. 2.58 ± 1.79, p=0.7346 • 6 months: 1.73 ± 1.71 vs. 2.08 ± 1.80, p=0.4772 • 12 months: 1.63 ± 1.64 vs. 2.16 ± 1.84, p=0.3058 • 6 month Δ: –0.69 ± 1.49 vs. –0.52 ± 1.26, p= 0.5091 • 12 month Δ: –0.67 ± 1.61 vs. –0.44 ± 1.26, p=0.3587 **SF-36 QOL, Mean ± SD** • Baseline: 81.35 ± 17.16 vs. 87.04 ± 16.66, p>0.05 • 6 months: 73.04 ± 14.16 vs. 83.67 ± 16.46, p=0.0161 • 12 months: 71.96 ± 12.79 vs. 83.13 ± 15.59, p=0.0097	**Adverse Events, % (n/N)‡‡** • 73.07% (19/26) vs. 53.85% (25/26), p=0.1144 **Severe Adverse Events, % (n/N)** • Infection of knee joint: 0% (0/26) vs. 3.85% (1/26), p=NR • Death: 0% (0/26) vs. 0% (0/26)

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
	Proportion of patients reaching a pre-defined improvement rate in WOMAC-total, % (n/N) • 6 months - 20% improvement: 58% (15/26) vs. 42% (11/26), p>0.05 - 50% improvement: 23% (6/26) vs. 8% (2/26), p>0.05 - 70% improvement: 12% (3/26) vs. 0% (0/26) • 12 months - 20% improvement: 54% (14/26) vs. 50% (13/26), p=0.6458 - 50% improvement: 35% (9/26) vs. 4% (1/26), p=0.0038 - 70% improvement: 19% (5/26) vs. 4% (1/26), p=0.0742 **WOMAC-function, Mean ± SD** • Baseline: 23.65 ± 14.60 vs. 22.35 ± 13.29, p=0.7369 • 6 months: 17.00 ± 13.40 vs. 18.52 ± 12.85, p=0.6171	• Baseline: 5.50 ± 2.48 vs. 4.96 ± 2.46, p=0.4355 • 6 months: 3.00 ± 2.62 vs. 4.50 ± 2.71, p=0.0348 • 12 months: 2.78 ± 2.58 vs. 4.40 ± 2.43, p=0.0178		**Received TKA (withdrew from trial)** 4% (1/26) vs. 0% (0/26); timing unclear	

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
	• 12 months: 15.67 ± 13.38 vs. 18.20 ± 12.23, p=0.3265 • 6 month Δ: –6.65 ± 7.11 vs. –4.32 ± 7.24, p=0.2538 • 12 month Δ: –7.04 ± 8.06 vs. –4.64 ± 6.41, p=0.2072				
Emadedin 2018 N=47 (n = 19 vs. 24) Those lost to follow-up (n=4) were not included in the analysis Iran RCT Moderately High	*BM-MSCs vs. Placebo* **WOMAC-total, Mean (95% CI)** • Baseline: NR • 3 month Δ: –21.5 (–33.1 to –10) vs. –10.1 (–16.1 to –4.1), MD –11.4 (–23.1 to 0.2), p=0.055, effect=NR • 6 month Δ: –25.7 (–35.4 to 16) vs. 5.5 (–2.8 to 13.8), MD –13.5 (–24.3 to 2.7), p=0.01, effect 0.7 (0.1 to 1.4) **WOMAC-function, Mean (95% CI)** • Baseline: NR • 3 month Δ: –16 (–24.9 to –7.1) vs. –6.8 (–11.2 to –2.4), MD –9.2 (–18.9 to 0.4), p=0.06, effect NR	*BM-MSCs vs. Placebo* **VAS-pain, Mean (95% CI)** • Baseline: NR • 3 month Δ: –23.8 (–38.1 to –9.5) vs. –16.8 (–31.1 to –2.6), MD –6.9 (–26.4 to –12.5), p=0.46 • 6 month Δ: –20.8 (–34.5 to 7.1) vs. –15.7 (–33.9 to 2.4), MD –5 (–28.1 to 18), p=0.65, effect NR **WOMAC-pain, Mean (95% CI)** • Baseline: NR • 3 month Δ: –27.9 (–38.7 to –17.1) vs. –11.7 (–17.9 to –5.5), MD –16.2 (–27.5 to –4.8), p=0.006, effect 0.9 (0.2 to 1.5) • 6 month Δ: –35 (–44.9 to 25) vs. –12.2 (–18.5 to	NR	*BM-MSCs vs. Placebo* **WOMAC-stiffness, Mean (95% CI)** • Baseline: NR • 3 month Δ: –14.1 (–30.6 to 2.3) vs. –5.3 (–16.8 to 6.1), MD –8.8 (–27.4 to 9.8), p=0.34 • 6 month Δ: –-6.9 (–30.4 to 3.5) vs. –13.1 (–20.7 to 5.4), MD –7.4 (–25.4 to 10.5), p=0.40, effect NR	*BM-MSCs vs. Placebo* **Treatment related AEs, % (n/N)** • Infections and infestations -Grade III: 5.3% (1/19) vs. 0% (0/24) • General disorders and administration site condition -Grade II: 15.8% (3/19) vs. 0% (0/24) • Musculoskeletal and connective tissue disorders -Grade I: 0% (0/19) vs. 4.2% (1/24) -Grade II: 89.5% (17/19) vs. 83.3% (2/24) -Grade III: 5.3% (1/19) vs. 8.3% (2/24) • Skin and subcutaneous tissue disorders

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
	• 6 month Δ: –22.9 (–32.9 to 12.9) vs. –9.5 (–21.8 to 2.7), MD –11.3 (–22.1 to 0.4), p=0.04, effect 0.6 (0.03 to 1.2) **Proportion of patients meeting MCID (< –9.3) for WOMAC-function, % (n/N)** • 3 months: 57.9% (11/19) vs. 41.7% (10/24), p=0.18 • 6 months: 73.7% (14/19) vs. 54.2% (13/24), p=0.18 **Proportion of patients meeting PASS§§ for WOMAC-function, % (n/N)** • 3 months: 26.3% (5/19) vs. 4.2% (1/24), p= 0.02 • 6 months: 36.8% (7/19) vs. 12.5% (3/24), p=0.06	5.9), MD –21.8 (–33.8 to 9.9), p=0.001, effect 1.1 (0.4 to 1.7) **Proportion of patients meeting MCID for WOMAC-pain (< –9.7), % (n/N)** • 3 months: 47% (9/19) vs. 37.5% (9/24), p=0.47 • 6 months: 36.8% (7/19) vs. 29.2% (7/24), p=0.44 **Proportion of patients meeting PASS for WOMAC-pain, % (n/N)** • 3 months: 21.1% (4/19) vs. 29.2% (7/24), p=0.38 • 6 months: 15.8% (3/19) vs. 25% (6/24), p=0.46			-Grade I: 0% (0/19) vs. 4.2% (1/24)
Khalifeh Soltani 2019 N=20 (n=10 vs. 10) Iran RCT Moderately Low	*Placenta MSCs vs. Placebo* **KOOS-ADL, Mean***** • Baseline: 34.60 vs. 45.70, p=0.193 **KOOS-sport, Mean***** • Baseline: 0.00 vs. 3.00, p=0.658 **KOOS-function, Mean****	*Placenta MSCs vs. Placebo* **VAS-pain, Mean** • Baseline: 6.9 vs. 6.9, p=1.000 • 2 weeks: 4.4 vs. 4.4, p>0.05 • 2 months: 4.6 vs. 4.2, p>0.05 • 6 months: 5.1 vs. 3.3, p>0.05	NR	*Placenta MSCs vs. Placebo* **KOOS-QOL, Mean***** • Baseline: 18.20 vs. 41.30, p=0.001	**Adverse Events, % (n/N)** • Increased local pain and mild effusion (resolved within 48 to 72 hours post injections): 40% (4/10) vs. 0% (0/10) • No ectopic mass formation occurred

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	• Baseline: NR	Group X Time interaction p=0.401 **KOOS-pain, Mean***** • Baseline: 34.8 vs. 40.10, p=0.626 **KOOS-symptom, Mean***** • Baseline: 41.10 vs. 38.80, p=0.626			
Lee 2019††† N=24 (n = 12 vs. 12) South Korea RCT Moderately Low	*Autologous-Adipose-MSCs vs. Placebo* **WOMAC-general, Mean ± SD** • Baseline: 60.0 ± 17.0 vs. 56.4 ± 16.3 • 3 months: 40 ± NR vs. 55 • 6 months: 26.7 ± 13.3 vs. 44 ± NR **WOMAC-physical, Mean** • Baseline: 43 vs. 40 • 3 months: 30 vs. 39 • 6 months: 20 vs. 35 **KOOS-symptom, Mean** • Baseline: 53 vs. 53 • 3 months: 60 vs. 52 • 6 months: 70 vs. 58	*Autologous-Adipose-MSCs vs. Placebo* **VAS-pain, Mean ± SD** • Baseline: 6.8 ± 0.6 vs. • 3 months: 4.9 ± NR vs. 6.0 ± NR • 6 months: 3.4 ± 1.5 vs. 5.5 ± NR **KOOS-pain, Mean** • Baseline: 49 vs. 51 • 3 months: 59 vs. 46 • 6 months: 69 vs. 56 **WOMAC-pain, Mean** • Baseline: 12 vs. 12 • 3 months: 7 vs. 11 • 6 months: 5 vs. 10	NR	*Autologous-Adipose-MSCs vs. Placebo* **KOOS-QOL, Mean ± SD** • Baseline: 25 vs. 35 • 3 months: 41 vs. 41 • 6 months: 50 vs. 40 **WOMAC-stiffness, Mean** • Baseline: 5 vs. 5 • 3 months: 3.5 vs. 4.5 • 6 months: 2 vs. 4	*Autologous-Adipose-MSCs vs. Placebo* **Treatment related Adverse Events, % (n/N)** • Arthralgia: 50% (6/12) vs. 0% (0/12) • Joint effusion: 17% (2/12) vs. 8% (1/12) (All treatment-related adverse events were recovered by the use of intermittent acetaminophen) **Non-treatment related AEs, % (n/N)** • 17% (2/12) vs. 50% (6/12) **Adverse Events by Grade, n events** • Grade 1: 22 vs. 11

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	KOOS-ADL, Mean • Baseline: 51 vs. 55 • 3 months: 60 vs. 56 • 6 months: 70 vs. 59 **KOOS-sport, Mean** • Baseline: 18 vs. 27 • 3 months: 32 vs. 26 • 6 months: 43 vs. 29				• Grade 2: 9 vs. 1 • Grade 3: 3 vs. 0 • No severe AEs were reported
Shapiro 2017, 2018 N=25 (50 knees) (n = 25 vs. 25 knees) USA RCT Moderately High	NR	*BMAC vs. Placebo* **ICOAP-total pain, Median (range)** • Baseline: 32 (18 to 91) vs. 32 (0 to 73), p=NR • 1 week: 16 (0 to 73) vs. 18 (0 to 55), p=NR • 3 months: 18 (0 to 73) vs. 11 (0 to 70), p=NR • 6 months: 16 (0 to 75) vs. 9 (0 to 66), p=NR • 12 months: 18 (0 to 50) vs. 9 (0 to 55) • 1 week Δ: –16 (–68 to 16) vs. –16 (–39 to 27), p=0.57 • 3 month Δ: –21 (–71 to 21) vs. –18 (–59 to 43), p=0.24	Before the study, 100% of patients were using over-the-counter or prescription medications for pain, which decreased at the 3- and 6-month time points, to 24% and 36%, respectively.	No patient required a surgery or additional injections during follow-up	*BMAC vs. Placebo* **Adverse Events, % knees** • Effusions: 58% vs. 25%

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
		• 6 month Δ: –14 (–77 to 34) vs. –11 (–64 to 39), p=0.54 • 12 months Δ: −18 (−84 to 23) vs. −18 (−73 to 11), p=0.68 **ICOAP-constant pain, Median (range)** • Baseline: 25 (0 to 80) vs. 25 (0 to 70) • 1 week: 15 (0 to 70) vs. 10 (0 to 50), p=NR • 3 months: 5 (0 to 70) vs. 0 (0 to 65), p=NR • 6 months: 0 (0 to 65) vs. 0 (0 to 65), p=NR • 12 months: 5 (0 to 50) 0 (0 to 50), p=NR • 1 week Δ: –10 (–55 to 25) vs. –10 (–45 to 25), p=0.67 • 3 month Δ: –15 (–60 to 25) vs. –10 (–70 to 40), p=0.53 • 6 month Δ: –10 (–80 to 35) vs. –10 (–70 to 30), p=0.89 • 12 months Δ: −15 (−80 to 30) vs. −15 (−70 to 15), p=0.97			

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
		ICOAP-intermittent pain, Median (range) • Baseline: 42 (21 to 100) vs. 42 (21 to 75), p=NR • 1 week: 25 (0 to 75) vs. 21 (0 to 58), p=NR • 3 months: 21 (0 to 75) vs. 17 (0 to 75), p=NR • 6 months: 21 (0 to 83) vs. 17 (0 to 67), p=NR • 12 months: 42 (21 to 100) vs. 42 (0 to 75) • 1 week Δ: –17 (–79 to 8) vs. –21 (–50 to 29), p=0.41 • 3 month Δ: –21 (–83 to 21) vs. –25 (–50 to 46), p=0.09 • 6 month Δ: –17 (–88 to 38) vs. –21 (–58 to 46), p=0.49 • 12 months Δ: −21 (−88 to 17) vs. −13 (−75 to 13), p=0.54 **VAS-pain, Median (range)** • Baseline: 3.1 (0 to 8.1) vs. 2.9 (0 to 7.0), p=NR • 1 week: 1.3 (0 to 7.4) vs. 0.9 (0 to 7.7), p=NR • 3 months: 0.9 (0 to 8.3) vs. 1.0 (0 to 8.2), p=NR			

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		• 6 months: 1.5 (0 to 6.8) vs. 0.8 (0 to 9.2), p=NR • 12 months: 1.2 (0 to 5.5) vs. 0.7 (0 to 5.6), p=NR • 1 week Δ: –1.2 (–6.3 to 3.9) –1.5 (–6.5 to 5.2), p=0.47 • 3 months Δ: –1.5 (–6.9 to 2.9) vs. –1.5 (–6.8 to 5.7), p=0.88 • 6 months Δ: –1.1 (–5.4 to 5.3) vs. –1.3 (–6.8 to 6.4), p=0.44 • 12 months Δ: −1.4 (−6.9 to 4.2) vs. −1.8 (−5.8 to 4.2), p=0.98			
Freitag 2019 N=30 (n=10 vs. 10 vs. 10) Australia RCT Moderately High	*MCS-1 vs. MCS-2 vs. UC* **WOMAC-general ‡‡‡, Mean ± SD** • Baseline: 59.6 (17.9) vs. 54.4 (18.2) vs. 58.8 (12.8), p>0.05 • 1 month: 71 (14.5) vs. 71.8 (15.9) vs. 67.1 (12.1), p>0.05 • 3 months: 82.6 (11.3) vs. 79.2 (14.3) vs. 65.7 (9.1) *MSC-1 vs. UC*, p=0.003 • 6 months: 83 (9.9) vs. 72.2 (25.8) vs. 64.4 (12.2) *MSC-1 vs. UC*, p=0.002	*MCS-1 vs. MCS-2 vs. UC* **NPRS, Mean ± SD** • Baseline: 6.7 (1.7) vs. 6.5 (1.4) vs. 6.5 (1.4), p>0.05 • 1 month: 4.4 (2.4) vs. 4.2 (1.5) vs. 5.8 (1.1), p>0.05 • 3 months: 2.6 (2.3) vs. 4.2 (1.7) vs. 5.9 (1) *MSC-1 vs. UC*, p=0.001 • 6 months: 2.9 (1.9) vs. 4.3 (2.7) vs. 5.9 (1.1) *MSC-1 vs. UC*, p=0.002 • 12 months: 2.6 (1.8) and 2.3 (2) vs. 6.1 (2.6) *MSC-1 vs. UC*, p=0.000	NR	*MCS-1 vs. MCS-2 vs. UC* **KOOS-QOL, Mean ± SD** • Baseline: 29.4 (20.5) vs. 19.4 (13.1) vs. 30.1 (15.9), p>0.05 • 1 month: 37.4 (18.8) vs. 36.3 (15.9) vs. 40 (20.6), p>0.05 • 3 months: 51.6 (23.7) vs. 44.6 (15.3) vs. 29.9 (14.6) *MSC-1 vs. UC*, p=0.016 • 6 months: 63.3 (12.2) vs. 45 (23.1) vs. 31.9 (19.7) *MSC-1 vs. UC*, p=0.001	*MCS-1 vs. MCS-2 vs. UC* • Minor discomfort and bruising was commonly noted in both treatment groups after their lipoharvest procedure. This resolved without further intervention indicating a mild expected AE. **% of Patients experiencing adverse events post intra-articular injection** • None

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
	• 12 months: 84 (9.4) vs. 87.3 (8) vs. 59.1 (12.8) *MSC-1 vs. UC*, p=0.000 *MSC-2 vs. UC*, p=0.000 **% of patients achieving an MCID of 8 points for WOMAC-general** • 12 months: 100% vs. 90% vs. 20% **KOOS-symptom, Mean ± SD** • Baseline: 63.6 (21.3) vs. 56.5 (19.7) vs. 46.1 (11) *MSC-1 vs. UC*, p=0.016 • 1 month: 67 (12.1) vs. 63.8 (15.9) vs. 52.4 (17.7), p>0.05 • 3 months: 79.6 (12.9) vs. 70.2 (15.4) vs. 48.1 (13.1) *MSC-1 vs. UC*, p=0.000 *MSC-2 vs. UC*, p=0.005 • 6 months: 80.1 (13.7) vs. 64.8 (25.8) vs. 45.3 (13) *MSC-1 vs. UC*, p=0.000 *MSC-2 vs. UC*, p=0.014 • 12 months: 82.6 (14.1) vs. 78.1 (13.3) vs. 47.9 (13.6) *MSC-1 vs. UC*, p=0.000 *MSC-2 vs. UC*, p=0.000	*MSC-2 vs. UC*, p=0.000 **% of patients achieving an MCID of a decrease of 1 point for NPRS** • 12 months: 87.5% vs. 100% vs. 40% **KOOS-pain, Mean ± SD** • Baseline: 53 (14.5) vs. 52.1 (15.1) vs. 52.8 (10.8), p>0.05 • 1 month: 63.7 (13.2) vs. 66.1 (14.6) vs. 57.6 (7.9), p>0.05 • 3 months: 77.4 (15.8) vs. 73.4 (18.7) vs. 54.9 (7.4) *MSC-1 vs. UC*, p=0.02 *MSC-2 vs. UC*, p=0.03 • 6 months: 76.4 (12.4) vs. 65.9 (27.7) vs. 55.3 (11.4) *MSC-1 vs. UC*, p=0.02 • 12 months: 77.3 (11.3) vs. 80.5 (10.7) vs. 48.9 (12.7) *MSC-1 vs. UC*, p=0.03 *MSC-2 vs. UC*, p=0.02 **% of patients achieving an MCID of 8 points for KOOS-pain** • 12 months: 90% vs. 80% vs. 10%		• 12 months: 61.8 (13) vs. 56.3 (18) vs. 33.9 (18.9) *MSC-1 vs. UC*, p=0.003 *MSC-2 vs. UC*, p=0.006 **% of patients achieving an MCID of an increase of 8 points for KOOS-QOL** • 12 months: 88.9% vs. 80% vs. 20%	- MSC-1: 20% - MSC-2 (1st injection): 10% -MSC-2 (2nd injection): 0% • Mild - MSC-1: 60% - MSC-2 (1st injection): 50% -MSC-2 (2nd injection): 40% • Moderate - MSC-1: 10% - MSC-2 (1st injection): 30% -MSC-2 (2nd injection): 60% • Severe - MSC-1: 10% - MSC-2 (1st injection): 10% -MSC-2 (2nd injection): 0% • Serious - MSC-1: 0% - MSC-2 (1st injection): 0% -MSC-2 (2nd injection): 0%

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
	% of patients achieving an MCID of 8 points for KOOS-symptom • 12 months: 66.7% vs. 70% vs. 30% **KOOS-ADL, Mean ± SD** • Baseline: 58.8 (19.8) vs. 53.8 (18.3) vs. 59.4 (13.6), p>0.05 • 1 month: 70.9 (16.3) vs. 72.3 (16.3) vs. 65.3 (14.1), p>0.05 • 3 months: 82.5 (12.3) vs. 80 (14.4) vs. 67.1 (9.8) *MSC-1 vs. UC*, p=0.01 • 6 months: 83.6 (9.6) vs. 72.8 (26) vs. 65.5 (14.4) *MSC-1 vs. UC*, p=0.003 • 12 months: 84.3 (9.4) vs. 88.8 (8.4) vs. 60.7 (13.5) *MSC-1 vs. UC*, p=0.025 *MSC-2 vs. UC*, p=0.017 **% of patients achieving an MCID of 8 points for KOOS-ADL** • 12 months: 77.8% vs. 90% vs. 30% **KOOS-sport, Mean ± SD**				

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
	• Baseline: 39 (26.2) vs. 18 (12.7) vs. 26 (20.4), p>0.05 • 1 month: 42.8 (11.8) vs. 43.5 (21.9) vs. 32.8 (29), p>0.05 • 3 months: 63.8 (22.5) vs. 39.4 (20.7) vs. 27.5 (21.9) *MSC-1 vs. UC*, p=0.000 • 6 months: 66.9 (15.3) vs. 49.4 (27.8) vs. 31 (29.8) *MSC-1 vs. UC*, p=0.000 • 12 months: 67.8 (17.5) vs. 70 (17.8) vs. 31.5 (33) *MSC-1 vs. UC*, p=0.000 *MSC-2 vs. UC*, p=0.000 **% of patients achieving an MCID for KOOS-Sport** • 12 months: 77.8% vs. 100% vs. 30% **% of patients achieving an MCID when combining all pain and functional outcomes measures** • 12 months: 84.1% vs. 87.1% vs. 25.7%				
Centeno 2018 N=48 (n= 26 vs. 22)	*BMAC vs. Exercise* **LEAS, Mean (n=24 vs. 21)**	*BMAC vs. Exercise*	NR	*BMAC vs. Exercise*	• No serious adverse events were identified in any

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
USA RCT Moderately High	• Baseline: NR • 3 month Δ: 0.8 vs. −1.1, p=0.002 **KSS-knee score, Mean (n=23 vs. 22)** • Baseline: NR • 3 month Δ: 12.0 vs. 0.6, p<0.001 **KSS- function, Mean (n=24 vs. 22)** • Baseline: NR • 3 month Δ: 7.5 vs. 2.3, p=0.17	**VAS-pain, Mean (n=24 vs. 22)** • Baseline: NR • 3 month Δ: −12.5 vs. −8, p=0.40		**SF-12 PCS, Mean (n=24 vs. 22)** • Baseline: NR • 3 month Δ: 4.9 vs. 2.4, p=0.27 **SF-12 MCS, Mean (n=24 vs. 22)** • Baseline: NR • 3 month Δ: −2.4 vs. −1.5, p=0.68 **Total knee arthroplasty (withdrawn from trial):** n=3 at 3, 6, and 18 months; unclear to which group patients were initially randomized ‡‡‡ **Additional treatments outside study protocol (e.g., HA) (withdrawn from trial)** n=7; n=1, 3, 2, 1 at 3, 6, 12 and 24 months; unclear to which group patients were initially randomized‡‡‡ **Additional PRP injections for recurrent knee pain** N=17 (19 injections; 1 injection [n=15], 2 injections [n=2]); 4, 3, 10, 1	study patients during follow-up for either group. • The most common complaint was (16 patients complained of pain after treatment – unclear which treatment group they belonged to) • One patient reported swelling and grinding with pain • One patients had persistent popliteal fossa fluid accumulation, which was aspirated.

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
				and 1 injection given at 3, 6, 12, 18 and 24 months; unclear to which group patients were initially randomized‡‡‡	
Bhattacharya 2011 N=52 (n=26 vs n=26) Prospective Comparative Cohort ROB India	*Amniotic fluid vs. Triamcinolone Acetonide* **WD mean ± SD meters** • Baseline: 39.8 ± 3.8 vs. 38.6 ± 4.8 • 3 months: 58.6 ± 6.9 vs. 51 ± 4.8 • 6 months: 61.4 ± 7.2 vs. 42.2 ± 4.8	*Amniotic fluid vs. Triamcinolone Acetonide* **VAS mean ± SD** • Baseline: 57 ± 10.20 vs. 56 ± 11.30 • 3 months: 17 ± 3.4 vs. 21 ± 6.47 • 6 months: 12 ± 4.8 vs. 32 ± 4.8 **Proportion showing improvement based on clinical assessment, mean % ± SD** • 1 month: 88.46% ±2.8% vs. 92.3% ± 3.6% • 2 months: 84.61% ± 7.3% vs. 57.69% ± 4.8% • 3 months: 80.76% ± 7.4% vs. 46.15% ± 7.4% • 4 months: 73.07% ± 6.8% vs. 30.76% ± 2.9% • 5 months: 65.38% ± 4.9% vs. 26.92% ± 2.9% • 6 months: 57.69% ± 4.9% vs. 23.07% ± 2.2%	NR	*Amniotic fluid vs. Triamcinolone Acetonide* **Proportion of patients reporting satisfaction, % (n/N)** • 1 month: 88.5% (23/26) vs. 92.3% (24/26) • 2 months: 84.6% (22/26) vs. 57.7% (15/26) • 3 months: 80.8% (21/26) vs. 46.1% (12/26) • 4 months: 73.1% (19/26) vs. 30.8% (8/26) • 5 months: 65.4% (17/26) vs. 26.9% (7/26) • 6 months: 57.7% (15/26) vs. 23.1% (6/26) • 9 months: 53.8% (14/26) vs. 19.2% (5/26) • 12 months: 50% (13/26) vs. 15.4% (4/26) • 24 months: 46.2% (12/26) vs. 15.4% (4/26)	NR

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
		• 9 months: 53.84% ± 4.4% vs. 19.23% ± 2.1% • 12 months: 50% ± 4.3% vs. 15.38% ± 2.2% • 24 months: 46.15% ± 5.4 vs. 15.38% ± 2.2% **HAQ mean ± SD** • Baseline: 2.4 ± 0.3 vs. 2.2 ± 2 • 3 months: 2.1 ± 0.12 vs. 2.3 ± 0.2 • 6 months: 1.8 ± 0.31 vs. 2.2 ± 0.4			
Garay-Mendoza 2018 N=61 (n=26 vs.25) (Those lost to follow-up (n=10) were not included in the f/u analysis.) Prospective Comparative Cohort ROB Mexico	*Auto-BM-MSCs vs. Acetaminophen* **WOMAC-general, Mean ± SD** • Baseline: 62.61 ± 18.55 vs. 69.93 ± 17.89, p=0.12 • 1 week: 80.72 ± 20.41 vs. 71.62 ± 14.62, p=0.07 • 1 month: 88.58 ± 17.12 vs. 69.92 ± 14.87, p<0.0001 • 6 months: 91.73 ± 9.45 vs. 72.96 ± 15.04, p<0.0001 **WOMAC-physical, Mean**	*Auto-BM-MSCs vs. Acetaminophen* **VAS-pain, Mean ± SD** • Baseline: 5.27 ± 2.196 vs. 4.32 ± 2.35, p=0.10 • 1 week: 2.31 ± 2.24 vs. 4.40 ± 2.4, p=0.003 • 1 month: 1.62 ± 2.04 vs. 4.24 ± 2.72, p<.0001 • 6 months: 0.92 ± 1.29 vs. 4.64 ± 2.43, p<0.0001 **WOMAC-pain, Mean** • Baseline: NR • 1 week: 82.59 ± 15.15 vs. 71.07 ± 17.12, p=0.011	NR	*Auto-BM-MSCs vs. Acetaminophen* **WOMAC-stiffness, Mean** • Baseline: NR • 1 week: 85.26 ± 18.95 vs. 65.59 ± 22.40, p=0.001 • 1 month: 88.88 ± 20.31 vs. 67.59 ± 23.57, p=0.001 • 6 months: 92.30 ± 11.22 vs. 70.00 ± 21.65, p<0.001	*Auto-BM-MSCs vs. Acetaminophen* **Adverse Events, % (n/N)** • Swelling and pain in the knee the day after injection: 3.3% (1/30) vs. 0% (0/31) • Bone pain due to growth factor stimulation: 40% (12/30) vs. 0% (0/31) • Some patients referred slight pain and stiffness during the first 48 hours after the injection

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
	• Baseline: NR • 1 week: 80.50 ± 19.65 vs. 74.52 ± 15.95, p=0.218 • 1 month: 87.62 ± 17.61 vs. 73.34 ± 16.22, p=0.003 • 6 months: 91.48 ± 9.79 vs. 72.29 ± 14.84, p<0.001	• 1 month: 88.70 ± 17.24 vs. 70.35 ± 17.37, p<0.001 • 6 months: 92.30 ± 9.40 vs. 68.80 ± 18.44, p<0.001			
Centeno 2014 N=840 procedures on 681 patients (n=616 treated knees on 518 patients vs. n=224 treated knees on 163 patients) USA Registry study ROB	Outcomes not relevant for the purposes of this review	Outcomes not relevant for the purposes of this review	Outcomes not relevant for the purposes of this review	Outcomes not relevant for the purposes of this review	*BMC+PRP+PL vs. BMC+PRP+PL+Fat graft* **Number of Adverse Events in each group classified by category, severity, relation to preexisting condition, procedure and injected component, and outcomes** • Total: 37 vs. 20 • Category - Pain/swelling: 23 vs. 13 - Miscellaneous: 7 vs. 2 - Skin reactions: 1 vs. 0 - Neurologic: 0 vs. 2 - Neoplasm: 2 vs. 0 - Immune/allergic: 2 vs. 0 - Cardiac: 0 vs. 2 - Bleeding/hematoma: 2 vs. 0 - Renal: 0 vs. 1 • Severity - Mild: 26 vs. 14 - Moderate: 9 vs. 5

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
					- Severe: 2 vs. 1 - Related to preexisting condition: 9 vs. 5 • Relation to procedure - Definitely related: 4 vs. 5 - Likely related: 0 vs. 0 - Possibly related: 17 vs. 12 - Unlikely related: 11 vs. 2 - Not related: 5 vs. 1 • Relation to injected components - Definitely related: 1 vs. 3 - Likely related: 0 vs. 0 - Possible related: 16 vs. 8 - Unlikely related: 14 vs. 4 - Not related: 6 vs. 5 • Outcome - Resolved/recovered: 22 vs. 17 - Ongoing: 8 vs. 3 - Not recovered: 1 vs. 0 - Fatal: 2 vs. 0 - Unknown: 3 vs. 0 - Not categorized: 2 vs. 0

Δ = change; ADL = activities of daily living; AE = adverse events; BM = bone marrow; BMAC = bone marrow aspirate concentrate; BMC = bone marrow concentrate; BMI = body mass index; BM-MNCs = bone marrow mononuclear cells; BM-MSCs = bone marrow derived mesenchymal stem/stromal cells; CI = confidence interval; COI = conflict of interest; F/U = follow-up; HA = hyaluronic acid; haMPC = human autologous adipose-derived mesenchymal progenitor cells; HAQ = health assessment questionnaire; HIV = human immunodeficiency virus; ICOAP = Osteoarthritis Research Society International Intermittent and Constant Osteoarthritis Pain; IQR = inter-quartile range; K-L = Kellgren=Lawrence; KOA = knee osteoarthritis; KOOS = knee injury and osteoarthritis outcome score; KSS = knee society score; LEAS = lower extremity activity scale; LEFS = lower extremity functional score; MCID = minimal clinically important difference; MCS = mental component score; MD = mean difference; MRI = magnetic resonance imaging; MSCs = mesenchymal stem/stromal cells; NPRS = numeric pain rating scale; NPS = numerical pain score; NR = not reported; NSAID = non-steroid anti-inflammatory drug; OA = osteoarthritis; OTC = over the counter; PASS = patient acceptable symptom state; PCS = physical component score; PL = platelet lysate; PRP = platelet rich

plasma; PT = physical therapy; QOL = quality of life; RCT = randomized controlled trial; ROB = risk of bias; ROM = range of motion; SAE = severe adverse events; SD = standard deviation; SE = standard error; SF-12 = short form 12 question health related quality of life questionnaire; SF-36 = short form 36 question health related quality of life questionnaire; SVF = stromal vascular fraction; tx = treatment; UC = usual care; VAS = visual analogue scale; WD = walking distance; WOMAC = Western Ontario and McMaster Universities Osteoarthritis

* 1 week, 3 month, and 6 month data for WOMAC-general, WOMAC-pain, VAS-pain, and Lequesne are estimated from graphs.

† To include menstrual disorders, influenza, migraine, toothache, restlessness, memory loss, testicular pain, rhinitis, sensitive hand alteration, sleepiness, allergic reaction, tinnitus, dental implant, lipoma, skin tumor.

‡ SDs are estimated from Figure 4

§ Estimated from Figure 6

** Authors indicate that only the patients who had been treated with BM-MSCs met criteria to be considered WOMAC responders in the long term (12 and 48 months). According to previous literature, patients were considered WOMAC responders when they reported an improvement of 20 % in at least two items together with an improvement of ten points in the overall scale.

†† All data for WOMAC scores, including WOMAC-total, were abstracted from Supplemental Table S1. There was a discrepancy between the text and Table S1 in terms of what was reported for WOMAC-general scores. The decision was made to abstract all data from the supplemental Table S1.

‡‡The most common adverse events were transient pain and swelling of injection-site joint, all of which were mild to moderate and were spontaneously relieved within 7 days without special treatment.

§§ Authors do not define what the PASS values were set at.

***While authors report KOOS scores data, the supplemental graphs from which this data would be derived are of too poor quality to gather accurate data and this have not been reported here.

††† All data without an SD was estimated from figures.

‡‡‡ All exercise therapy patients crossed-over to receive a BMC injection at 3 months so the majority of these patients had received a BMC injection at some point.

Appendix Table F3: Study characteristics, demographics, and data abstraction for case series and treatment registries evaluating the safety of stem cell therapies for knee osteoarthritis

Author (year) N Country Study design *HIGH*	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
Soler 2016 N=15 Spain *HIGH*	Inclusion: 1. Gonarthrosis grade II–III of Kellgren and Lawrence assessed by two observers 2. Chronic knee pain with mechanical characteristics 3. Absence of local or systemic septic process 4. Haematological and biochemical laboratory tests without significant alterations that contraindicate treatment 5. Informed Consent Form signed by the patient 6. The patient is able to understand the nature of the study Exclusion: 1. Patients <18 years or legally dependent 2. Patients >65 years 3. Previous surgery of the knee 4. Intraarticular treatment in the past six months 5. Knee ligament or ruptured meniscus observed by MRI 6. Any sign of infection 7. Positive serology for HIV I–II, Hepatitis B, Hepatitis C and syphilis.	*Autologous culture expanded BM-derived MSCs* **Cell Type**: MSCs **Cell Source**: BM **Cell Expansion**: Yes **Cell Concentration**: Mean ± SD: $40.9 \times 10^6 \pm 0.4 \times 10^6$ **Cell Delivery**: medial parapatellar approach **Anesthetic Use**: No **Number of injections**: 1 **Co-interventions**: NR **Post treatment protocol**: Use of crutches was recommended with partial weight bearing for eight days	**% male**: 40% **Median age (range)**: 52 (33-64) **KL OA Grade** II: 60% (9/15) III: 40% (6/15) **Laterality, % (n/N)** -Left: 60% (9/15) -Right: 40% (6/15) (all treated unilaterally)	F/U 12 months 48 months % Followed 12 months: 100% (15/15) 48 months: 87% (13/15)	**Funding**: Government **COI:** None	**Number of patients with at least one AE by type of event, % (n/N)** **Any AE** • Mild: 86.7% (13/15) • Moderate: 20.0% (3/15) **Upper respiratory tract infection** • Mild: 6.7% (1/15) • Moderate: 0% (0/15) **Dental infection** • Mild: 0% (0/15) • Moderate: 6.7% (1/15) **Fall** • Mild: 6.7% (1/15) • Moderate: 0% (0/15) **Contusion** • Mild: 6.7% (1/15) • Moderate: 0% (0/15) **Ligament sprain** • Mild: 6.7% (1/15) • Moderate: 0% (0/15) **Muscle rupture** • Mild: 6.7% (1/15) • Moderate: 0% (0/15) **Ovarian Cystectomy**

Author (year) N Country Study design *HIGH*	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
	8. Congenital or acquired malformation resulting in significant deformity of the knee and leading to problems in application or evaluation of results. 9. Overweight expressed as Body Mass Index (BMI) greater than 30.5 (obesity grade II). 10. Pregnant women or intend to become pregnant or breast-feeding 11. Neoplasia 12. Immunosuppressive states 13. Participation in another clinical trial or treatment with a different investigational product within 30 days prior the inclusion in the study 14. Other pathologic conditions or circumstances that difficult participation in the study according to medical criteria					• Serious: 6.7% (1/15) **Vaginal hemorrhage** • Mild: 6.7% (1/15) • Moderate: 0% (0/15) **Abdominal pain** • Mild: 6.7% (1/15) • Moderate: 0% (0/15) **Arthralgia** • Mild: 53.3% (8/15) • Moderate: 6.7% (1/15) **Joint Lock** • Mild: 6.7% (1/15) • Moderate: 0% (0/15) **Back pain** • Mild: 20% (3/15) • Moderate: 6.7% (1/15) **Joint Swelling** • Mild: 13.3% (2/15) Moderate: 0% (0/15) **<u>Number of AEs by System Organ Class</u>** **Total Number of AEs across all System Organ Classes** • Mild: 22 events • Moderate: 3 events

Author (year) N Country Study design *HIGH*	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
						Infections and infestations • Mild: 1 event • Moderate: 1 event **Injury, poisoning and procedural complications** • Mild: 4 events • Moderate: 0 events **Surgical and medical procedures** • Serious: 1 event **Reproductive system and breast disorders** • Mild: 1 event • Moderate: 0 events **Gastrointestinal disorders** • Mild: 1 event • Moderate: 0 events **Musculoskeletal and connective tissue disorders** • Mild: 14 events • Moderate: 2 events
Orozco 2013/2014 N=12 Spain *HIGH*	Inclusion: Failure of conservative treatment Exclusion: NR	*Autologous culture expanded BM-MSCs* **Cell Type**: MSCs **Cell Source**: Bone marrow (mean volume 86±9 mL; mean number of mononuclear cells	**% male**: 50% **Mean age ± SD**: 49 ± 5 years **Undergone previous treatment, % (n/N)**	F/U 1-year 2-years % Followed 100% (12/12)	**Funding**: Unclear **COI:** None	**Study related or possibly study related minor AEs, % (n/N)** • Post-implantation pain at days 1-6: 50% (6/12) • Articular inflammation attributable to knee overloading: 25% (3/12)

Author (year) N Country Study design *HIGH*	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
		obtained 1.13±0.21x10^9; mean viability 91%) **Cell Expansion**: Yes (mean expansion time 22 days) **Cell Concentration**: 40±1 X 10^6 suspended in Ringerlactate at 5x10^6 cells/mL **Cell Delivery**: Intraarticular injection **Anesthetic Use**: NR **Number of injections**: 1 **Co-interventions**: NR **Post treatment protocol**: NR	Surgery: 75% (9/15) Rehabilitation: 100% (12/12) NSAIDS: 100% (12/12) Corticoids: 33% (4/12) HA: 17% (2/12) PRP: 42% (5/12)			• Unexpected knee inflammation with synovial fluid effusion and articular swelling: 25% (3/12) • Low Back Pain: 25% (3/12) • Pain in contra lateral knee: 25% (3/12) • Ischiotibial tendonitis: 8% (1/12) **Non-study related minor AEs, % (n/N)** • Arthroscopic surgery in the contralateral knee: 8% (1/12) • Dental implant: 8% (1/12) • Influenza: 8% (1/12) • Intolerance to gluten and to lactose: 8% (1/12) **No serious adverse effects appeared during the second year.**
Bui 2014 N=21 Vietnam *HIGH*	Inclusion: All patients were aged above 18 years, had osteoarthritis from cartilage injury at grade II to III, had failed in drug treatment as well as autologous cartilage transplantation, had a Lysholm score lower than 65, were committed with a surgical condition, and were HIV negative Exclusion: NR	*Autologous adipose tissue-derived MSCs (as SVF) + PRP* **Cell Type**: SVF **Cell Source**: adipose tissue (50-100 mL) 20 ml of peripheral blood was also collected **Cell Expansion**: No **Cell Concentration**: NR **Cell Delivery**: Injection **Anesthetic Use**: NR **Number of injections**: 1 **Co-interventions**: NR	NR	F/U 1 month 3 months 6 months % Followed NR	**Funding**: Industry **COI:** NR	• No patient experienced side-effects or complications related to the procedure, such as microorganism infection or tumor formation at the joint.

Author (year) N Country Study design *HIGH*	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
		Post treatment protocol: NR				
Yokota 2017 N=13 (26 joints treated) Japan *HIGH*	Inclusion: All patients responded inadequately to conservative treatment commonly provided at authorized insurance medical institutions in Japan. Specifically, they were recommended to undergo artificial joint replacement after poor response to oral medication for pain relief and hyaluronic acid injection. Exclusion: NR	*Autologous adipose-derived SVF* **Cell Type**: SVF **Cell Source**: ~200 mL or more of subcutaneous adipose tissue from the lower abdomen or the inside of the thigh **Cell Expansion**: No **Cell Concentration**: total SVF cell dose was not assessed for this cohort, but authors note that processing 200 mL of adipose tissue typically yields 4 to $8x10^7$ viable nucleated SVF cells for an estimated average dose of $3x10^7$ SVF cells/knee. **Cell Delivery**: intra-articular knee injection **Anesthetic Use**: **Number of injections**: **Co-interventions**: See below **Post treatment protocol**: Post-treatment physical therapy was restricted to requesting that patients perform a target of 100 'bend-and-stretch' exercise of the knees on	**% male**: 15% **Mean age (range)**: 74.5 (65 to 82) **KL OA Grade** III: 15% (2/13) IV: 85% (11/13)	F/U 6 months % Followed 100% (13/13)	**Funding**: NR **COI:** NR	• No serious adverse events (as defined by the International Conference of Harmonisation guidelines) • Pain and swelling at the injection and fat harvesting sites that lasted for a few days was observed • There were no reports of other potential treatment-related adverse events such as reduced range of motion of the knee, fat embolism, deep venous thrombosis, sepsis caused by intra-articular infection, adhesion of the knee associated with SVF injection, or superficial infection or intra-articular bleeding at the injection sites in the knee.

Author (year) N Country Study design *HIGH*	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
		the day of SVF injection and each day thereafter. Oral medication for pain relief and prophylactic antibiotics was prescribed for outpatient use for four and three days respectively. All patients received no other treatment or intervention during the evaluation period.				
Shaw 2018 N=15 (20 knees) USA *HIGH*	Inclusion: NR Exclusion: NR	*Autologous BMC* **Cell Type**: BMC **Cell Source**: Posterior superior iliac spine **Cell Expansion**: No **Cell Concentration**: NR **Cell Delivery**: Ultrasound guidance into the knee joint capsule. If an effusion was noted, after local anesthesia it was aspirated with an 18-gauge needle prior to the injection of cells via the same needle. **Anesthetic Use**: Yes **Number of injections**: 4 injections scheduled to be 14 days apart **Co-interventions**: NR **Post treatment protocol**: NR	**% male**: 33% **Mean age (range)**: 67.67 ± 7.90	F/U 3 months (86 days after first treatment) % Followed NR	**Funding**: None **COI:** M.D. is the primary physician at Darrow Stem Cell Institute, where all study procedures were performed**.**	• When patients were asked whether they experienced adverse side effects at each follow-up, the most common complaints were pain at the extraction site and inflammation at the injection site. • Grinding, popping, and snapping sensations in the knee joint were common with specific movements, as was joint stiffness, especially 1 to 2 days following BMC treatment. • One patient reported having fallen (which could have hindered healing) • There were no other reported incidents that would have negatively influenced the results.

Author (year) N Country Study design *HIGH*	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
Kim 2014 N=41 patients (75 knees) [84% of treatments were injection alone*] South Korea *HIGH*	Inclusion: Outpatients with chief complaint of knee pain were performed thorough clinical history, physical and neurologic examination, laboratory test, X-ray, and MRI of the knee. Diseases of the knees included in this study were limited to osteoarthritis, and the study was performed only if the patients understood and agreed about treatment method and procedure. Exclusion: NR	*Autologous BMC + adipose tissue* **Cell Type**: MSCs **Cell Source**: BM from the posterior or anterior superior iliac spine (120 cc); Adipose tissue from the abdomen (20 cc) **Cell Expansion**: **Cell Concentration**: 7 cc BMC + 10 cc adipose tissue) **Cell Delivery**: NR **Anesthetic Use**: NR **Number of injections**: **Co-interventions**: 1 **Post treatment protocol**: 3 hours bed rest then return to normal activities. There was no limitation on daily lives other than the instruction to refrain from extreme exercise for 6 weeks after the operation	**% male**: 41.5% **Mean age (range)**: 60.7 (53 to 80) years **KL OA grade, % knees** I: 16% (12/75) II: 32% (24/75) III: 44% (33/75) IV: 8% (6/75)	Mean F/U 8.7 months (range, 6 to 19) % Followed NR	**Funding**: NR **COI:** None	**Adverse Events, % (n/N)** • Joint swelling: 92% (69/75 knees) • Pain: 41.3% (31/75 knees)
Al-Najar 2017 N=13 *HIGH*	Inclusion: 1. Chronic knee joint pain and or swelling (more than 6 months) 2. Grade II–III KOA confirmed by two observers 3. Absence of local or systemic infection 4. Absence of significant hematological disease	*Autologous expanded BM-derived MSCs* **Cell Type**: MSCs **Cell Source**: BM from the iliac crest (35 to 40 mL) **Cell Expansion**: Yes **Cell Concentration**: 30.5×10^6 per dose; 70 to 80% confluence	**% male**: 46.2% **Mean age (range)**: 50 (34 to 63 years) **KL OA grade** II: 38% (5/13) III: 62% (8/13)	F/U 48 months % Followed NR	**Funding**: University **COI:** None	**Adverse Events, % (n/N)** • Pain in injected joint requiring cold compress and resting for several hours: 15.4% (2/13) • Pain and swelling in injected joint requiring cold compress and mild oral analgesia: 7% (1/13)

Author (year) N Country Study design *HIGH*	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
	5. Absence of significant biochemical or hematological laboratory tests abnormalities 6. Informed consent form signed by the patient Exclusion: 1. Age less than 18 or older than 65 years 2. Intra-articular treatment in the past 6 months 3. Significant deformity of the knee 4. Knee ligament injury or ruptured meniscus observed by MRI 5. Infection or positive serology for transmissible agents 6. Body mass index (BMI) greater than 30.5 7. Women in childbearing age 8. Malignancy 9. Immunosuppressive drugs	**Cell Delivery**: intraarticular injection **Anesthetic Use**: **Number of injections**: 2 injections 1 month apart **Co-interventions**: NR **Post treatment protocol**: NR				
Ahmad 2014 N=10 (20 knees) Egypt *HIGH*	Inclusion: Osteoarthritis diagnosed by X-ray and MRI and end stage osteoarthritis candidate for total knee replacement. Exclusion: Pregnancy or lactating, positive tests for HIV, HCV, and HBV,	*Autologous peripheral blood stem cells* **Cell Type**: Peripheral blood stem cells **Cell Source**: Peripheral blood **Cell Expansion**: NR **Cell Concentration**: NR	**% male**: 30% **Mean age (range)**: 51 (38 to 64) years **Mean BMI ± SD**: 32 ± 1.2	F/U 12 months % Followed 100% (10/10)	**Funding**: None **COI:** None	• No signs of infection or post-operative complications were reported except swelling, warmth in knee, difficulty in moving knee, and pain at injection site within the first 2 weeks.

Author (year) N Country Study design *HIGH*	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
	any bleeding disorders or blood diseases, active neurologic disorder, end organ damage, and uncontrolled endocrine disorders.	**Cell Delivery**: intra-articular injection **Anesthetic Use**: NR **Number of injections**: 3 8mL injections **Co-interventions**: NR **Post treatment protocol**: NR				
Bansal 2017 N=10 patients (13 knees) India *HIGH*	Inclusion: Patients age 50 or older who present with symptomatic primary osteoarthritis of the knee, defined by daily pain for the previous 3 months, analgesics usage at least once a week, less than 30 min of morning stiffness and a WOMAC score of ≤75 in the target knee. The radiographic eligibility criteria included Brandt Radiographic Grading Scale of Osteoarthritis grade 1 and 2. Exclusion: Evidence of secondary knee osteoarthritis, severe osteoarthritis (joint space width—JSW <2 mm), prior intra articular injections within the previous 1 year prior to inclusion and patients with clinically significant systemic disease	*Autologous SVF (from adipose) + PRP* **Cell Type**: SVF **Cell Source**: 100 mL of abdominal adipose tissue; 20 mL peripheral blood for PRP **Cell Expansion**: Yes **Cell Concentration**: 87.4% viability Mean 1×10^6/ml **Cell Delivery**: intra-articular injection **Anesthetic Use**: NR **Number of injections**: NR **Co-interventions**: NR **Post treatment protocol**: NR	**% male**: 60% **Mean age**: 58.4 years	F/U 24 months % Followed 100% (10/10)	**Funding**: Industry **COI:** KC is an officer of US Stem Cell, Inc.	• Local pain and swelling at the lipoaspiration site: 10% (1/10) • Synovitis: 10% (1/10) • No serious side effects were reported

Author (year) N Country Study design *HIGH*	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
Goncars 2019 N=32 patients (34 knees) Latvia *HIGH*	Inclusion: 1. Degenerative osteoarthritis of the knee 2. K-L grade II-III 3. At least 6 months of persisting pain 4. Some of OA symptoms Exclusion: 1. Over 75 years old. 2. Oncologic diseases. 3. Severe renal, pulmonary, or hepatic impairment. 4. Hematologic diseases. 5. Diabetes mellitus of the first type. 6. Severe effusion. 7. Contracture or instability and axial deformities more than 10º in the knee joint. 8. Septic arthritis or skin disorders. 9. Use of corticosteroids and immunosuppressive agents. 10. Previous injection in the target knee within 2 months.	*BM-derived mononuclear cells* **Cell Type**: BM MNCs **Cell Source**: 45 mL of red bone barrow **Cell Expansion**: NR **Cell Concentration**: mean 45.56 ± 34.94 x 10^6 cells **Cell Delivery**: Anterolateral approach in the flexed knee **Anesthetic Use**: None **Number of injections**: NR **Co-interventions**: NR **Post treatment protocol**: No restriction on further activities. Recommended to avoid excessive physical activity and sport exercises exceeding normal everyday activities and habits.	**% male**: 50% **Mean age ± (SD)**: 53.96 ± 14.15 years **Mean symptom duration (range)**: NR **KL OA grade, % knees** II: 47% (16/34) III: 53% (18/34) **Proportion of patients treated bilaterally, % (n/N):** 6.3% (2/32)	F/U 1 month 3 month 6 month 12 month % Followed 100%	**Funding**: University + Industry + government **COI:** None reported	• No adverse effects after the injection were observed. • Patients reported the procedure of the iliac crest puncture as painless, and no complications in donor sites were observed. • Pain and swelling in the knee joint caused by the puncture and injection decreased during the first 24 hours in the majority of patients. No additional treatment was applied.
Roato 2019 N=20	Inclusion: Men and women with BMI > 20 kg/m^2, regular renal and	*Concentrated adipose tissue* **Cell Type**: SVF	**% male**: 45% **Mean age (SD)**: 59.6 ± 10.5 years	F/U 3 months 6 months	**Funding**: Government + non profit	• Most patients reported the feeling of a “tied knee” (inability to move

Author (year) N Country Study design *HIGH*	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
Italy *HIGH*	coagulation conditions, and classified according to the Kellgren-Lawrence grading scale for the radiographic osteoarthritis classification. Exclusion: End stage patients (grade IV) OA; BMI > 39 kg/m^2; patients who underwent surgical procedures other than diagnostic arthroscopy; patients with osteochondral focal lesions or clinically relevant axial defects, outcome of articular fractures; patients currently treated with corticosteroids and hyaluronic acid injection to the affected knee joint within the previous six months.	**Cell Source**: sub-abdominal adipose tissue **Cell Expansion**: NR **Cell Concentration**: 31,220,000 ± 268,428, with the mean ASC percentage of 14.2% (range: 2.7 to 18%) **Cell Delivery**: Intraarticular injection **Anesthetic Use**: spinal anesthesia **Number of injections**: **Co-interventions**: Subcutaneous abdominal liposuction + diagnostic knee arthroscopy. **Post treatment protocol**: Weight-bearing to be avoided, and the leg to be immobilized for ten days. Only isometric exercises for the quadriceps were allowed. Patients were sent to physiotherapy to recover full articulation of the join, muscular tone, and correct gait pattern.	**Mean symptom duration (range)**: NR **Mean BMI ± SD**: 25.1 ± 3.8 **KL OA grade, % patients** I: 15% (3/20) II: 55% (11/20) III: 30% (6/20)	18 months % Followed 100%	**COI:** One author (Giuseppe Perale) is affiliated with the company manufacturing the bone substitute used in this study.	freely), but this symptom progressively waned one month after the operation. • Appearance of an indolent swelling in suprapatellar area two months after surgery: 5% (1/20) • Dropped out of study to undergo knee replacement surgery: 10% (2/20) • No cases of infection, thromboembolism, adverse reaction at knee level, or worsening of the arthritic symptoms were reported.
Hudetz 2017 N=17 (32 knees) Croatia	Inclusion: 1. Patients with Kellgren Lawrence OA stages III and IV.	*Microfragmented adipose tissue product (MSCs)* **Cell Type**: MSCs **Cell Source**: Adipose tissue **Cell Expansion**: None	**% male**: 29% (5/17) **Mean age (SD)**: 69 ± 12 years	F/U Baseline 3 months 6 months 12 months	**Funding**: None **COI:** None	• No adverse events or infections were reported in this cohort.

Author (year) N Country Study design *HIGH*	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
HIGH	2. Onset of symptoms of the index knee at six or more months ago. 3. Ability to follow instructions of the study. 4. Age 40 to 85 years. Exclusion: 1. Age < 40 or > 85 years. 2. Chondromatosis or villonodular synovitis of the knee. 3. Recent trauma (<3 months) of the symptomatic knee. 4. Infectious joint disease. 5. Malignancy. 6. Pregnancy. 7. Patients on anticoagulant therapy with prothrombin time (<0.70) or suffering from thrombocytopenia and/or coagulation disorder. 8. Hypersensitivity to local anesthetics.	**Cell Concentration**: NR **Cell Delivery**: Intraarticular injection **Anesthetic Use**: Lidocaine **Number of injections**: 1 **Co-interventions**: NR **Post treatment protocol**: NR	**Mean symptom duration (range)**: NR	% Followed 100%		
Hudetz 2019 N=20 Croatia	Inclusion: 1. Patients with Kellgren Lawrence OA stages III and IV. 2. Onset of symptoms of the index knee at six or more months ago.	*Microfragmented adipose tissue product (MSCs)* **Cell Type**: MSCs **Cell Source**: Adipose tissue **Cell Expansion**: None **Cell Concentration**: NR	**% male**: 75% **Mean age (range)**: NR **Mean symptom duration (range)**: NR	F/U Baseline 12 months % Followed 85% (17/20)†	**Funding**: None **COI:** One author (Ozren Polasek) is a member of the *Croatian Medical Journal's* Editorial	• No adverse events or infections were reported in this cohort.

Author (year) N Country Study design *HIGH*	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
HIGH	3. Ability to follow instructions of the study. 4. Age 40 to 85 years. Exclusion: 1. Age < 40 or > 85 years. 2. Chondromatosis or villonodular synovitis of the knee. 3. Recent trauma (<3 months) of the symptomatic knee. 4. Infectious joint disease. 5. Malignancy. 6. Pregnancy. 7. Patients on anticoagulant therapy with prothrombin time (<0.70) or suffering from thrombocytopenia and/or coagulation disorder. 8. Hypersensitivity to local anesthetics.	**Cell Delivery**: Intraarticular injection **Anesthetic Use**: Lidocaine **Number of injections**: 1 **Co-interventions**: NR **Post treatment protocol**: NR	**KL OA grade, % knees:** III: 20% (4/20) IV: 80% (16/20)		Board.	
Pintat 2017 N=19 France *HIGH*	Inclusion: 1. Persistent symptomatic patellofemoral OA with normal radiographs and pathologic magnetic resonance images. 2. Age 20 to 60 years. Exclusion: 1. Pregnancy. 2. Infections.	*Autologous adipose-derived MSCs + PRP* **Cell Type**: MSCs + PRP **Cell Source**: Adipose tissue from subcutaneous medial knee fat + venous blood **Cell Expansion**: NR **Cell Concentration**: 6 mL of stromal vascular fraction containing MSCs + 3 mL of PRP	**% male**: 52.6% **Mean age (range)**: 43.1 (27 to 57) years **Mean symptom duration (range)**: 12 (7 to 19) months	F/U 6 months 12 months % Followed 79% (15/19)‡	**Funding**: NR **COI:** None	• No clinical complications were reported.

Author (year) N Country Study design *HIGH*	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
	3. Previous corticosteroid injection of the knee. 4. Immunodeficiency. 5. Patients who received additional treatment after MDC + PRP injection during follow-up (medical or surgical) were also excluded from long term follow-up assessment.	**Cell Delivery**: Intramuscular 21-guage needle inserted on lateral side of knee into the patellofemoral joint **Anesthetic Use**: Lidocaine **Number of injections**: 1 **Co-interventions**: NR **Post treatment protocol**: NR				
Oliver 2015 N=70 patients (122 knees) USA *HIGH*	Inclusion: All patients in a single center outpatient clinic undergoing a BMC procedure for knee OA between April 2014 and October 2014 identified as having grade II, III, or IV OA of the knee. Exclusion: NR	*BMAC* **Cell Type**: BMC **Cell Source**: Bone marrow harvested from the posterior superior iliac crest **Cell Expansion**: NR **Cell Concentration**: 5-7 cc per affected knee **Cell Delivery**: 1 cc of BMC and 1 cc of lipoaspirate were placed along medial joint capsule under ultrasound guidance **Anesthetic Use**: ethyl chloride + lidocaine **Number of injections**: NR **Co-interventions**: 2 cc of lipoaspirate **Post treatment protocol**: - Patients with grade III or IV OA were prescribed a	**% male**: 31%§ **Mean age (range)**: 60 (28 to 83) years **Mean symptom duration (range)**: NR **Proportion of patients treated bilaterally, % (n/N):** 74% (54/70) **KL grade:** II: 13% (9/70) III: 41% (29/70) IV: 46% (32/70)	F/U Baseline 3 months 6 months % Followed Procedure: 100% (70/70) 3 months: 95% (67/70) 6 months: 97% (68/70)	**Funding**: NR **COI:** NR	• Transient increase in pain: 80.3% (57/70) • Short-term swelling: 57.8% (41/70) • No serious adverse events such as neoplasm or thrombosis were reported and no minor adverse events such as skin reactions or allergic responses.

Author (year) N Country Study design *HIGH*	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
		Don-Joy or Bledsoe off-loader brace for the affected side and asked to wear the brace a minimum of four hours a day while weight bearing for eight weeks. - All patients were instructed to gently ambulate as tolerated for first 3 to 7 days. They were also given a home exercise program 1 week after treatment, and were allowed to return to light activity as tolerated. Formal physical therapy was offered at 4 weeks but not required. - Allowed to return to full activities at 6 weeks, but discouraged distance running and other plyometric activities in patients with grade III or IV OA. - All patients instructed to avoid oral NSAIDs for 4 to 6 weeks post procedure.				
Adriani 2017 N=30	Inclusion: 1. Stable or progressive knee OA for at least 12 months.	*Adipose derived stem cells* **Cell Type**: ASCs	**% male**: 40% **Mean age (range)**: 63.3 (50 to 80) years	F/U Baseline 1 week 1 month	**Funding**: NR **COI:** NR	• Pain in the abdominal region with important hematoma: 3% (1/30)

Author (year) N Country Study design *HIGH*	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
Italy *HIGH*	2. no other injective treatments during the last 12 months. 3. no previous knee surgeries. 4. no infections or systemic inflammatory diseases. <u>Exclusion</u>: 1. Narcotic use. 2. non-OA joint pain. 3. systemic conditions. 4. other ongoing or previous injective OA treatments. 5. Younger than 18 years old.	**Cell Source**: 20 mL of Fat harvested from the abdomen **Cell Expansion**: NR **Cell Concentration**: 6 mL **Cell Delivery**: intra-articular percutaneous injection **Anesthetic Use**: Local anesthesia **Number of injections**: 1 **Co-interventions**: None **Post treatment protocol**: Avoid sports activities for 7 days. Abdominal girdle was applied to all patients for 15 days, while a pressure dressing was applied to the knee for 1 day. All patients followed a rehabilitation protocol to improve posture and muscle toning.	**Mean symptom duration (range)**: NR **Mean BMI ± SD**: 25.1 ± 1.7	3 months 6 months 12 months <u>% Followed</u> 100%		• Developed less important hematoma of the abdominal region: 7% (2/30) • Developed joint swelling that required aspiration resulting in resolution of symptoms: 6% (2/30) • Developed mild swelling that resolved during rehabilitation: 10% (3/30) • No infection or neurovascular complications
Rajput 2018 N=11 India *HIGH*	<u>Inclusion</u>: 1. Both sexes 2. 40 to 75 years old 3. Established OA of the knee 4. Normal liver and renal function 5. Controlled diabetes (if diabetic) <u>Exclusion</u>:	*Autologous bone marrow MNCs* **Cell Type**: BM-MNCs **Cell Source**: 40-60 mL of bone marrow suspension harvested from posterior iliac crest **Cell Expansion**: None	**% male**: 36.36% **Mean age (range)**: 61.2 (45 to 75) years **Mean symptom duration (range)**: NR **Mean BMI ± SD**: NR	<u>F/U</u> Baseline 1 month 3 months 6 months 12 months <u>% Followed</u> 100%	**Funding**: None **COI:** None	• No adverse events during 1-year follow-up

Author (year) N Country Study design *HIGH*	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
	1. Structural defects 2. Any other cause of leg paint 3. Arthritis other than degenerative	**Mean Cell Concentration**: 300.45 x 10^6 (3 mL injectate per knee) **Cell Delivery**: Intra-articular injection **Anesthetic Use**: Local anesthesia **Number of injections**: 1 **Co-interventions**: None **Post treatment protocol**: All patients advised to avoid weight bearing in the injected limb for three weeks. Patients told to use cold compression to control expected minor joint pain.				
Soler 2015 N=50 Spain *HIGH*	Inclusion: NR Exclusion: NR	*Autologous bone marrow mononuclear cells* **Cell Type**: BM-MNCs **Cell Source**: 100 mL of bone marrow collected from the iliac crest **Cell Expansion**: Yes **Cell Concentration**: 1.13 ± 0.21x10e^9 **Cell Delivery**: intra-articular injection **Anesthetic Use**: Local anesthesia **Number of injections**: 1 **Co-interventions**: None	**% male**: 60% **Mean age ± SD**: 57.8 ± 14.1 years **Mean symptom duration (range)**: NR **Mean BMI ± SD**: NR	F/U Baseline 12 months % Followed 100%	**Funding**: None **COI:** None	• No serious adverse events occurred. • Transient mild local pain and discomfort in injected knee during first 1 to 6 days: 50% (25/50).

Author (year) N Country Study design *HIGH*	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
		Post treatment protocol: NR				
Themistocleous 2018 N=121 Greece *HIGH*	Inclusion: Longstanding knee pain from idiopathic OA unresponsive to activity modification, weight loss, physical therapy, bracing, analgesics, nonsteroidal anti-inflammatory drugs, injection therapy, or arthroscopy for at least 6 weeks with a Kellgren-Lawrence grade III or higher radiographic OA. Exclusion: 1. Post-traumatic OA. 2. Previous knee surgery. 3. Age less than 50 or more than 85 years old. 4. Active infection. 5. Uncontrolled diabetes mellitus, rheumatological, or other systemic disease. 6. Malignancy. 7. Treatment with immunosuppressive drugs. 8. Patients who elected to participate in the study and had a follow-up time of less than 60 days. 9. Patients who elected to proceed with total knee arthroplasty before their post-procedure evaluation.	*Autologous BMAC* **Cell Type**: BMAC **Cell Source**: Bone marrow from the iliac crest **Cell Expansion**: None **Cell Concentration**: 10 mL per knee **Cell Delivery**: intra-articular injection **Anesthetic Use**: None **Number of injections**: 1 **Co-interventions**: None **Post treatment protocol**: Allowed full weight bearing, instructed to return to light activities as tolerated avoiding NSAIDs and corticosteroids for at least four weeks. Allowed to return to full activities in six weeks.	**% male**: 29.75% **Mean age (range)**: 70 (50 to 85) years **Mean symptom duration (range)**: NR **Mean BMI ± SD**: NR **Laterality, % (n/N)** - Left: 37.2% (45/121) -Right: 62.8% (76/121) (all treated unilaterally)	Mean F/U (range) 11 (6 to 30) months % Followed 100%	**Funding**: None **COI:** None	• No adverse events or complications and all patients recovered completely.

* The injection with arthroscopic debridement was performed in 8.0% (6/75) of cases, with arthroscopic microfracture in 6.7% (5/75) of cases, and with high tibial osteotomy in 1.3% (1/75) of cases.
† 15% (3/20) of patients received a total knee replacement and were not followed up completely.
‡ 5.2% (1/19) left the study before early magnetic resonance and clinical follow-up; 15.8% (3/19) left before 12-month clinical follow-up.
§ Article reports female=49, male=22 (n=71); doesn't match up with n=70 throughout rest of article.
AE = adverse events; BM = bone marrow; BMAC = bone marrow aspirate concentrate; BMC = bone marrow concentrate; BMI = body mass index; BM-MNCs = bone marrow mononuclear cells; BM-MSCs = bone marrow derived mesenchymal stem/stromal cells; CI = confidence interval; COI = conflict of interest; F/U = follow-up; K-L = Kellgren=Lawrence; KOA = knee osteoarthritis; NR = not reported; OA = osteoarthritis; PL = platelet lysate; PRP = platelet rich plasma; PT = physical therapy; ROB = risk of bias; SAE = severe adverse events; SD = standard deviation; tx = treatment

Appendix Table F4: Study characteristics and demographics for studies evaluating the use of stem cell therapies for hip osteoarthritis

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention	Patient Demographics	F/U	Outcomes	Funding COI
Centeno 2014 N=216 hips among 196 patients USA Case Series (Registry study) High	Inclusion criteria and registry information: Registry data for all patients who underwent a BMC procedure for hip OA from April 2010 to December 2013 were included in the study. Only patients who had responded to the outcome questionnaires at 1, 3, 6, 12 months, and annual follow-up points following the procedure were included in the outcomes analysis. There were 17 outpatient facilities that contributed patients to the registry; however the majority of cases (67.7%) were performed at a single center at which the primary author (CJC) is affiliated. Patients were tracked via an electronic database system using Clin Capture software. Complications were monitored by e-mail or during clinic visit preoperatively and at 1, 3, 6 months, and annually after the procedure by a dedicated registry staff. Exclusion: NR	Prolotherapy + Autologous BMC + PRP + PL Patient's hip underwent a pre-injection of a hypertonic dextrose solution into the hip joint intra-articular two to five days before BMC injection **Cell Type**: BMC **Cell Source**: Whole bone marrow aspirate was harvested from the patients' iliac crest. Approximately 10-15 cc of BMA was withdrawn from 6-8 sites **Cell Preparation**: Coincident with this BMA, approximately 60ccs of heparinized intravenous blood was drawn to be used for isolating platelet rich plasma (PRP) and platelet lysate (PL). **Cell Expansion**: No **Cell Concentration**: Mean cell count=527 million (range, 108 million to 1518.9 million **Cell Delivery**: Cannulation of the intra-articular hip joint was confirmed by fluoroscopy or ultrasound. 1-4 ccs (mean 2.5 ccs) of bone marrow	**% male**: 57% **Mean age ± SD**: 57 ± 10.6 years **Laterality, % (n/N)** -Bilateral: 18.5% (40/216 procedures); 10.2% (20/196 patients) **Mean BMI**: 26.2 kg/m^2 **KL OA Grade, %** - I: 32.2% - II/III: 46% - IV: 21.8% **% (n/N) of joints considered to candidates for THA**: 67.8% (118/216)	Mean F/U by Outcome Reported OHS: 4.9 months NPS: 5.9 months Perceived Improvement: 9 months % Followed by outcome reported - OHS: 26.4% (57/216 of all treated hips) - NPS: 37.5% (81/216 of all treated hips) - Perceived Improvement: 62.5% (135/216)	• Oxford Hip Scale (OHS) (0-48, higher=increased function) • Numeric Pain Scale (NPS) (0-10, higher=worse pain) • Patient perceived improvement	**Funding**: Industry **COI**: Centeno is a shareholder and director of Regenerative Sciences, LLC. Al-Sayegh is employed by Regenerative Sciences, LLC.

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention	Patient Demographics	F/U	Outcomes	Funding COI
		concentrate, 1cc of PRP, and 1cc of PL was injected. **Anesthetic**: NR **Number of injections**: 1 **Co-interventions**: Additional injectate was also injected into painful or otherwise damaged structures (i.e. psoas tendon or the trochanteric area if painful). **Post-tx protocol**: Patients were discharged with instructions to be light weight bearing for several days if there was significant post-op pain, but then to return to full weight bearing as soon as was comfortable. Post-operative instruction sheets regarding activity were provided to all patients, describing a gradual return to full activities over approximately 6 weeks. Patients were encouraged to participate in appropriate physical therapy, but this was not required nor was it controlled.				
Mardones 2017 N=10 (13 treated knees)	Inclusion: Age ≥60 years, radiological evidence of osteodegenerative disease changes (level to moderate) in one or both joint hip (s) and pain levels (refractory to	*Autologous culture expanded BM-derived MSCs* **Cell Type**: BM MSCs	**% male**: 50% **Mean age**: 49.7 years **Laterality**: 30% of patients received bilateral **Co-morbidities** Hypothyroidism: 40% (4/10)	Mean F/U 35.7 (range, 16 to 40) months % Followed 100% (10/10)	• Harris Hip Score (HHS) (0-100, higher=increased function) • Western Ontario and McMaster	**Funding**: NR **COI**: None reported

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention	Patient Demographics	F/U	Outcomes	Funding COI
Chile Retrospective Case Series High	analgesics and/or hyaluronic acid or cortisone injection treatment) ≥40 on VAS. <u>Exclusion</u>: Evidence of intraarticular space ≤1 mm, indication of cartilage's loss of volume, as measured by MRI and/or failure to complete the protocols established number of cell infusions.	**Cell Source**: 30 mL BMA form the Iliac crest (60 mL for those being treated bilaterally) **Cell Preparation**: NR **Cell Expansion**: Yes **Cell Concentration**: 3 injections of $20x10^6$ cells for a total of $60x10^6$ cells delivered over 2 weeks. **Cell Delivery**: Infusion to hip. **Anesthetic**: NR **Number of injections**: 3 **Co-interventions**: NR **Post-tx protocol**: NR	Arrhythmia: 10% (1/10) Hypertension: 10% (1/10) Cervical Dysplasia: 10% (1/10) Dyslipidemia: 20% (2/10) Asthma: 20% (2/10) Mood Disorder: 10% (1/10) (4 patients had no comorbidities)		Universities Osteoarthritis Index (WOMAC) (0-100, higher=greater disability) • Vail Hip Score (VHS) (scale NR) • Visual Analog (VAS) (0-100, higher=increased pain) • Adverse Events	

BM = Bone Marrow; BMA = Bone Marrow Aspirate; BMC = Bone Marrow Concentrate; BMI = Body Mass Index; COI = Conflict of Interest; F/U = follow-up; HHS = Harris Hip Score; KL = Kellgren Lawrence; MSC = Mesenchymal Stromal/Stem Cell; NPS = Numeric Pain Scale; NR = Not Reported; OA = Osteoarthritis; OHS = Oxford Hip Score; PL = Platelet Lysate; PRP = Platelet Rich Plasma; ROB = Risk of Bias; SD = Standard Deviation; THA = Total Hip Arthroplasty; USA = United States of America; VAS = Visual Analog Scale; VHS = Vail Hip Score; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Appendix Table F5: Data abstraction for studies evaluating the use of stem cell therapies for hip osteoarthritis

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
Centeno 2014 N=216 hips among 196 patients USA Case Series (Registry study) High	*Prolotherapy + Autologous BMC + PRP + PL* **OHS, Mean ± SD (n=57)** • Baseline: 26.6 ± 8.8 • Final follow-up: 33.0 ± 8.7, p<0.001 • Mean Δ: 6.4 **Proportion of hips meeting the minimal important change of 4.9 points on the OHS**: 64% (28/44 available hips)	*Prolotherapy + Autologous BMC + PRP + PL* **NPS, Mean ± SD (n=81)** • Baseline: 4.5 ± 2.0 • Final follow-up: 3.3 ± 2.3, p<0.001 **Proportion of hips meeting the minimal important change of 2 points on the NPS**: 59% (35/59 available hips)	NR	*Prolotherapy + Autologous BMC + PRP + PL* **Percentage improvement scale, Mean ± SD (n=135)**: 31.2% ± 38.6% **Proportion of hips achieving a change in improvement of ≥50%**: 43% (43/100 available hips)	*Prolotherapy + Autologous BMC + PRP + PL* **Adverse Events, % (n/N)** • Experienced at least one AE: 6.1% (12/196 patients) - Pain/swelling: 6 events - Skin reaction: 2 events - Mild transitory drop in white blood cell count: 1 event - Persistent popping/cracking in the joint: 1 event - Boney growth at the joint: 1 event (Later determined to be continued osteophyte formation due to advancing degenerative joint changes) - Other: 3 events • Eight of these events were classified as mild and four were deemed moderate. • There were no severe or serious AEs. • 1 AE was assessed as likely related to the

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
					procedure, 8 were possibly related, and 3 were unlikely to be related. • At the time of reporting, 10 AEs were resolved/recovered and two were ongoing. • No AE resulted in significant disability.
Madrones 2017 N=10 Chile Retrospective Case Series High	*Autologous culture expanded BM-derived MSCs* **WOMAC-general, Mean ± SEM** • Baseline: 34.5 ± 8.2 • Final Follow-up: 19.2 ± 6.1, p=0.15 **HHS, Mean ± SEM** • Baseline: 61.9 ± 6.1 • Final Follow-up: 85.7 ± 3.9, p=0.003 **VHS, Mean ± SEM** • Baseline: 61.2 ± 4.5 • Final Follow-up: 85.7 ± 3.9, p=0.02	*Autologous culture expanded BM-derived MSCs* **VAS, Mean ± SEM** • Baseline: 4.2 ± 0.5 • Final Follow-up: 1.1 ± 0.3, p=0.0001	NR	NR	*Autologous culture expanded BM-derived MSCs* **Adverse Events** • After bone marrow aspiration, no bleeding, infection and/or other complications were identified. • No complications and/or adverse events occurred post-infusion

AE = Adverse Event; BM = Bone Marrow; BMC = Bone Marrow Concentrate; HHS = Harris Hip Score; MSC = Mesenchymal Stromal/Stem Cell; NPS = Numeric Pain Scale; NR = Not Reported; OHS = Oxford Hip Score; PL = Platelet Lysate; PRP = Platelet Rich Plasma; QOL = Quality of Life; ROB = Risk of Bias; SD = Standard Deviation; SEM = Standard Error Mean; THA = Total Hip Arthroplasty; USA = United States of America; VAS = Visual Analog Scale; VHS = Vail Hip Score; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Appendix Table F6: Study characteristics and demographics for studies evaluating the use of stem cell therapies for degenerative disc disease

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
Autologous MSCs (not expanded)						
Pettine 2015 [2016, 2017] N=26 USA Prospective Case Series *High*	Inclusion: Patients with centralized chronic low back pain that increased with activity and lasted ≥6 months; undergone nonoperative (conservative) management for 3 months without resolution; shown change in normal disc morphology as defined by MRI evaluation; have a modified Pfirrmann score of 4–7; have Modic Grade II change or less; disc height loss of <30% compared to an adjacent nonpathologic disc; pretreatment baseline ODI score of ≥30 on the 100-point scale; and pretreatment baseline low back pain of ≥40 mm on the 100 mm VAS. An intact annulus was not required to be in the study. Exclusion: Patients with abnormal neurologic exam; symptomatic compressive pathology due to stenosis or herniation; spondylolysis or any spondylolisthesis	*Autologous Bone Marrow Concentrate (BMC) Injection* **Cell Type:** autologous, nonexpanded bone marrow concentrated cell, containing a variety of stem and progenitor cells including MSCs **Cell Preparation:** BMA (55 ml) was collected over acid citrate dextrose anticoagulant (5 ml) from the patient's posterior iliac crest. **Cell Expansion:** No (centrifuged for 12 minutes after aspiration, prior to injection) **Cell Concentration**: 2–3 ml of BMC was used per symptomatic lumbar disc injection -Total Nucleated Cell count/ml in BMC: 121(±11)X 10^6 -viability greater than 98%±1% **Cell Delivery:** percutaneous injection into symptomatic disc(s) **Anesthetic Use:** 1% buffered lidocaine	**% Male**: 42.3% **Median Age(range)**: 40 (18-61) **BMI**: 26.6 (19-37) **Number of discs treated** Single level: 50% (13/26) Two adjacent levels: 50% (13/26)	F/U: 12 months % Followed: 100% (26/26)	• VAS (Lumbar Pain + Sciatic Pain) 0-100, higher scores indicate severity of pain) • Oswestry Disability Scale (ODI) (0-100%, higher scores indicate greater disability) • Adverse Events • Subsequent Treatment	Funding: NR COI: Three authors are employees of the company that provided bone marrow concentration devices used in the study.

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
		Co-interventions: None reported **Post-tx protocol**: After injection, patients were prescribed pain medicine to be used as needed for 3 days and put on restricted physical activity for 2 weeks.				
Comella 2017 N=15 USA Case Series *High*	Inclusion: Patients age 18–90 years with degenerative disease of one, two or three lumbar discs with predominant back pain after conservative treatment (physical and medical) for over 6 months. Patients must have a fibrous ring capable of holding the cell implantation as demonstrated by MRI image Exclusion: Patients with congenital or acquired diseases leading to spinal deformations, active cancer or infections including human immunodeficiency virus, hepatitis B or C, or cytomegalovirus, patients with spinal segmental instability, spinal canal stenosis, isthmus pathology, more than 50% loss of height, or modic III changes on MRI images	*Autolgous SVF + PRP* **Cell Type**: Adipose derived MSCs **Cell Source**: Abdominal adipose tissue **Cell Preparation**: aprox. 60 mL of fat was collected. Tissue was washed with buffered saline and digested using collagenase, the centrifuged to collect SVG pellet. Pellet was suspended in 1-3 ccs of autologous PRP which was prepared by collecting peripheral blood and centrifuging **Cell Expansion**: No **Cell Concentration**: Approximately 30–60 million SVF cells in 1–3 ccs volume of PRP **Cell Delivery**: Injection under fluoroscopy guidance. If more than one disc was symptomatic, the SVF was divided and	% male: 73% Mean age (range): 51.5 (32-76) years	2 months 6 months % Followed: 100% (15/15)	• Visual analogue scale (VAS-pain) 0-100, higher scores indicate severity of pain) • Present pain index (PPI) • Dallas Pain Questionnaire (DPQ) • Oswestry Disability Scale (ODI) (0-100%, higher scores indicate greater disability) • Short Form McGill Pain Questionnaire (SF-MPQ) • Short Form 12 QOL (SF-12) (0-100, higher=increased QOL) • Adverse Events & Subsequent Treatment	**Funding**: Industry **COI**: KC is an officer of US Stem Cell, Inc. MP is an employee of US Stem Cell, Inc.

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
		prepared with approximately 1 cc of PRP **Anesthetic Use**: Yes – local anesthetic **Co-interventions**: NR **Post-tx protocol**: NR				
Autologous Hematopoietic (not expanded)						
Haufe 2006 N=10 USA Prospective Case Series *High*	Diagnosis: Degenerative Disc Disease <u>Inclusion</u>: NR <u>Exclusion:</u> NR	After extraction of bone marrow aspirate, patients underwent 2 weeks of daily hyperbaric oxygen therapy, followed by intradiscal injection of HSCs administered under local anesthesia. **Cell Type**: Hematopoietic Stem Cells **Cell Source:** autologous (bone marrow aspirate) **Cell Preparation:** BMA extracted from pelvic crest -bone marrow volume: 5cc **Cell Expansion:** NR **Cell Concentration:** 1 cc of HSCs **Cell Delivery:** percutaneous injection into symptomatic disc **Anesthetic Use:** lidocaine **Co-interventions**: All of the patients had attempted an endoscopic discectomy as an attempt to eliminate their low back pain and their next option	% male: 50% Mean Age (range): NR (32-74) years Prior Surgery: 100%	F/U: 12 months % Followed: 100% (10/10	• VAS (0-10, higher scores indicate severity of pain) • Subsequent Treatment (Surgery)	NR

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
		was either a fusion or artificial disc replacement surgery.* **Post-tx protocol**: Patients underwent a 2-week course of hyperbaric oxygen therapy to assist in oxygen delivery to the discs, which are known for their poor blood flow. The hyperbaric oxygen therapy consisted of daily treatment (Monday through Friday) of 100% oxygen at 2 atmospheres for 2 weeks. Patients were given the following restrictions for 1 month—no lifting greater than 10 pounds and no excessive bending.				
Autologous Expanded MSCs						
Kumar 2017 10 South Korea Retrospective Case Series *High*	Inclusion: both sexes; age 19-70 years; with ≥4/10 on VAS; disability level ≥ 30% on the ODI; failure to respond to conventional treatments including medication, intensive physical rehabilitation, and local anesthetic infiltration in facet joints or medial branches; moderate grade of IVD degeneration (Pfirrmann's grade III–IV at one or two levels based on T2-weighted	AT-MSCs Liposuction harvested adipose tissue, processed into MSCs, and transplanted into patients along with Hyaluronic Acid **Cell Type:** Autologous, MSCs with Hyaluronic Acid **Cell Source:** subcutaneous abdominal adipose tissue-derived (via liposuction) **Cell Preparation:**	% male: 60% Mean Age: 43.5 years Mean Disease Duration: 48.3 mos. Levels Treated: -L4-5: 9 -L5-S1 + L4-5: 1 Comorbidities, %: -hypertension: 20%	1 month 3 months 6 months 9 months 12 months % Followed: 91% (10/11)	• Oswestry Disability Scale (ODI) (0-100%, higher scores indicate greater disability) • Pain Visual Analogue Scale (VAS-pain) (0-10, higher scores indicate severity of pain) • Adverse Events	**Funding**: Government **COI**: NR

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
	MRI); and degenerative symptomatic discs confirmed by discography Exclusion: pregnancy or breastfeeding; previous history of surgery of the lumbo-sacral area; severe herniated disc or stenosis requiring surgery; Modic type 3 change; evidence of spinal infection on MRI; disc space collapse > 50%; uncontrolled hypertension despite receiving optimal medication; uncontrolled diabetes despite receiving optimal medication; other serious systemic diseases such as cancer, autoimmune disease, blood disease, kidney disease, and liver disease; and allergies to HA	Autologous MSCs were isolated from adipose tissue and cultured for 3 weeks. **Cell Expansion:** Yes **Cell Concentration**: The first five consecutive subjects received a mixture of 0.5 ml of stem cell suspension (2×10^7 cells/disc), 0.5 ml of normal saline, and 1 ml of Tissuefill® (hyaluronic acid derivative) (1%), and the second five consecutive subjects received a mixture of 1.0 ml of stem cell suspension (4×10^7 cells/disc) and 1 ml of Tissuefill® (1%). Cell viability ranged from 87.13 to 97.57% **Cell Delivery:** percutaneous injection into symptomatic disc **Anesthetic Use:** 1% buffered lidocaine **Co-interventions**: NR **Post-tx protocol**: NR	-Smoking History: 20% -Prior Surgery: 0% (exclusion criteria)			
Orozco 2011 10 Spain Retrospective Case Series *High*	Inclusion: Patients with DDD with preserved annulus fibrous, persistent low-back pain, non-responsive to conservative treatment; fibrous ring capable of holding the cell implantation, demonstrated by discography (stages 2, 3 and 4 of Adams); >50% decrease in disc height by radiographic measure; absence of spinal infection;	Autologous MSCs MSCs derived from bone marrow harvested from the iliac crest. **Cell Type:** MSCs **Cell Source:** autologous (bone marrow) **Cell Preparation:** bone marrow volume - 89±5 mL	% male: 40% Mean Age(SD): 35(7) years Levels Treated: -L4-5: 20% -L5-S1: 60% -L4-5 & L5-S1: 20% Comorbidities: - Smoking: NR	3 months 6 months 12 months % Followed: 100% (10/10)	• VAS (Lumbar Pain + Sciatic Pain) 0-100, higher scores indicate severity of pain) • Oswestry Disability Scale (ODI) (0-100%, higher scores indicate greater disability)	**Funding**: Government **COI**: None reported

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
	no significant alterations that contraindicates intervention <u>Exclusion:</u> Patients over 65 or under 18; infection signs or positive HIV, hepatitis or syphilis test; allergy to gentamicin or bovine, cattle or horse serum; congenital or acquired diseases leading to spine deformations that may upset cell application; Spinal segmental instability, spinal canal stenos, isthmus pathology and other conditions that may compromise the study; Modic changes on MRI images; Overweight with body mass index (mass in Kg/size in m2) greater than 30.5 (obesity grade II; Pregnancy or breast-feeding; neoplasia; immunosuppression; participation in other clinical trial or treated with investigational products	Number of mononuclear cells obtained - 794±34X10^6 Expansion time - 24±4days viability at application – 83%±5% **Cell Expansion:** Yes **Cell Concentration:** 10±5X10^6 cells per disc **Cell Delivery:** percutaneous injection into symptomatic disc(s) **Anesthetic Use:** local anesthesia (NR) **Cointerventions:** None **Post-tx protocol**: NR	-Prior Surgery: NR		• Short Form-36 Quality of Life (SF-36) (0-100%, higher=increased QOL) • Adverse Events	
• **Allogenic Expanded Cells**						
Noriega 2017 N=24 Spain RCT	<u>Inclusion</u>: Age 18-75; with DDD, 1-2 lumbar discs with predominant, persistent low back pain (not defined) unresponsive to conservative treatment (physical and medical) for over 6 months. Fibrous ring capable of holding the cell implantation, demonstrated by MRI (stages 2-4 of Pfirrmann). Decrease	<u>Allogenic BM derived MSC group (n=12)</u> Donor-harvested bone marrow-derived MSCs administered under local anesthesia. Quantitative MRI exploration at Visit 0, Visit 4, and Visit 5 to assess disc height	<u>All patients</u> % male: 71% Mean Age ± SD: 38 ± 2 years Levels Treated, n: -L1-2: 1 -L2-3: 1 -L3-4: 3	<u>F/U</u> 1 week, 3 months, 6 months, 12 months <u>% Followed</u> 100% (24/24)†	• ODI (0-100, higher=greater disability) • VAS pain (0-100, higher=greater pain) • SF-12 (0-100, higher=improved QOL)	**Funding**: Government **COI**: None reported

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
Moderately High	of disc height >20 % (radiographic measurement in side image). Absence of spinal infection. Hematological, biochemical analysis with no significant alterations that contraindicate intervention, capable of understand nature of study; informed written consent of the patient; in fertile women, negative pregnancy test result, agreement to adequate contraceptive methods. Exclusion: Allergy to gentamicin or to bovine, cattle or horse serum; congenital or acquired diseases leading to spine deformations that may upset cell application; Spinal segmental instability, spinal canal stenosis, isthmus pathology and other conditions that may compromise the study; Modic III changes on MRI; Overweight, body mass index (kg/m2) greater than 35 (obesity grade II); breastfeeding; Neoplasia; Immunosuppression; Hypersensitivity to amidetype local anaesthetics or other known contraindications or interactions of mepivacaine; Participation in another clinical trial or treatment with another investigational product <30 days before inclusion in the study; other conditions that may, according	**Cell Type**: Allogenic MSCs (5 donors) **Cell Source**: Bone marrow harvested from iliac crest **Cell Preparation**: - BM volume: 105 ± 5 mL - Mean number mononuclear cells obtained: 1.23 ± 0.25x10^9 - Mean ± SD expansion time: 27 ± 2 days, suspended in Ringerlactate at 12.5x10^6 cells/mL - Viability greater than 98% ± 1% **Cell Expansion**: Yes **Cell Concentration**: 25x10^6 MSC in 2 mL of saline/disc **Cell Delivery**: percutaneous injection into symptomatic disc **Anesthetic Use**: local anesthesia (type NR) **Number of injections**: 1 Sham Control Group (n=12) Sham infiltration of paravertebral musculature close to the affected disc(s) with 2 mL of 1% mepivacaine. Quantitative MRI exploration performed at Visit 0, Visit 4, and Visit 5 to assess disc height and water content of the discs.	-L4-5: 18 -L5-S1: 15		• Radiographic measures (disc height) • Adverse events	

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
	to medical criteria, discourage participation in the study.	Co-interventions (across all tx groups) NR Post-treatment protocol (across all tx groups): NR				

AT-MSCs, autologous mesenchymal stem cells; BMA, Bone marrow aspirate; BMC, Bone Marrow Concentrate; BMI, body mass index; cc, cubic centimeters; COI, conflict of interest; Degenerative Disc Disease; FRI, Functional Rating Index; F/U, follow-up; HSCs, Hematopoietic Stem Cells; IVD, Intervertebral Disc; LBP, low back pain; mL, milliliter; mm, millimeters; mos, months; mSANE, modified Single Asssessment Numeric Evaluation; MSCs, mesenchymal stem cells; ND+, Novocart Disc Plus; NDBasic, Novocart Disc Basic; NR, not reported; NPRS, numeric pain rating scale; ODI, Oswestry Disability Index; SD, standard deviation; SF-36, Short-Form 36 Quality of Life Survey; VAS, visual analogue scale

*The repeat discograms and stem cell injections were delayed until the patients were at least 3 months post the endoscopic discectomy so that the endoscopic discectomy could be ruled out as a source of improvement.

†Percentages based on those randomized, information on total eligible patients was not available.

Appendix Table F7: Data abstraction for studies evaluating the use of stem cell therapy for degenerative disc disease

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
Autologous MSCs (not expanded)					
Pettine 2015 [2016, 2017] N=26 USA Prospective Case Series *High*	*Autologous BMC* **ODI, Mean ± SE (n=26 across all time periods)** • Baseline: 56.5±NR • 3 months: 22.8±NR, p<0.0001 • 6 months: 24.4±NR, p<0.0001 • 12 months: 25.0±NR, p<0.0001 **% Reduction in ODI Score (n=26 across time periods)** • 3 months: 58.1% • 6 months: 55.5% • 12 months: 56.8% *Data from Surgery Survivors* **% Reduction in ODI among patients who did not Progress to Surgery (n=21 across time periods)** • 3 months: 65% • 6 months: 66%, • 12 months: 60% • 24 months: 67%	*Autologous BMC* **VAS-pain, Mean±SE (n=26 across time periods):** • Baseline: 79.3±NR • 3 months: 29.2±NR, p<0.0001 • 6 months: 26.3±NR, p<0.0001 • 12 months: 33.2.±NR, p<0.0001 **% Reduction in VAS-pain (n=26 across time periods)** • 3 months: 64.6% • 6 months: 64.2% • 12 months: 58.0% *Data from Surgery Survivors* **% Reduction in VAS among patients who did Progress to Surgery (n=21 across time periods)** • 3 months: 67% • 6 months: 77% • 12 months: 66% • 24 months: 72%	NR	*Autologous BMC* **Proportion of Patients who Elected to Undergo a Second BMC Injection** • 6 months: 7.7% (2/26) <u>Proportion of Participants who Progressed to Spine Surgery at a later date, (n/N)</u> • 12 months: 7.7% (2/26) • 24 months: 19.2% (5/26) • 36 months: 23.1% (6/26)	*Autologous BMC* **Treatment-Related Adverse Events:** None reported. **Treatment-Related Serious Adverse Events:** None reported.

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
	ODI Score Among Patients who did not Progress to Surgery within 24 mos, Mean±SE (n=21 across time periods) • Baseline: 56.2±NR • 3 months: 19.9±NR • 6 months: 19.0±NR • 12 months: 22.3±NR • 24 months: 18.3±NR **ODI Score Among Patients who did not Progress to Surgery within 36 months, Mean±SE (n=20 across time periods)** • Baseline: 56.7±3.6 • 36 months: 17.5±3.2, p<0.001	**ODI Score Among Patients who did not Progress to Surgery within 24 mos, Mean±SE (n=21 across time periods)** • Baseline: 81.5±NR • 3 months: 27.0±NR • 6 months: 18.7±NR • 12 months: 28.1±NR • 24 months: 22.9±NR **VAS Score Among Patients who did not Progress to Surgery within 36 mos, Mean±SE (n=20 across time periods)** • Baseline: 82.1±2.6 • 36 months: 21.9±4.4, p<0.001			
Comella 2017 N=15 USA Case Series *High*	*Autolgous SVF + PRP* **ODI, Mean±SD (n=15 across all time periods)** • Baseline: 32±NR • 2 months: 28±NR, p=0.30 • 6 months: 30±NR, p=0.31	*Autolgous SVF + PRP* **VAS, Mean±SD (n=15 across all time periods)** • Baseline: 5.6±NR • 2 months: 4.2±NR, p=0.09 • 6 month: 3.6±NR, p=0.01 **PPI, Mean±SD (n=15 across all time periods)**		*Autolgous SVF + PRP* **SF-12 PCS, Mean±SD (n=15 across all time periods)** • Baseline: 30±NR • 2 months: 30±NR, p=0.41 • 6 months:35±NR, p=0.03 **SF-12 MCS, Mean±SD (n=15 across all time periods)**	*Autolgous SVF + PRP* **Adverse Events** • Soreness in the abdomen after the mini-liposuction procedure and/or soreness in the back after injections were reported (data NR) • Patients were instructed to take previously

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
		• Baseline: 2.6±NR • 2 months: 2.0±NR, p=0.12 • 6 months: 1.8±NR, p=0.03 **SF-MPQ, Mean±SD (n=15 across all time periods)** • Baseline: 16±NR • 2 months: 12±NR, p=0.24 • 6 months: 11.5±NR, p=0.05 **Dallas Pain Questionnaire – Daily Activities, Mean±SD** • Baseline: 69±NR • 2 months: 62±NR, p=NR • 6 months: 60±NR, p=NR **Proportion of patients with improvements in Dallas Pain Questionnaire – Daily Activities, %** • 2 months: 61% • 6 months: 60% **Dallas Pain Questionnaire – Work/Leisure Activities, Mean±SD** • Baseline: 60±NR • 2 months: 58±NR, p=NR • 6 months: 58±NR, p=NR		• Baseline: 45±NR • 2 months: 49±NR, p=0.32 • 6 months: 44±NR, p=0.47	prescribed opioids for pain and all events resolved within 7–10 days. • There were no incidences of infection. **Severe Adverse Events** • None reported

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
		Proportion of patients with improvements in Dallas Pain Questionnaire – Daily Activities, % • 2 months: 52% • 6 months: 60% **Dallas Pain Questionnaire – Anxiety/Depression, Mean±SD** • Baseline: 28±NR • 2 months: 31±NR, p=NR • 6 months: 38±NR, p=NR **Proportion of patients with improvements in Dallas Pain Questionnaire – Daily Activities, %** • 2 months: 54% • 6 months: 30% **Dallas Pain Questionnaire – Social Interest, Mean±SD** • Baseline: 27±NR • 2 months: 33±NR, p=NR • 6 months: 35±NR, p=NR **Proportion of patients with improvements in Dallas Pain Questionnaire – Social Interest, %** • 2 months: 54%			

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
		• 6 months: 40%			
Autologous Hematopoietic (Not expanded)					
Haufe 2006 N=10 USA Case Series *High*	NR	*Hematopoietic Stem Cells* **Proportion with VAS Pain Reduction, % (n/N)** • 12 months: 0% (0/10)	NR	*Hematopoietic Stem Cells* **Proportion of Participants who Progressed to Spine Surgery at a later date, % (n/N)** • Spinal Fusion: 75% (7/10)* • Artificial Disc Replacement: 10% (1/10)	NR
Autologous Expanded MSCs					
Kumar 2017 N=11 South Korea Retrospective Case Series *High*	*Autologous MSCs + HA* **ODI, Mean ± SD (n=10 across all time periods)** • Baseline: 42.8±15.03 • 1 month: 31.2±13.86, p=0.002 • 3 months: 31.7±14.22, p=0.01 • 6 months: 21.3±7.42, p=0.002 • 12 months: 16.8±9.77, p=0.002 **Proportion of Patients who Achieved Treatment Success (≥50% reduction in**	*Autologous MSCs + HA* **VAS-pain, Mean ± SD (n=10 across all time periods)** • Baseline: 6.5±1.27 • 1 month: 4.6±1.07, p=0.01 • 3 months: 4.3±1.63, p=0.02 • 6 months: 3.2±1.40, p=0.004 • 12 months: 2.9±1.66m p=0.002	NR	NR	*Autologous MSCs + HA* **Adverse Events** <u>Treatment-Related Adverse Events:</u> None reported. <u>Treatment-Related Serious Adverse Events:</u> None reported.

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
	VAS & ODI compared to pretreatment, (n/N) • 6 months: 70% (7/10) • 12 months: 60% (6/10)				
Orozco 2011 N=10 Spain Retrospective Case Series *High*	*Autologous MSCs* **ODI, Mean ± SE (n=10 across all time periods)** • Baseline: 25.0±4.1 • 3 months: 13.0±3.2, p<0.05 • 6 months: 9.4±2.7, p<0.01 • 12 months 7.4±2.3, p<0.001	*Autologous MSCs* **VAS Lumbar Pain, Mean ± SE (n=10 across time periods)** • Baseline: 68.9±3.3 • 3 months: 26.5±5.6, p<0.001 • 6 months: 21.6±6.0, p<0.001 • 12 months: 20.0±6.5, p<0.001 **VAS Sciatic Pain, Mean ± SE (n=6 across all time periods)†** • Baseline: 37.0±9.3 • 3 months: 24.3±12.6, p=NS • 6 months: 7.8 ±6.9, p<0.001 • 12 months: 5.3±5.1, p<0.001	NR	*Autologous MSCs* **SF-36 PCS Mean ± SE (n=NR across time periods)** • Baseline: 12.7±3.7 • 12 months: 24.8±3.9, p<0.05 **SF-36 MCS Mean ± SE (n=NR across time periods)** • Baseline: 54.1±10.6 • 12 months: 49.7±10.5, p=0.77	*Autologous MSCs* **Adverse Events** <u>Treatment-Related Adverse Events:</u> NR <u>Treatment-Related Serious Adverse Events:</u> None reported.
Allogenic Expanded					
Noriega 2017 N=24 (n = 12 vs. 12)	*Allogenic MSCs vs. Sham* **ODI, Mean ± SD‡**	*Allogenic MSCs vs. Sham*	NR	*Allogenic MSCs vs. Sham* **SF-12 PCS, Mean ± SE‡**	**Proportion of participants who experienced minor**

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
Spain RCT Moderately High	• Baseline: 34 ± 23 vs. 24 ± 14, MD 10 (95% CI -6.1 to 26.1), p=0.2116 • 1 week: 27 ± 17 vs. 20 ± 16 • 3 months: 16 ± 20 vs. 25 ± 15-9 (95% CI -23.9 to 6.0), p=0.2255 • 6 months: 20 ± 24 vs. 30 ± 20, MD -10 (95% CI -28.7 to 8.7), p=0.2795 • 12 months: 22 ± 24 vs. 34 ±2 5, MD -12 (95% CI -32.7 to 8.7), p=0.2431	**Lumbar Pain VAS, Mean ± SD** • Baseline: 67 ± 26 vs. 62 ± 23, MD 5 (95% CI -15.8 to 25.8), p=0.6228 • 1 week: 63 ± 26 vs. 45 ± 25 • 3 months: 43 ± 30 vs. 46 ± 27, MD -3 (95% CI 27.2 to 21.2), p=0.7992 • 6 months: 40 ± 29 vs. 51 ± 29, MD -11 (95% CI -35.5 to 13.5), p=0.3629 • 12 months: 47 ± 36 vs. 47 ± 28, MD 0 (95% CI -27.3 to 27.3), p=1.000		• Baseline: 39 ± 2 vs. 40 ± 3, MD -1 (-8.42 to 6.42), p=0.7825 • 1 week: 39 ± 2 vs. 43 ± 3 • 3 months: 47 ± 3 vs. 43 ± 3, MD 4 (-4.7 to 12.7), p=0.3518 • 6 months: 46 ± 3 vs. 39 ± 3, MD 7 (-1.7 to 15.7), p=0.1102 • 12 months: 45 ± 3 vs. 42 ± 3, MD 3 (-5.7 to 11.7), p=0.483 **SF-12 MCS, Mean ± SD** • Baseline: 46 ± 3 vs. 52 ± 3, MD -6 (-14.7 to 2.7), p=0.1677 • 1 week: 47 ± 3 vs. 50 ± 2 • 3 months: 50 ± 2 vs. 46 ± 3, MD 4 (-3.4 to 11.4), p=0.2758 • 6 months: 52 ± 2 vs. 48 ± 3, MD 4 (-3.4 to 11.4), p=0.2758 • 12 months: 48 ± 3 vs 50 ± 3, MD -2 (-10.7 to 6.7), p=0.6390	**pain requiring NSAIDs, % (n/N)** • 25% (3/12) vs 66.6% (8/12) **Proportion of Participants who experienced pain requiring opioids, % (n/N)** • 8.3% (1/12) vs 8.3% (1/12) **Number of Serious Adverse Events, (n/N)** • 0% (0/12) vs. 0% (0/12)

AT-MSCs, autologous mesenchymal stem cells; BMA, Bone marrow aspirate; BMC, Bone Marrow Concentrate; BMI, body mass index; cc, cubic centimeters; COI, conflict of interest; Degenerative Disc Disease; FRI, Functional Rating Index; F/U, follow-up; HSCs, Hematopoietic Stem Cells; IVD, Intervertebral Disc; LBP, low back pain; MD, mean difference; mL, milliliter; mm, millimeters; mos, months; mSANE, modified Single Asssessment Numeric Evaluation; MCS, Mental component score; MSCs, mesenchymal stem cells; ND+, Novocart Disc Plus; NDBasic, Novocart Disc Basic; NR, not

reported; NPRS, numeric pain rating scale; ODI, Oswestry Disability Index; PCS, Physical Component Score; SD, standard deviation; SE. standard error; SF-36, Short-Form 36 Quality of Life Survey; VAS, visual analogue scale

*Haufe et al., reported progression to spine surgery value as 75%, despite their in-text statement that 7/10 patients went on to receive fusion surgery.

†Four patients were excluded from sciatic pain measurements because of a lack of sciatic pain

‡MDs calculated by AAI as authors did not provide this data.

§P-values represent change from baseline across follow-up periods.

Appendix Table F8: Study characteristics and demographics for studies evaluating the use of stem cell therapies for partial rotator cuff tears

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
Kim 2018 N=24 South Korea Prospective Comparative Cohort Moderately High	Inclusion: (1) no history of shoulder surgery during the past 3 months, (2) no abnormal findings on simple radiography, (3) partial tear of the rotator cuff tendon diagnosed with ultrasound or magnetic resonance images, (4) no abnormalities in blood coagulation and routine laboratory examination, (5) no history of steroid injection during the past 3 months, (6) no history of malignancy, (7) shoulder pain for minimum 2 months, (8) no improvement with oral medication of physical modalities Exclusion: (1) history of shoulder surgery within 3 months, (2) presence of osteophyte or bony deformity on simple radiography, (3) complete tear of the rotator cuff tendon, (4) presence of abnormality in blood coagulation, complete blood count, or blood chemistry, (5) positive urine pregnancy test in case of fertile woman, (6) recent steroid injection within 3 months, (7) history of malignancy.	AutologousBMAC + PRP injection (n=12) **Cell Type**: BM MSCs **Cell Source**: BM from the Iliac crest **Cell Preparation**: BMAC was centrifuged with a BIOMET MarrowStim™ Mini kit. Peripheral blood (30 ml) was acquired from the left antecubital vein and was centrifuged with a BIOMET GPS™ III kit to extract PRP **Cell Expansion**: No **Cell Concentration**: NR **Cell Delivery**: 2 ml BMACs + 1 ml of PRP delivered under ultrasound guidance to the tear site **Number of injections**: 1 Physical Therapy (n=12) Rotator cuff exercise comprised of stretching, scapular stabilization exercise, and strengthening exercise. Patients were asked to perform the program daily on their own for 3 months. All the patients in the control	*All patients* **% male**: 42% vs. 67% **Mean age**: 54.9 vs. 59.6 years **Symptom duration**: 7.3 vs. 5.1 months **Laterality**: all patients had a unilateral tear	F/U 3 weeks 3 months % Followed 100% (24/24)	• Pain Visual Analouge Scale (VAS-pain) (0-10, higher=increased pain • American Shoulder and Elbow Surgeons score (ASES) (0-100, higher=increased function) • Medication use • Adverse Events	**Funding**: Government **COI**: None

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
		group performed the rotator cuff exercise daily without omission. Co-interventions (across all tx groups): NR Post-treatment protocol (across all tx groups) No post-treatment PT was given to the BMAC group after injection				

Δ = change from baseline; ASES = american shoulder and elbow surgeon score; BM = bone marrow; BMAC = bone marrow aspirate concentrate; BMC = bone marrow concentrate; BMI = body mass index; BM-MSCs = bone marrow derived mesenchymal stem/stromal cells; COI = conflict of interest; F/U = follow-up; DASH = Disbailities of the arm, shoulder, and hand; MCS = mental component score; NPS = numerical pain score; NR = not reported; OA = osteoarthritis; PL = platelet lysate; PRP = platelet rich plasma; PT = physical therapy; ROB = risk of bias; SD = standard deviation; tx = treatment; VAS = visual analogue scale

Appendix Table F9: Data abstraction for studies evaluating the use of stem cell therapies for partial rotator cuff tears

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
Kim 2018 N=24 South Korea Prospective Comparative Cohort Moderately High	*BMAC+PRP vs. PT* **ASES, Mean ± SD** • Baseline: 39.4 ± 13.0 vs. 45.9 ± 12, p=0.228 • 3 weeks: 54.5 ± 11.5 vs. 56.3 ± 12.3, p=0.712 • 3 months: 74.1 ± 8.5 vs. 62.2 ± 12.2, p=0.011	*BMAC+PRP vs. PT* **VAS, Mean ± SD** • Baseline: 5.8 ± 1.9 vs. 5.7 ± 1.6, p=0.906 • 3 weeks: 2.3 ± 0.8 vs. 3.6 ± 2.3, p=0.147 • 3 months: 1.9 ± 0.7 vs. 3.7 ± 1.8, p=0.039	*BMAC+PRP vs. PT* **Proportion of patients changing frequency or dose of medication at 3 months, % (n/N)** • Decreased use: 50% (6/12) vs. 17% (2/12) • Increased use: 8% (1/12) vs. 25% (3/12) • Remained the same: 42% (5/12) vs. 58% (7/12) p=0.189	NR	*BMAC+PRP vs. PT* **Adverse Events, % (n/N)** • Increased pain as a result of treatment: 17% (2/12) vs. 25% (3/12) • There were no side effects during bone marrow aspiration or injection of BMAC-PRP, and no complications in the follow-up period.

Δ = change from baseline; ASES = american shoulder and elbow surgeon score; BM = bone marrow; BMAC = bone marrow aspirate concentrate; BMC = bone marrow concentrate; BMI = body mass index; BM-MSCs = bone marrow derived mesenchymal stem/stromal cells; COI = conflict of interest; F/U = follow-up; DASH = Disbailities of the arm, shoulder, and hand; MCS = mental component score; NPS = numerical pain score; NR = not reported; OA = osteoarthritis; PL = platelet lysate; PRP = platelet rich plasma; PT = physical therapy; ROB = risk of bias; SD = standard deviation; tx = treatment; VAS = visual analogue scale

Appendix Table F10: Study characteristics and demographics for studies evaluating the use of stem cell therapies for Achilles tendinopathy

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
Usuelli 2018 N=44 patients, 56 tendons Italy RCT ROB	Inclusion: unilateral or bilateral chronic tendinopathy of the Achilles tendon recalcitrant to traditional conservative treatments including non-steroidal anti-inflammatory drugs, eccentric loading exercises, stretching and biophysical therapy; symptoms lasting for at least 3 months; age between 18 and 55, VAS (visual analogue scale) pain at the first visit >5. Exclusion: Patients with clinical suspect of other musculoskeletal lesions of the Achilles tendon (insertional disorders, tendon rupture or tears), platelet count in whole blood <150 × 103/µl, inflammatory disease or other conditions that affected the joints, immuno-mediated pathology, any conditions that could increase the interventional risk, use of tendon-detrimental drugs (i.e. fluoroquinolones), patients who received any previous injective treatment of the target Achilles	Adipose tissue-derived SVF (n=21 patients, 28 tendons) **Cell Type**: SVF **Cell Source**: abdominal subcutaneous adipose tissue (50 ml). (Two very thin patients required to have adipose tissue harvested from the internal side of the thigh). SVF obtained using FastKit system. Adipose tissue was centrifuged for 10 min at 400 g. **Cell Expansion**: No **Cell Concentration**: NR **Cell Delivery**: 4 ml of SVF injected into the lesion location under ultrasound guidance **Anesthetic Use**: NR **Number of injections**: 1 PRP (n=23 patients, 28 tendons) 54 ml of peripheral blood were collected from the patients and added to 6 ml of anticoagulant. The whole blood was transferred to a disposable separation tube that was centrifuged at 3200 rpm for 15 min in a customized centrifuge provided by the manufacturer. Platelet poor plasma (PPP) was removed and platelets were suspended by gently shaking the tube for 30 seconds. The resulting PRP (around 6 ml) was	*SVF vs. PRP* **% male**: 67% vs. 35%, p<0.05 **Mean age**: 47.3 vs. 46.6, p<0.05 **Laterality, n** - Unilateral treatment: 67% (14/21 patients) vs. 78% (18/23) patients - Bilateral treatment: 33% (7/21 patients) vs. 22% (5/23 patients)	F/U 2 weeks 1 month 2 months 4 months 6 months % Followed 100% (44/44)	• Pain Visual Analog Scale (VAS-pain) (0-10, higher=increased pain) • Victorian Institute of Sport Assessment-Achilles (VISA-A) (0-100, higher=less symptoms) • American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Score (0-100, higher=increased function) • SF-36 QOL (0-100, higher=increased QOL)	**Funding**: NR **COI**: NR

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
	tendon, patients pregnant or breast-feeding	extracted from the tube using a 10-ml syringe. <u>Co-interventions (across all tx groups)</u> Patients who presented with a VAS >3 and AOFAS <70 at 2-month follow-up were supposed to receive a second injection of the same product injected the first time* <u>Post-treatment protocol (across all tx groups)</u> Patients were asked to walk with crutches for the first 24 hours after treatment and only paracetamol could be administered to control pain. No specific physical therapy was prescribed and the patients were allowed to progressively resume their normal life and sport activities.				

AOFAS = American Orthopaedic Foot and Ankle Society; COI = conflict of interest; F/U = follow-up; NR = not reported; PRP = platelet rich plasma; RCT = randomized control trial; SF-36 QOL = short form 36 quality of life health related quality of life questionnaire; SVF = stromal vascular fraction; Tx = treatment;VAS = visual analog scale; VISA-A = Victorian Institute of Sport Assessment-Achilles
* At 2-month follow-up, all the patients had VAS and AOFAS score that met the study protocol requirement (>3 and <70, respectively), so no one received a second injection at the Achilles tendon.

Appendix Table F11: Data abstraction for studies evaluating the use of stem cell therapies for Achilles tendinopathy

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
Usuelli 2018 N=44 patients, 56 tendons (n=21 vs. 23 patients) Italy RCT ROB	*SVF vs. PRP* **VISA, Mean ± SD** • Baseline: 41.6 ± 13.6 vs. 46.5 ± 23.6, p>0.0.5 • 2 weeks: 43 ± NR vs. 43 ± NR, p>0.05 • 1 month: 59 ± NR vs. 47 ± NR, p<0.05 • 2 months: 66 ± NR vs. 59 ± NR, p>0.05 • 4 months: 70 ± NR vs. 65 ± NR, p>0.05 • 6 months: 71 ± NR vs. 71 ± NR, p>0.05 **AOFAS, Mean ± SD** • Baseline: 63.4 ± 20.1 vs. 63.2 ± 17.7, p>0.0.5 • 2 weeks: 80 ± NR vs. 67 ± NR, p<0.05 • 1 month: 80 ± NR vs. 72 ± NR, p>0.05 • 2 months: 85 ± NR vs. 79 ± NR, p>0.05 • 4 months: 80 ± NR vs. 80 ± NR, p>0.05 • 6 months: 87 ± NR vs. 87 ± NR, p>0.05	*SVF vs. PRP* **VAS, Mean ± SD** • Baseline: 6.5 ± 1.6 vs. 6.3 ± 1.2, p>0.0.5 • 2 weeks: 2.5 ± NR vs. 4.4 ± NR, p<0.0.5 • 1 month: 2.0 ± NR vs. 3.8 ± NR, p<0.0.5 • 2 months: 1.8 ± NR vs. 2.5 ± NR, p>0.0.5 • 4 months: 2.0 ± NR vs. 3.0 ± NR, p>0.0.5 • 6 months: 1.8 ± NR vs. 1.8 ± NR, p>0.05	NR	*SVF vs. PRP* **SF-36 PCS, Mean ± SD** • Baseline: 42.2 ± 5.5 vs. 38.5 ± 7.9, p>0.0.5 • 2 weeks: 42.5 ± NR vs. 39.5 ± NR, p>0.0.5 • 1 month: 47.5 ± NR vs. 46.5 ± NR, p>0.0.5 • 2 months: 50.5 ± NR vs. 46.5 ± NR, p>0.0.5 • 4 months: 50 ± NR vs. 47.5 ± NR, p>0.0.5 • 6 months: 52 ± NR vs. 51 ± NR, p>0.05 **SF-36 MCS, Mean ± SD** • Baseline: 48.7 ± 5.7 vs. 51.21 ± 8, p>0.0.5 • 2 weeks: 51.5 ± NR vs. 51 ± NR, p>0.0.5 • 1 month: 52 ± NR vs. 52 ± NR, p>0.0.5 • 2 months: 52 ± NR vs. 51.5 ± NR, p>0.0.5 • 4 months: 49 ± NR vs. 52.5 ± NR, p>0.0.5 • 6 months: 51 ± NR vs. 52 ± NR, p>0.05	• No serious adverse events in either group were observed during the follow-up period. • 25% (5/21) of the SVF patients complained for hematoma and cutaneous discomfort at the adipose tissue harvest site

AOFAS = American Orthopaedic Foot and Ankle Society; COI = conflict of interest; F/U = follow-up; NR = not reported; PRP = platelet rich plasma; RCT = randomized control trial; SF-36 QOL = short form 36 quality of life health related quality of life questionnaire; SVF = stromal vascular fraction; Tx = treatment;VAS = visual analog scale; VISA-A = Victorian Institute of Sport Assessment-Achilles
* With the exception of baseline data, all data are estimated from figures.

Appendix Table F12: Study characteristics and demographics for studies evaluating the use of stem cell therapies for elbow tendinopathy

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
Singh 2014 N=30 patients India Prospective Case Series High	**Inclusion criteria:** Adult patients, 18 to 65 years old, were recruited from orthopedic and physiotherapy Out-patient Department of a tertiary medical college. Only patients of previously untreated tennis elbow and having no other identifiable cause of lateral elbow pain **Exclusion:** NR	*Autologous BMA containing BM-MNC + PRP* **Cell Type**: BMA **Cell Source**: Anterior-superior iliac spine of pelvis (volume = 10 mL + 1 mL of heparin.) **Cell Preparation**: BMA + 1 mL of 2% lignocaine solution. Bone marrow centrifuged for approximately 20-30 minutes at 2000 rpm. Only clear upper layer + buffy coat layer containing mononuclear cells used for injection and approximately 4-5 mL obtained from each patient. **Cell Expansion**: No **Cell Concentration**: NR **Cell Delivery**: Injection into the point of maximal tenderness at the extensor origin of the lateral epicondyle of the humerus **Anesthetic**: Lignocaine **Number of injections**: 1 **Co-interventions**: NR **Post-tx protocol**: All patients advised to rest + moderate their activities to avoid aggravation of their symptoms.	**% (n/N) male**: 60% (18/30) **Mean age ± SD**: 35.2 ± 6.84 years **Mean BMI**: NR **Mean symptom duration ± SD**: 7.33 ± 2.49 weeks **Laterality, % (n/N)** -Left: 42% (11/26) -Right: 58% (15/26) (Data on treatment side are only available for the 26 patients evaluated at follow-up)	**F/U** 2 weeks 1.5 months 3 months **% Followed (n/N)** 86% (26/30 patients)	- Patient-Rated Tennis Elbow Evaluation (PRTEE) (0-100; higher = decreased function and increased pain)	**Funding**: None **COI**: None reported.

ATI = autologous tenocyte injection; BM = Bone Marrow; BMA = Bone Marrow Aspirate; BM-MNC = bone marrow mononuclear stem cells; BMC = Bone Marrow Concentrate; BMI = Body Mass Index; CEO = Common Extensor Origin; COI = Conflict of Interest; F/U = follow-up; GMP = Good Manufacturing Practice; NR = Not Reported; QuickDash = Quick Disabilities of the Arm, Shoulder and Hand; PRP = Platelet Rich Plasma; PRTEE = Patient-rated Tennis Elbow Evaluation; ROB = Risk of Bias; SD = Standard Deviation; UK = United Kingdom; VAS = Visual analog scale

Appendix Table F13: Data abstraction for studies evaluating the use of stem cell therapy for elbow tendinopathy

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
Singh 2014 N=30 India Prospective Case Series High	**PRTEE score, Mean ± SD (n=26)** - Baseline: 72.8 ± 6.97 - 2 weeks: 40.93 ± 5.94, p<0.0001* - 1.5 months: 24.46 ± 4.58, p<0.0001* - 3 months: 14.86 ± 3.48, p<0.0001*	NR	NR	NR	NR

BM = Bone Marrow; BMA = Bone Marrow Aspirate; BM-MNC = bone marrow mononuclear stem cells; BMC = Bone Marrow Concentrate; BMI = Body Mass Index; COI = Conflict of Interest; F/U = follow-up; IQR = Interquartile range; NR = Not Reported; PRP = Platelet Rich Plasma; PRTEE = Patient-rated Tennis Elbow Evaluation; ROB = Risk of Bias; SD = Standard Deviation; VAS = Visual analog scale

* p-values are for difference from baseline

Appendix Table F14: Study characteristics and demographics for studies evaluating the use of stem cell therapies for ACL tears

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
Centeno 2018 N=29 USA Case Series (Registry study) High	Inclusion: Patients who were diagnosed with a functional disability and significant ligamentous laxity on examination with Lachman testing (in comparison with the uninvolved side). Patients agreeing to enroll in the treatment registry and undergo BMC and platelet products treatment, patients who displayed a grade 1, 2, or 3 ACL tear on MRI. If a high-grade tear, only those with less than 1 cm of ligament retraction were included. No limitations were placed on duration of injury. Exclusion: Patients younger than 15 years, Active neoplasm within the past 5 years, Anemia, Grade 3 ACL tear with > 1 cm retraction.	*Autologous BM-MSCs* Patient's hip underwent a pre-injection of a hypertonic dextrose solution into the hip joint intra-articular two to five days before BMC injection **Cell Type**: BM-MSCs **Cell Source**: 60–120 cc of whole bone marrow aspirate was removed from 6 to 10 sites of the posterior superior iliac crest. Concurrently, 60 cc of venous blood was drawn and centrifuged to isolate PRP and PL **Cell Expansion**: No **Cell Concentration**: Total nucleated cell count (mean ± SD): 690 × 10^6 ± 328 x 10^6 **Cell Delivery**: Using fluoroscopy, 2–3 cc of solution containing BMC, PRP and PL was injected directly into the ligament after contrast. The needle was withdrawn from the ligament approximately 1 cm, and while still in the joint, approximately 2–4 cc of a mixture of 1–1 cc of PRP and PL	**% male**: 41% **Mean age (range)**: 52.6 (41-67) years **Mean symptom duration (range)**: 33 (6-144) months **ACL grade*** - Grade 1: 21% (6/29) - Grade 2: 45% (13/29) - Grade 3: 34% (10/29)	F/U • 1 months • 3 months • 6 months • 18 months • 24 months • 36 months • Mean F/U: 23 ± 10 months % Followed NR	• Lower Extremity Functional Scale (LEFS) (0-80, higher=no functional disability) • International Knee Documentation Committee (IKDC) (0-100, higher=no functional disability) • Numerical Pain Scale (NPS) (0-10, higher=increased pain) • Modified Single Assessment Numeric Evaluation (M-SANE) (-100% to 100%, positive= improvement, negative=worsening) • Need for secondary surgery • Adverse Events	**Funding**: Industry **COI**: CC is a shareholder and chief medical officer of Regenexx, LLC, and president and owner of the Centeno-Schultz Clinic. JM, ED, CW, MH, TI and MF have declared no competing interests.

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Outcomes	Funding COI
		along with any remaining BMC were injected into the joint. **Anesthetic Use**: NR **Number of injections**: 1 **Co-interventions**: pre injection of hyper-osmolar dextrose 2-5 days before procedure (28% of patients did not receive this injection). **Post treatment protocol**: Patients were instructed to engage in activity as tolerated. Post-treatment bracing was not used. Patients were encouraged to undergo physical therapy, but this was neither controlled nor required.				

BM = bone marrow; BMC = bone marrow concentrate; BMI = body mass index; BM-MSCs = bone marrow derived mesenchymal stem/stromal cells; COI = conflict of interest; F/U = follow-up; IKDC = International Knee Documentation Committee score; IQR = inter-quartile range; K-L = Kellgren=Lawrence; LEFS = lower extremity functional score; MCID = minimal clinically important difference; M-SANE = Modified Single Assessment Numeric Evaluation; NPS = numerical pain score; NR = not reported; OA = osteoarthritis; PRP = platelet rich plasma; ROB = risk of bias; SD = standard deviation; tx = treatment

* Grade 1 sprain: the ligament is partially torn, with less than half of the ligament substance disrupted; Grade 2 sprain: the ligament is partially torn, with more than half of the ligament substance disrupted; Grade 3 sprain: the ligament is completely torn.

Appendix Table F15: Data abstraction for studies evaluating the use of stem cell therapies for ACL tears

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
Centeno 2018 N=23 USA Case Series (Registry study) High	*Autologous BM-MSCs* **LEFS, Mean** • Baseline: 51.1 (n=23) • 1 month: 61.4, p<0.05 (n=14) • 3 month: 65.7, p<0.05 (n=19) • 6 month: 72.0, p<0.05 (n=19) • 12 month: 72.2, p<0.05 (n=19) • 18 month: 74.1, p<0.05 (n=16) • 24 month: 75.9, p<0.05 (n=17) • 36 month: 72.6, p<0.05 (n=8) **Proportion of patients meeting the MCID of 9 points on the LEFS, % (n/N)** • Final follow-up: 82.6% (19/23) **IKDC, Mean** • Baseline: 53.4 (n=20) • 1 month: 67.6, p<0.05 (n=14) • 3 month: 72.9, p<0.05 (n=18) • 6 month: 82.4, p<0.05 (n=18) • 12 months: 80.1, p<0.05 (n=19) • 18 month: 83.7, p<0.05 (n=16) • 24 month: 87.0, p<0.05 (n=18) • 36 month: 87.9, p<0.05 (n=8) **Proportion of patients meeting the MCID on the IKDC, % (n/N)** • 6 months: 95% (18/19) (MCID=6.3)	*Autologous BM-MSCs* **NPS, Mean** • Baseline: 2.5 (n=25) • 1 month: 1.9, p>0.05 (n=15) • 3 month: 1.8, p>0.05 (n=20) • 6 month: 1.0, p<0.05 (n=19) • 12 months: 1.4, p>0.05 (n=19) • 18 month: 1.1, p<0.05 (n=16) • 24 month: 0.8, p<0.05 (n=18) • 36 month: 1.0, p>0.05 (n=8)	NR	*Autologous BM-MSCs* **M-SANE (Patient Perceived Improvement), Mean** (p-values are for change from 1 month) • 1 month: 25.0 (n=14) • 3 month: 65.3, p<0.05 (n=19) • 6 month: 75.5, p<0.05 (n=19) • 12 months: 66.7, p<0.05 (n=21) • 18 month: 78.8, p<0.05 (n=16) • 24 month: 82.6, p<0.05 (n=17) • 36 month: 88.8, p<0.05 (n=8) • Final follow-up: 72% ± 35% **Proportion of patients receiving ACL reconstruction surgery, % (n/N)** • Due to treatment failure: 17.4% (4/23) • Due to a re-tear: 4.3% (1/23) (two were grade 1, two were grade 2, and one was grade 3)	**Adverse Events, % (n/N)** Swelling: 4.3% (1/23) Vasovagal episode: 4.3% (1/23)

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
	• 12 months: 100% (14/14) (MCID=16.7)				

Δ = change from baseline; BM = bone marrow; BMC = bone marrow concentrate; BMI = body mass index; BM-MSCs = bone marrow derived mesenchymal stem/stromal cells; COI = conflict of interest; F/U = follow-up; IKDC = International Knee Documentation Committee score; IQR = inter-quartile range; K-L = Kellgren=Lawrence; LEFS = lower extremity functional score; MCID = minimal clinically important difference; M-SANE = Modified Single Assessment Numeric Evaluation; NPS = numerical pain score; NR = not reported; OA = osteoarthritis; PRP = platelet rich plasma; ROB = risk of bias; SD = standard deviation; tx = treatment

Appendix Table F16: Study characteristics and demographics for studies evaluating the use of stem cell therapies in patients with various orthopedic conditions (safety & effectiveness data)

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention	Patient Demographics	F/U	Outcomes	Funding COI
Sampson 2016 N=125 USA Prospective Case Series High	Inclusion: aged ≥18 years, fluent in English, >3 months of symptomatic OA unresponsive to at least two of the following: activity modification, physical therapy, bracing, assistive devices, acupuncture, nonsteroidal anti-inflammatory medications, local steroid injections, hyaluronic acid injections or arthroscopy, Kellgren–Lawrence grade III or higher radiographic OA and treated with our intra-articular BMC injection protocol for	*Autologous BMC + PRP* **Cell Type**: BM MSCs **Cell Source**: Iliac crest **Cell Preparation**: A 20 cc syringe was flushed with heparin (1000 µ/cc) and then filled with 2 cc heparin, of which 0.5 cc was injected into the marrow cavity. Then 60 cc of BM was aspirated and centrifuged **Cell Expansion**: No **Cell Concentration**: Cell count was not measured	[Data are for all 125 patients initially enrolled in the study] **% male**: NR **Mean age (range)**: 57 (23-79) years **Mean BMI**: 26.8 kg/m^2 **Injection location:** Ankle (n=6), Bilateral knees (n=27), C-spine (n=5), hip (n= 14), Unilateral knee (n=46), Shoulder	F/U 148 days (range: 56–673) across 87 patients with complete follow-up data % Followed 69.6% (87/125)	• Pain Visual Analog Scale (VAS-pain, 0-10 higher=increased pain) • Global patient satisfaction (0-10, higher=more satisfied) • Adverse Events	**Funding**: NR **COI**: None

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention	Patient Demographics	F/U	Outcomes	Funding COI
	symptomatic OA between January 2012 and September 2013. Exclusion: Pregnancy or breastfeeding at the time of treatment, participating or planning to participate in a worker's compensation program at the time of the treatment or follow-up period, pending or planned legal action pertaining to knee pain, intolerance to acetaminophen or Vicodin®, history of drug abuse, cortisone injection into the affected joint within 6 weeks of intra-articular BMC injection, use of a nonsteroidal anti-inflammatory medication <1 week prior to BMC, history of anemia, bleeding disorders or inflammatory joint disease, surgical intervention of the affected or contralateral joint <3 months prior to BMC injection, infection of the joint scheduled for treatment within 6 months of BMC injection, active infection, active malignancy.	**Cell Delivery**: Ultrasound guided intraarticular injection **Anesthetic**: 45 min prior to bone marrow aspiration, patients were given 1 mg of oral lorazepam and 50 mg of tramadol. Cautions were taken to avoid intra-articular injection of local anesthetic. **Number of injections**: 2 (Patients received a single injection of BMC, with follow-up injection of PRP at 8 weeks) **Co-interventions**: For PRP delivery, whole venous blood was drawn from a peripheral vein of the patient, and centrifuged and injected via intra-articular injection **Post-tx protocol:** The joint was passively moved through flexion and extension, and the patient received Game Ready cryotherapy for 10 min. Patients were given tramadol for postop pain and instructed to limit the use of their affected joint for 48 hours. After that, patients were instructed to be weight bearing as tolerated (if a lower body joint was treated) with progression of daily activities as tolerated. No specific bracing protocol was followed. Most	joint (n=18), Other (n=9)			

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention	Patient Demographics	F/U	Outcomes	Funding COI
		patients performed post procedure physical therapy or a home exercise program, but no standardized protocol was followed.				
Rodriguez-Fontan 2018 N=19 patients with 25 treated joints (10 knees, 15 hips) USA Prospective Case Series High	Inclusion: >18 years old undergoing first-time intra-articular BMC therapy; primary diagnosis: early knee OA, Kellgren-Lawrence (K-L) grade I-II, and/or early hip OA, Tonnis grade I-II; and did not respond to nonoperative treatments including physical therapy and nonsteroidal anti-inflammatory drugs for at least 6 months Exclusion: Age <18 years old; pregnancy; malignancy; rheumatologic diseases; infection; K-L grade IIIIV; Tonnis grade III; joint space narrowing <2 mm; patients previously treated with intra-articular steroids injections; avascular necrosis of the femoral head; and previous surgery in the affected joint.	*Autologous BMC* **Cell Type**: BM MSCs **Cell Source**: Superior iliac spine (a total of 120 mL was obtained) **Cell Preparation**: BM was centrifuged to create a final BMC volume of 12 mL **Cell Expansion**: No **Cell Concentration**: NR **Cell Delivery**: radio-graphic or ultrasound guided intra-articular injection **Anesthetic**: NR **Number of injections**: 1 **Co-interventions**: **Post-tx protocol**: All patients were allowed immediate full weight bearing activity and encouraged to perform gradual physical activity. Patients were asked not to take nonsteroidal anti-inflammatory drugs for 3 weeks postoperatively. Ice therapy was indicated.	**% male**: 16% **Mean age ± SD**: 58 ± 12.7 **Laterality** - Bilateral hip procedures: 10.5% (2/19 patients) - Bilateral knee procedures: 15.8% (3/19 patients) - 1 hip and 1 knee procedure: 5.3% (1/19 patients) **Mean BMI**: 25.9 kg/m^2 **Comorbidities** Osteoporosis: 26.3% (5/19) Diabetes: 10.5% (2/19) Hypothyroidism: 21.1% (4/19)	Mean F/U ± SD: 13.2 ± 6.3 months % Followed: 100% (19/19)	• Western Ontario and McMaster Universities Arthritis Index (WOMAC) (0-100, higher=greater disability) • Patient satisfaction • Adverse Events	**Funding**: Professional Society and Industry **COI**: NR

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention	Patient Demographics	F/U	Outcomes	Funding COI
Centeno 2015 N=102 with 115 treated shoulders (OA, n=34 shoulders; Rotator Cuff Tear, n=81 shoulders) USA Case Series (Registry study) High	Inclusion criteria and registry information: Patients with presenting symptoms of shoulder pain who were subsequently diagnosed with glenohumeral OA and/or partial or full-thickness rotator cuff tears were culled from a treatment registry designed to track the safety and efficacy of patients presenting to a network of 13 clinics for cell therapy. Patients were tracked via an electronic database system using Clin Capture software. Exclusion: Patients with less than a 3-month follow-up or a rotator cuff tear greater than 1.5 cm and evidence of retraction were excluded	*Prolotherapy + Autologous BMC + PRP + platelet lysate* To prompt a brief inflammatory response before receiving the BMC, patients were pre-injected with a hypertonic dextrose solution into the joint structures **Cell Type**: BM-MSCs **Cell Source**: Posterior iliac crest **Cell Preparation**: BM total volume collected was between 60 and 90 mL. For each 1 mL of whole bone marrow aspirate collected, 1,000 units of heparin was added and the cell suspension was serially centrifuged. In addition to BMC isolation, 60 mL of intravenous blood was drawn for the isolation of PRP and platelet lysate. **Cell Expansion**: No **Mean Cell Concentration**: - OA patients (n=24): $3.85x10^8$ - Rotator cuff patients (n=57): $4.99x10^8$ **Cell Delivery**: Ultrasound or fluoroscopy guided intra-articular or rotator cuff tear needle placement. When fluoroscopy was used to	*Autologous BMC + PRP + platelet lysate* **OA Patients** **% Male:** 79.4% **Mean age:** 52.1 years **Mean BMI:** 25.3 **Rotator Cuff Tear Patients** **% Male:** 65.4% **Mean age:** 59.5 years **Mean BMI:** 26.6	Mean F/U by Outcome Reported (across both patient populations) DASH: 7.1 months NPS: 8.3 months Perceived Improvement: 11.2 months % Followed by outcome reported **OA patients** DASH: 29.4% (10/34) NPS: 41.2% (14/34) Improvement score: 70.6% (24/34) **Rotator Cuff Tear patients** DASH: 37.0% (30/81) NPS: 50.6% (41/81) Improvement score: 75.3% (61/81)	• Disabilities of the arm, shoulder, and hand (DASH) (0-100, higher=greater disability) • Numeric Pain Scale (NPS) (0-10, higher=worse pain) • Patient perceived improvement (-100%-100%, higher=greater improvement)	**Funding**: Industry **COI**: Dr Christopher Centeno is a shareholder and director of Regenerative Sciences, LLC. Hasan Al-Sayegh is an employee of the Centeno Schultz Clinic, Regenerative Sciences, LLC. Dr Jamil Bashir is a fellow trainer at the Centeno Schultz Clinic. Dr Shaun Goodyear and Dr Michael Freeman have no conflicts of interest.

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention	Patient Demographics	F/U	Outcomes	Funding COI
		confirm intra-articular needle placement, iodixanol radiographic contrast agent was injected followed by a second injection of 3–5 mL of 12.5% dextrose and 0.1% lidocaine or 0.25% ropivicaine in normal saline. Two to five days after the pre-injection, again using ultrasound or fluoroscopic guidance, 10–15 mL of bone marrow aspirate per **Number of injections**: 1 SCT injection				

Δ = change from baseline; BM = bone marrow; BMC = bone marrow concentrate; BMI = body mass index; BM-MSCs = bone marrow derived mesenchymal stem/stromal cells; COI = conflict of interest; DASH = Disbailities of the arm, shoulder, and hand; F/U = follow-up; IQR = inter-quartile range; K-L = Kellgren=Lawrence; NPS = numerical pain score; NR = not reported; OA = osteoarthritis; PRP = platelet rich plasma; ROB = risk of bias; SCT = stem cell therapy; SD = standard deviation; tx = treatment; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis

Appendix Table F17: Data abstraction for studies evaluating the use of stem cell therapies in patients with various orthopedic conditions (safety & effectiveness data)

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
Sampson 2016 N=125 USA Case Series High	NR	*Autologous BMC + PRP* **VAS, Median (IQR) (n=83)** **<u>All patient populations</u>** • Baseline: 7.0 (2 to 10) (5.0 to 9.0) • Final follow-up: 2.0 (0 to 10) (1.0 to 3.0) • Follow-up Δ: –5.0 (–9.0 to 6.0) (–7.0 to –3.0) • Mean % reduction from baseline: 71.4%, p<0.0001 **VAS, Median (IQR) absolute change from baseline by injection site** • Unilateral Knees (n=31): –5.0 (–6.0 to 2.0) • Bilateral Knees (n=21): –6.0 (–8.0 to –4.5) • Shoulder (n=13): –5.0 (–8.0 to –3.5) • Hip (n=10): –3.0 (–4.0 to –0.8) • Ankle (n=6): –3.0 (–4.0 to 1.8) • Cervical Spine (n=2): –7.0 (–7.0 to –7.0) • Other (n=4): –3.5 (–6.3 to 0.8) **VAS, Median % change (IQR) from baseline by injection site** • Unilateral Knees (n=31): –67% (–89% to –44%)	NR	*Autologous BMC + PRP* **<u>All patient populations (n=83)</u>** **Patient Satisfaction, Median (IQR)** • 9.0 (7.0 to 10.0) **Proportion of patients indicating they would repeat the procedure, % (n/N)** • 91.7% (77/84) **Proportion of patients indicating they would recommend the procedure to a friend, % (n/N)** 94% (79/84)	*Autologous BMC + PRP* **Adverse Events** • With respect to the 125 patients who received an injection, no acute adverse events were reported. • With respect to the 87 patients with complete follow-up data, no adverse effects were reported during the follow-up period.

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
		• Bilateral Knees (n=21): –80% (–100% to –69%) • Shoulder (n=13): –63% (–94% to –53%) • Hip (n=10): –50% (–80% to –15%) • Ankle (n=6): –44% (–68% to 25%) • Cervical Spine (n=2): –89% (–100% to –78%) • Other (n=4): –70% (–95% to 4%)			
Rodriguez-Fontan 2018 N=19 patients with 25 treated joints (10 knees, 15 hips) USA Prospective Case Series High	*Autologous BMC* **WOMAC-general, Mean ± SD (n=19)** • Baseline: 40.8 ± 18.3 • 6 months: 19.2 ± 18.2 • 6 month Δ from baseline: 21.6 ± 5.1 (95% CI 11.3 to 32), p<0.001 • Final follow-up: 20.6 ± 17 • Final follow-up Δ from baseline: 20.2 ± 5.0 (95% CI 10.2 to 30.3), p<0.001 **Proportion of patients meeting the MCID of 9.15 points, % (n/N)** • 64% (n's NR)	NR	NR	*Autologous BMC* **Proportion of patients designating that they were satisfied with the procedure, % (n/N)** • 6 months: 63.2% (12/19) **Proportion of patients designating that they experienced mild improvement, no improvement, or worsening of symptoms, % (n/N)** • 6 months: 36.8% (8/19) **Proportion of patients going on to receive Total Hip Arthroplasty, % (n/N)** • 10.5% (2/19) [at 8 months post-treatment]	*Autologous BMC* **Adverse Events, % (n/N)** • No patient developed major complications. • 57.9% (11/19) patients experienced at least 1 minor complication. • Mild pain at the site of BMC extraction during the first 24 postoperative hours: 15.8% (3/19) • Hip joint discomfort during the first days after the procedure: 36.8% (7/19) • Pain during first 2 weeks after BMC injection: 26.3% (5/19) • Swelling: 5.2% (1/19)

Author (year) N Country Study design ROB	Primary Outcomes – Function	Primary Outcomes – Pain	Primary Outcomes – objective measures of medication use, return to normal activities	Secondary and Intermediate Outcomes – Time to recovery, QOL, Patient satisfaction, Recurrence, Secondary procedures	Adverse Events, Harms, Complications
Centeno 2015 N=102 with 115 treated shoulders (OA, N=34 shoulders; Rotator Cuff Tear, N=81 shoulders) USA Case Series (Registry study) High	*Phototherapy + Autologous BMC + PRP + platelet lysate* **<u>Osteoarthrosis Patients</u>** **DASH, Mean Δ from baseline to final follow-up ± SD (n=10)** • -18.7 ± 11.2 **<u>Rotator Cuff Patients</u>** **DASH, Mean Δ from baseline to final follow-up ± SD (n=30)** • -19.1 ± 20.9 **<u>Across both patient populations</u>** **Proportion of hips meeting the minimal important change of 10 point reduction on the DASH**: 65% (26/40 available shoulders)	*Phototherapy + Autologous BMC + PRP + platelet lysate* **<u>Osteoarthrosis Patients</u>** **NPS, Mean Δ from baseline to final follow-up ± SD (n=14)** • -1.6 ± 2.1 **<u>Rotator Cuff Patients</u>** **NPS, Mean Δ from baseline to final follow-up ± SD (n=41)** • -2.1 ± 2.5 **<u>Across both patient populations</u>** **Proportion of hips meeting the minimal important change of 2 point reduction on the NPS**: 58.2% (32/55 available shoulders)	NR	*Phototherapy + Autologous BMC + PRP + platelet lysate* **<u>Osteoarthrosis Patients</u>** **Improvement Rating Score, Mean Δ from baseline to final follow-up ± SD (n=NR)** • 50.4% ± 34.8% **<u>Rotator Cuff Patients</u>** **Improvement Rating Score, Mean Δ from baseline to final follow-up ± SD (n=NR)** • 48.1% ± 47.4%	*Phototherapy + Autologous BMC + PRP + platelet lysate* **<u>Reported across both patient groups</u>** **Adverse Events, % (n/N)** • Any event: 4.9% (5/102) -Pain: 3% (3/102) -Cardiac event: 1% (1/102) -Other: 1% (1/102)

Δ = change from baseline; BM = bone marrow; BMC = bone marrow concentrate; BMI = body mass index; BM-MSCs = bone marrow derived mesenchymal stem/stromal cells; COI = conflict of interest; DASH = Disbailities of the arm, shoulder, and hand; F/U = follow-up; IQR = inter-quartile range; K-L = Kellgren=Lawrence; NPS = numerical pain score; NR = not reported; OA = osteoarthritis; PRP = platelet rich plasma; ROB = risk of bias; SD = standard deviation; tx = treatment; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis

Appendix Table F18: Study characteristics, demographics, and data abstraction for studies evaluating the use of stem cell therapies in patients with various orthopedic conditions (safety only)

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
Centeno 2010 N=227 patients (244 procedures) USA High	Inclusion: • Group 1 (treated between 2006 and 2009; n=45) 1. 18-65 years of age. 2. Chronic or degenerative joint disease causing significant functional disability. 3. Failure of conservative management. 4. Unwillingness to pursue surgical options. • Group 2 (treated between 2007 and 2009; n=182): Same as group 1 Exclusion: • Group 1 1. Active inflammatory or connective tissue disease (i.e. lupus, fibromyalgia, RA). 2. Active non-corrected endocrine disorder potentially associated with symptoms (i.e. hypothyroidism, diabetes). 3. Active neurologic disorder potentially associated with symptoms (i.e. peripheral neuropathy, multiple sclerosis). 4. Severe cardiac disease. 5. Pulmonary disease requiring medication usage.	*Autologous Culture Expanded BM MSCs* **Cell Type**: BM-MSCs **Cell Source**: Posterior iliac crest **Cell Expansion**: Yes **Cell Concentration**: NR **Cell Delivery**: Cultured MSCs (~80% confluence) were suspended in either 20% Platelet Lysate in phosphate buffered saline or conditioned serum of PRP and $CaCl_2$ **Anesthetic Use**: NR **Number of injections**: injected into peripheral joints or into intervertebral discs with use of c-arm fluoroscopy **Co-interventions**: restricted from taking corticosteroids or NSAIDs for one week prior to the marrow harvest procedure. **Post treatment protocol**: NR	**% male**: 62.1% **Mean age ± SD**: 52.8 ± 13.5 **% white**: 98.6% **Injection location, % (n/N)** Knee: 118 procedures Hip: 78 procedures Foot-ankle: 10 procedures Shoulder: 10 procedures Spinal disc: 13 procedures Hand/wrist: 6 procedures Other: 9 procedures	Mean ± SD F/U 10.6 ± 7.3 months % Followed 93.8% (213/227)*	**Funding**: Industry **COI**: Dr. Marasco is a consultant for and has equity ownership in NeoStem. Dr. Centeno, Dr. Schultz, Michelle Cheever, and Brent Robinson have equity ownership in Regenerative Sciences, LLC (RS). Dr. Centeno and Schultz as well as Brent Robinson act as consultants for RS, while Michelle Cheever is an RS employee.	**Adverse events adjudicated to be "probable" in relation to the procedure or the stem cells themselves, % (n/N)** • Moderate allergic reaction to radiographic contrast: 0.5% (1/227) • Mild abnormal blood work: 0.9% (2/227) • Increased pain and/or swelling: 4% (9/227)† -Mild: 4/9 -Moderate: 4/9 -NR: 1/9 • Moderate infection at the marrow draw site: 0.5% (1/227)‡

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
	6. History of active neoplasm within the past 5 years. 7. Anemia. • Group 2 1. Medical condition precluding the injection procedure 2. History of active neoplasm within the past 5 years 3. Anemia					
Centeno 2011 N=339 patients with 769 procedures USA High	Inclusion: • Group 1 (treated between 2006 and 2010; n=50) 1. 18-65 years of age. 2. Chronic or degenerative joint disease causing significant functional disability. 3. Failure of conservative management. 4. Unwillingness to pursue surgical options. • Group 2 (treated between 2007 and 2010; n=290): Same as group 1 except no age limitations Exclusion: • Group 1 1. Active inflammatory or connective tissue disease (i.e. lupus, fibromyalgia, RA). 2. Active non-corrected endocrine disorder potentially associated with symptoms (i.e. hypothyroidism, diabetes).	*Autologous Culture Expanded BM MSCs* **Cell Type**: BM-MSCs **Cell Source**: Posterior iliac crest **Cell Expansion**: Yes **Cell Concentration**: NR **Cell Delivery**: Cultured MSCs (~80% confluence) were suspended in either 20% Platelet Lysate in phosphate buffered saline or conditioned serum of PRP and $CaCl_2$ **Anesthetic Use**: NR **Number of injections**: injected into peripheral joints or into intervertebral discs with use of c-arm fluoroscopy **Co-interventions**: restricted from taking corticosteroids or NSAIDs for one week prior to the	**% male**: 63.1% **Mean age ± SD**: 53 ± 13.85 **% white**: 99% **Injection location, % (n/N)** Knee: 49% (374/769) Hip: 28% (218/769) Foot-ankle: 7% (54/769) Shoulder: 13% (48/379) Spinal disc: 4% (34/769) Hand/wrist: 2% (15/769) Other: 3%(26/769)	Mean ± SD F/U 14.5 ± 8.7 months % Followed 98% (332/339)*	**Funding**: Industry **COI**: Dr. Marasco is a consultant for and has equity ownership in NeoStem. Dr. Centeno, Dr. Schultz, Michelle Cheever, and Brent Robinson have equity ownership in Regenerative Sciences, LLC (RS). Dr. Centeno and Schultz as well as Brent Robinson act as consultants for	**Adverse events adjudicated to be "probable" in relation to the procedure or the stem cells themselves, % (n/N)** • Increased pain and swelling: 2.7% (9/339) -Mild: 5/8 -Moderate: 3/8 -Severe: 1/8** • Infection: 0% (0/339) • Transient, self-limited numbness and tingling in the arm used for blood draw: 0.3% (1/339)

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
	3. Active neurologic disorder potentially associated with symptoms (i.e. peripheral neuropathy, multiple sclerosis). 4. Severe cardiac disease. 5. Pulmonary disease requiring medication usage. 6. History of active neoplasm within the past 5 years. 7. Anemia. • Group 2 1. Medical condition precluding the injection procedure 2. History of active neoplasm within the past 5 years 3. Anemia	marrow harvest procedure. **Post treatment protocol**: NR			RS, while Michelle Cheever is an RS employee.	
Centeno 2016 N patients (N injections)§ - SD group: N=1590 patients with 1949 injections - AD group: N=247 patients with 364 injections - CE group: 535 patients with 699 injections USA High	**Inclusion**: All patients who underwent an MSC-based, percutaneous injection treatment of an orthopedic condition between December 2005 and September 2014 at one of 18 clinical facilities located in the United States or Australia and who had attained at least a three month follow-up period. Treated conditions included those resulting from degenerative joint changes (i.e. osteoarthritis, degenerative disc disease, degenerative disc disease) as well as trauma (e.g., anterior cruciate ligament injuries, rotator cuff tears, etc.).	3 different groups of patients were followed: 1. *SD (same day aspiration, isolation, and reinjection procedure with autologous BMC)* 2. *AD (same day aspiration, isolation, and re-injection procedure with autologous BMC plus adipose graft)* 3. *CE (culture expanded MSCs re-implanted weeks or months after bone marrow aspiration)*	**SD group** **% male**: 60.6% **Mean age ± SD**: 55.6 ± 14.2 years **Mean BMI ± SD**: 26.5 ± 4.8 **Injection location, % (n/N)** Knee: 55% (878/1590) Hip: 23% (366/1590) Foot-ankle: 8% (126/1590) Spine: 1% (15/1589) Shoulder: 9% (144/1590)	Mean F/U ± SD (range) SD group: 18 ± 13.2 (3 to 60) months AD group: 21.6 ± 13.2 (3 to 48) months CE group: 52.8 ± 21.6 (3 to 108) months % Followed Cannot be determined from information provided		**AEs and SAEs, % (n/N) [Incidence per 100 person-years]** **SD group** Total: 7.20% (114/1590) [4.87] Non-serious AE: 6.70% (107/1590) [4.66] SAE: 0.40% (7/1590) [0.3] Expected: 1% (16/1590) [0.77] Not expected: 6.20% (98/1590) [4.22] Related to procedure? Not related or unlikely: 2.40% (38/1590) [1.62] Possible: 3.50% (55/1590) [2.44] Definite: 1.30% (21/1590) [0.9]

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
	Treated areas of the body included the knee, hip, ankle/foot, hand/wrist, elbow, shoulder, and spine. Knee, hip, and shoulder patients constituted approximately 87 % of the population. **Exclusion**: There were no exclusion criteria for MSC-treated patients to enter the registry, patients were naturally excluded from treatment if they were found not to be a candidate for the treatment by the attending physician. Reasons for exclusion from treatment included conditions for which the only therapeutic alternative was deemed to be surgery as well as medical conditions that would make MSC therapy difficult. Examples include a completely torn and retracted tendon or ligament, a severely osteoarthritic knee with deformity, severe spinal stenosis with neurologic compromise, and severe rheumatologic conditions like rheumatoid arthritis or systemic lupus erythematosus.	All patients restricted from taking corticosteroids or NSAIDs for two week prior to the marrow harvest procedure. **Cell Type**: BM-MSCs **Cell Source**: Posterior iliac crest (10-15 cc at 3-4 sites each side) **Cell Expansion**: Yes for CE group only. In the CE group, MSCs isolated from the bone marrow aspirate were expanded in an autologous based culture media for 12–16 days prior to injection. **Cell Concentration**: -SD and AD group: BMC generally contained 0.2-1.5 × 10^8 nucleated cells -CE group: 1–3 cc MSCs in PL with dose ranges generally from 0.1-6 × 10^7 MSCs **Cell Delivery**: ultrasound or fluoroscopic guided injection. For SD and AD groups, 1-3 ccs of injectate was used. **Anesthetic Use**: NR	Hand/elbow: 3% (52/1590) General: 0.6% (9/1590) **AD group** **% male**: 54.3% **Mean age ± SD**: 60 ± 10.9 years **Mean BMI ± SD**: 27.1 ± 4.2 **Injection location, % (n/N)** Knee: 94.7% (878/247) Hip: 2.4% (6/247) Foot-ankle: 0.8% (2/247) Spine: 0% (0/247) Shoulder: 1.2% (3/247) Hand/elbow: 0.8% (2/247) General: 0% (0/247) **CE group** **% male**: 64.1% **Mean age ± SD**: 53.4 ± 13.2 years **Mean BMI ± SD**: 26.5 ± 4.5			Related to stem cells? Not related or unlikely: 4.30% (68/1590) [2.9] Possible: 2.40% (39/1590) [1.77] Definite: 0.40% (7/1590) [0.3] Category Allergic: 0.40% (6/1590) [0.26] Bone: 0% (0/1590) [0] Cardiac: 0.20% (3/1590) [0.13] Endocrine: 0% (0/1590) [0] Gastrointestinal: 0.10% (1/1590) [0.04] Immune: 0.20% (3/1590) [0.13] Infection: 0.10% (1/1590) [0.04] Lab work: 0.10% (2/1590) [0.09] Neoplasm: 0.10% (1/1590) [0.04] Neurologic: 0.10% (2/1590) [0.09] Other: 0.70% (11/1590) [0.47] Pain-other area: 0.40% (6/1590) [0.26] Pain-post procedure: 2.30% (37/1590) [1.58] Pain-DJD: 1.90% (30/1590) [1.28] Pulmonary: 0% (0/1590) [0] Renal: 0% (0/1590) [0] Rheumatological: 0.10% (1/1590) [0.04] Skin: 0.10% (2/1590) [0.09] Vascular: 0.50% (8/1590) [0.34] **SE group** Total: 12.2% (30/247) [6.79]

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
		Number of injections: NR, but patients could receive more than one injection **Co-interventions**: The SD and AD groups both had concurrent injections of PRP and PL. The AD group also had a concurrent injection of minimally processed lipo-aspirate. **Post treatment protocol**: NR	**Injection location, % (n/N)** Knee: 52% (278/535) Hip: 23.2% (124/535) Foot-ankle: 8% (43/535) Spine: 8% (44/535) Shoulder: 6% (30/535) Hand/elbow: 2% (13/535) General: 0.6% (3/535)			Non-serious AE: 10.6% (26/247) [5.89] SAE: 1.6% (4/247) [0.91] Expected: 0.8% (2/247) [0.45] Not expected: 11.4% (28/247) [6.34] <u>Related to procedure?</u> Not related or unlikely: 4.1% (10/247) [2.33] Possible: 6.1% (15/247) [3.4] Definite: 2% (5/247) [1.13] <u>Related to stem cells?</u> Not related or unlikely: 6.9% (17/247) [3.99] Possible: 4.9% (12/247) [2.72] Definite: 0.4% (1/247) [0.23] <u>Category</u> Allergic: 0% (0/247) [0] Bone: 0% (0/247) [0] Cardiac: 1.2% (3/247) [0.68] Endocrine: 0% (0/247) [0] Gastrointestinal: 0% (0/247) [0] Immune: 0% (0/247) [0] Infection: 0.4% (1/247) [0.23] Lab work: 0% (0/247) [0] Neoplasm: 0% (0/247) [0] Neurologic: 0.8% (2/247) [0.45] Other: 0.8% (2/247) [0.45] Pain-other area: 1.2% (3/247) [0.45] Pain-post procedure: 4.5% (11/247) [2.49]

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
						Pain-DJD: 2.4% (6/247) [1.36] Pulmonary: 0% (0/247) [0] Renal: 0.4% (1/247) [0.23] Rheumatological: 0% (0/247) [0] Skin: 0% (0/247) [0] Vascular: 0.4% (1/247) [0.23] **CE Group** Total: 34.2% (181/535) [7.79] Non-serious AE: 30.2% (160/535) [6.89] SAE: 4.7% (25/535) [1.11] Expected: 4% (21/535) [0.9] Not expected: 30.2% (160/535) [6.89] Related to procedure? Not related or unlikely: 21.4% (113/535) [4.99] Possible: 10.6% (56/535) [2.41] Definite: 2.3% (12/535) [0.52] Related to stem cells? Not related or unlikely: 25.7% (136/535) [5.86] Possible: 8.1% (43/535) [1.85] Definite: 0.4% (2/535) [0.09] Category Allergic: 0.9% (5/535) [0.22] Bone: 0.2% (1/535) [0.04] Cardiac: 0.4% (2/535) [0.09] Endocrine: 0.8% (4/535) [0.17]

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
						Gastrointestinal: 0.4% (2/535) [0.09] Immune: 1.1% (6/535) [0.26] Infection: 0.8% (4/535) [0.17] Lab work: 0.9% (5/535) [0.22] Neoplasm: 1.1% (6/535) [0.26] Neurologic: 1.9% (10/535) [0.43] Other: 2.6% (14/535) [0.6] Pain-other area: 1.5% (8/535) [0.34] Pain-post procedure: 8.5% (45/535) [1.94] Pain-DJD: 10.2% (54/535) [2.33] Pulmonary: 0.4% (2/535) [0.09] Renal: 0.6% (3/535) [0.13] Rheumatological: 0% (0/535) [0] Skin: 0.9% (5/535) [0.22] Vascular: 0.9% (5/535) [0.22]
Pak 2013 N=91 patients with 100 procedures joints (81 procedures on joints with hip or knee OA) South Korea High	Inclusion: Inclusion criteria: (i) age 18 and older; (ii) chronic or degenerative joint disease causing significant functional disability and/or pain; (iii) the failure of conservative treatments; and (iv) an unwillingness to proceed with surgical intervention. Exclusion: (i) active inflammatory or connective tissue disease thought to impact pain condition (i.e., lupus, rheumatoid arthritis, and fibromyalgia); (ii) active	*Autologous Adipose-derived MSCs + PRP + HA + $CaCl_2$* **Cell Type**: MSCs **Cell Source**: Adipose tissue. For liposuction procedure, the patients were sedated with propofol 2 mg IV push and 20–30 mg/h rate of continuous infusion. Volume = ~40mL. Cells were then centrifuged to separate the lipoaspirate and enzyme **Cell Expansion**: No **Cell Concentration**: NR	*Across all included patients* **% male**: 49.5% **Mean age**: 51.23 (18-78) years **Laterality, % (n/N)**: Bilateral knees treated: 6.6% (6/91 patients)	*Across all included patients* Mean F/U 26.62 months (outcomes measures reported at 1 and three months) % Followed 1 month: 100% (100/100 procedures) 3 months: 100% (100/100 procedures)	**Funding**: Nonprofit and Government **COI:** None	*Autologous Adipose-derived MSCs + PRP + HA + $CaCl_2$* Across all 100 procedures **Adverse Events, % (n/N)** • Pain and swelling: 37% (37/100) • Tendonitis/Tenosynovitis: 22% (22/100) • Skin rash: 1% (1/100) • Infection: 0% (0/100) • Neurological event: 1% (1/100) • Tumor: 0% (0/100)

Author (year) N Country Study design ROB	Inclusion & Exclusion Criteria	Intervention Comparator	Patient Demographics	F/U	Funding COI	Adverse Events, Harms, Complications
	noncorrected endocrine disorder that might impact pain condition (i.e., hypothyroidism and diabetes); (iii) active neurologic disorder that might impact pain condition (i.e., peripheral neuropathy and multiple sclerosis); (iv) pulmonary and cardiac disease uncontrolled with medication usage; (v) history of active neoplasm within the past five years; (vi) blood disorders documented by abnormal complete blood count within three months including severe anemia, thrombocytopenia, leukocytosis and/or leukopenenia; and (vii) medical conditions precluding the injection procedures.	**Cell Delivery**: ultrasound guided injection **Anesthetic Use**: Yes – 2% lidocaine **Number of injections**: 1 injection of Adipose-derived MSCs, PRP, HA, and $CaCl_2$ followed by 1 weekly injection of PRP for 4 weeks. **Co-interventions**: Three patients received two injections of stem cells on the same knee joints. **Post treatment protocol**: The patients were then instructed to remain still for 30 minutes to allow for cell attachment. As they were discharged to home, the patients were instructed to maintain activity as tolerated.		12 months: 100% (100/100 procedures) 24 months: 78% (78/100 procedures) 30 months: (17/100 procedures)		

AD = adipose; AE = adverse events; BM = bone marrow; BMAC = bone marrow aspirate concentrate; BMC = bone marrow concentrate; BMI = body mass index; BM-MNCs = bone marrow mononuclear cells; BM-MSCs = bone marrow derived mesenchymal stem/stromal cells; CE = culture expanded; COI = conflict of interest; F/U = follow-up; MCS = mental component score; NSAID = non-steroid anti-inflammatory drug; PRP = platelet rich plasma; ROB = risk of bias; SD = standard deviation;

* A patient was considered lost to follow-up when they failed to respond for three successive time points despite three attempts at contact at each time point. However, a patient who failed to respond to one time point may be "reacquired" at a later time point when they did respond

† 4 were self-limiting, 2 resolved with knee effusion drained via arthrocentesis, and 3 required joint arthroplasty

‡ An additional infection was identified by unconfirmed by his treating physician and not adjudicated as a possible complication

§ The higher number of procedures than patients indicates both serial procedures that occurred at different times and/or bilateral or multiple joint procedures that occurred in the same treatment session.

**This severe report of pain was not reported on in the literature, but I found it by going through the spreadsheet of events sent to us by Centeno. The study reports that there were no adjudicated severe adverse events but this was very clearly adjudicated according to the spread sheet. It states, “Patient was obese which made the procedure technically challenging”

Appendix Table F19. Non-treatment related AEs reported by across case series assessing cultured/expanded cells in patients with knee OA

Author Year	Age	% Male	Stem Cell Type	Source	Concentration	F/U (mos.)	AE	%	n	N
Orozco 2013	49	50%	MSCs	BM	$1.13 \pm 0.21 \times 10^9$	12	Arthroscopic surgery in contralateral knee	8%	1	12
Orozco 2013	49	50%	MSCs	BM	$1.13 \pm 0.21 \times 10^9$	12	Dental implant	8%	1	12
Orozco 2013	49	50%	MSCs	BM	$1.13 \pm 0.21 \times 10^9$	12	Influenza	8%	1	12
Orozco 2013	49	50%	MSCs	BM	$1.13 \pm 0.21 \times 10^9$	12	Intolerance to gluten and lactose	8%	1	12
Soler 2016	52 (median; range, 33-64)	40%	MSCs	BM	$40.9 \times 10^6 \pm 0.4 \times 10^6$	12, 48	Vaginal hemorrhage (mild)	7%	1	15
Soler 2016	52 (median; range, 33-64)	40%	MSCs	BM	$40.9 \times 10^6 \pm 0.4 \times 10^6$	12, 48	Ovarian cystectomy (serious)	7%	1	15
Soler 2016	52 (median; range, 33-64)	40%	MSCs	BM	$40.9 \times 10^6 \pm 0.4 \times 10^6$	12, 48	Fall (mild)	7%	1	15

AE = adverse event; BM = bone marrow; MSCs = mesenchymal stem/stromal cells

APPENDIX G. List of on-going studies

Appendix Table G1. Current trials of stem cell therapy in the USA

Title	Conditions	Interventions / Control	Study Design	N	Trial Number
Osteoarthritis					
Bone Marrow Aspirate Compared to Platelet Rich Plasma for Treating Knee Osteoarthritis	Knee OA	Pure PRP II vs. Pure BMC	RCT	120	NCT03289416
Efficacy of Micro-fragmented Adipose Tissue Injection for Knee Osteoarthritis.	Knee OA	Microfragmented Adipose Tissue (Lipogems) vs. Corticosteroid injection vs. Saline	RCT	100	NCT03379168
Conventional Platelet-Rich Plasma Versus Concentrated Bone Marrow Stem Cell Injections for Osteoarthritis of the Knee	Knee OA	Concentrated Bone Marrow Aspirate (BMAC) vs. Platelet-Rich Plasma (PRP)	RCT	24	NCT03271229
Intra-articular Transplantation of Autologous Adipose Derived Stromal Vascular Faction (SVF) for Treatment of Osteoarthritis of the Knee	Knee OA	Autologous Adipose-Derived SVF (Stromal Vascular Fraction) vs. Placebo	RCT	30	NCT03940950
Adipose-derived SVF for the Treatment of Knee OA	Knee OA	Low-dose SVF vs. High-dose SVF vs. Placebo	RCT	39	NCT02726945
A Phase 2 Study to Evaluate the Efficacy and Safety of JointStem in Treatment of Osteoarthritis	Knee OA	JointStem (autologous adipose tissue derived mesenchymal stem cells) vs. Synvisc-One (Hyalronic Acid)	RCT	28	NCT02674399
Adipose-Derived Stem Cell Injections for Knee Osteoarthritis	Knee OA	Autologous Adipose-derived Stem Cell injection vs. Corticosteroid injection	RCT	40	NCT03467919
Healing Osteoarthritic Joints in the Wrist With Adult ADRCs	Wrist OA	Adipose-derived stem cell injection vs. Corticosteroid injection	RCT	40	NCT03503305
Safety of Adipose-derived Regenerative Cells Injection for Treatment of Osteoarthritis of the Facet Joint	Facet Joint OA	Adipose-derived stem cell injection vs. Corticosteroid injection	RCT	40	NCT03513731

Title	Conditions	Interventions / Control	Study Design	N	Trial Number
Multicenter Trial of Stem Cell Therapy for Osteoarthritis (MILES)	OA	Autologous Bone Marrow Concentrate (BMAC) vs. Adipose-derived Stromal Vascular Fraction (SVF) vs. Biological: Umbilical Cord Tissue (UCT) vs. Depomedrol and Normal saline (Corticosteroid injection)	RCT	480	NCT03818737
Effect of Implanting Allogenic Cytokines Derived From Human Amniotic Membrane (HAM) and Mesenchymal Stem Cells Derived From Human Umbilical Cord Wharton's Jelly (HUMCWJ) on Pain and Functioning of Knee Osteoarthritis	Knee OA	Human Amniotic Membrane and Mesenchymal Stem Cells Derived From Human Umbilical Cord Wharton's Jelly Injections vs. Wait List Control	Compartive Cohort	60	NCT03337243
Injections of FloGraft Therapy, Autologous Stem Cells, or Platelet Rich Plasma for the Treatment of Degenerative Joint Pain	OA	FloGraft Therapy vs. Autologous Stem Cells vs. Platelet Rich Plasma	Compartive Cohort	300	NCT01978639
Correlating the OA Knee Microenvironment to Outcomes After Regenexx-SD Treatment: A Multi-Site Study	Knee OA	Bone Marrow Concentrate	Case series	600	NCT03898388
Evaluation of Safety and Exploratory Efficacy of an Autologous Adipose-derived Cell Therapy Product for Treatment of Single Knee Osteoarthritis	Knee OA	Autologous Adipose-derived Stromal Vascular Fraction	Case series	125	NCT04043819
Impact of Mesenchymal Stem Cells in Knee Osteoarthritis	Knee OA	Autologous Mesenchymal Stem Cells	Case series	16	NCT03477942
Intra-articular Autologous Bone Marrow Aspirate Injection for Knee Osteoarthritis	Knee OA	BMA Injection	Case series	13	NCT03130335
Safety & Effectiveness of Autologous Regenerative Cell Therapy on Pain & Inflammation of Osteoarthritis of the Hip	Hip OA	StroMed + platelet rich plasma (PRP) injection	Case series	4000	NCT02844764

Title	Conditions	Interventions / Control	Study Design	N	Trial Number
Safety & Effectiveness of Autologous Regenerative Cell Therapy on Pain & Inflammation of Osteoarthritis of the Shoulder	Shoulder OA	StroMed + platelet rich plasma (PRP) injection	Case series	4000	NCT02844738
Outcomes Data of Adipose Stem Cells to Treat Osteoarthritis	OA	Autologous Adipose Stromal Vascular Fraction	Case series	100	NCT02241408
Use of Autologous Adipose-Derived Stromal Vascular Fraction To Treat Osteoarthritis of Hip, Knee, Ankle, and Thumb Joints	OA	SVF injection	Case series	500	NCT03166410
Safety and Clinical Effectiveness of A3 SVF in Osteoarthritis	OA	Autologous Adipose Stromal Vascular Fraction	Case series	30	NCT01947348
Autologous **Culture Expanded** Adipose Derived MSCs for Treatment of Painful Hip OA	Hip OA	Autologous Adipose Derived Mesenchymal Stromal Cells (Single injection vs. Two injections)	RCT	24	NCT03608579
Autologous **Culture Expanded** Mesenchymal Stromal Cells for Knee Osteoarthritis	Knee OA	Autologous Adipose-Derived Mesenchymal Stromal Cells (various doses)	Comparative Cohort	24	NCT02805855
Degenerative Disc Disease					
Mesenchymal Stem Cells for Lumbar Degenerative Disc Disease	DDD	MSC Treatment group 1 (low dose) vs. MSC Treatment group 2 (high dose) vs. Healthy Control (no treatment)	RCT	24	NCT03692221
Study to Evaluate the Safety and Preliminary Efficacy of IDCT, a Treatment for Symptomatic Lumbar Intervertebral Disc Degeneration	DDD	Discogenic Cells + Sodium Hyaluronate Vehicle (low dose) vs. Discogenic Cells + Sodium Hyaluronate Vehicle (high dose) vs. Saline Solution vs. Sodium Hyaluronate	RCT	60	NCT03347708
A Prospective Study of Clinical Outcomes Following a Single Intradiscal Injection of Bone Marrow Aspirate Concentrate (BMAC) for Single Level Discogenic Low Back Pain	DDD	Autologous Bone Marrow Aspirate Concentrate (BMAC) Injection	Case series	20	NCT03912454
Autologous, **Culture-Expanded** Mesenchymal Stromal Cells for Degenerative Disc Disease	DDD	Autologous Adipose-Derived Mesenchymal Stromal Cells (low vs. high dose)	Comparative Cohort	16	NCT03461458

Title	Conditions	Interventions / Control	Study Design	N	Trial Number
Rotator Cuff Tear					
Safety and Efficacy of Adult Adipose-Derived Stem Cell Injection Into Partial Thickness Rotator Cuff Tears	Rotator Cuff Tear	Adipose-derived stem cells vs. Cortisone injection	RCT	15	NCT04077190
Stromal Vascular Fraction Cell Therapy to Improve the Repair of Rotator Cuff Tears	Rotator Cuff Tear	Autologous Stomal Vascular Fraction Material vs. Ringer's solution	RCT	56	NCT03332238
Regenexxâ„¢ SD Versus Exercise Therapy for Rotator Cuff Tears	Rotator Cuff Tear	Regenexx SD vs. Exercise Therapy	RCT	50	NCT01788683
Autologous Adult Adipose-Derived Regenerative Cell Injection Into Chronic Partial-Thickness Rotator Cuff Tears	Rotator Cuff Tear	Adipose Derived Regenerative Cells vs. Corticosteroid	RCT	246	NCT03752827
Other					
Use of Bone Marrow Concentrate for Treatment of Alar, Accessory, and Transverse Ligament Injuries	Craniocervical Injuries	Bone Marrow Concentrate treatment vs. Sham Control	RCT	80	NCT03517761
Regenexx Versus Exercise Therapy for ACL Tears	ACL Tear	Regenexx SD vs. Exercise Therapy	RCT	50	NCT01850758
Mixed Conditions					
Cellular & Biocellular Regenerative Therapy in Musculoskeletal Pain, Dysfunction,Degenerative or Inflammatory Disease	Mixed Conditions	Tissue Stromal Vascular Fraction vs. Normal Saline vs. Platelet Rich Plasma vs. Cellular Stromal Vascular Fraction	Comparative Cohort	300	NCT03090672
Evaluation of Outcomes With Amniotic Fluid for Musculoskeletal Conditions Musculoskeletal Conditions	Mixed Conditions	Amniotic	Case series	200	NCT03390920
Clinical Outcomes of Autologous Bone Marrow Aspirate Concentrate Injections for Musculoskeletal Conditions	Mixed Conditions	Bone Marrow Aspirate Concentrate Injection	Case series	300	NCT02981394

Title	Conditions	Interventions / Control	Study Design	N	Trial Number
A Clinical Registry of Orthobiologics Procedures	Mixed Conditions	Orthobiologic Procedures	Case series	50000	NCT03011398

Appendix Table G2. Current trials of stem cell therapy in countries outside of the USA

Title	Conditions	Interventions	Country	Trial Number
Osteoarthritis				
Clinical Trial to Compare ReJoinTM to Sodium Hyaluronate Injection for Knee Osteoarthritis Cartilage Defects	Knee OA	Biological: ReJoinTM|Drug: Sodium Hyaluronate	China	NCT02855073
The Comparison of Efficacy and Safety of the Mesenchymal Stem Cells From Adipose and Hyaluronic Acid	Knee OA	Biological: Mesenchymal Stem Cells from adipose|Biological: Hyaluronic Acid	China	NCT03357575
Autologous Micro-fragmented Adipose Tissue Injection for Knee Osteoarthritis	Knee OA	Device: Lipogems	China	NCT03788265
Clinical Study of Pulp Mesenchymal Stem Cells in the Treatment of Primary Mild to Moderate Knee Osteoarthritis	Knee OA	Biological: Low Dose of Mesenchymal stem cell|Biological: High Dose of Mesenchymal stem cell|Drug: Sodium Hyaluronate	China	NCT04130100
Mesenchymal Stem Cell Transplantation for Osteoarthritis	Knee OA	Biological: Auotologous BMSCs plus autologous PRP|Biological: Auotologous PRP	China	NCT03969680
Treatment of Early Knee Osteoarthritis With Autologous Adipose-derived Mesenchymal Stem Cells	Knee OA	Drug: Autologous adipose-derived mesenchymal stem cells|Procedure: abdominal liposuction	China	NCT03956719
Effectiveness of Autologous Adipose-derived Stem Cells in the Treatment of Knee Cartilage Injury	Knee OA	Other: Autologous Adipose-derived Mesenchymal Stem Cell Gel|Drug: Sodium Hyaluronate|Procedure: Extraction of abdominal fat	China	NCT03955497

Title	Conditions	Interventions	Country	Trial Number
The Maximum Tolerated Dose of Mesenchymal Stem Cells From Umbilical Cord	Knee OA	Drug: mesenchymal stem cells	China	NCT03357770
Clinical Study of Umbilical Cord Mesenchymal Stem Cells (UC-MSC) for Treatment of Knee Osteoarthritis	Knee OA	Biological: Umbilical-cord mesenchymal stromal cells (UC-MSCs)|Other: Hyaluronic acid	China	NCT03166865
The Safety/Efficacy of Human Umbilical Cord Mesenchymal Stem Cells Therapy for Patients With Osteoarthritis	Knee OA	Biological: Low dose mesenchymal stem cells|Biological: High dose mesenchymal stem cells|Procedure: Intraarticular injection	China	NCT03383081
Intra-articular Injection of MSCs in Treatment of Knee OA	Knee OA	Biological: Placenta Derived Mesenchymal Stem Cell|Drug: Sodium Hyaluronate	China	NCT03028428
Very Small Embryonic-like Stem Cells for Knee Osteoarthritis	Knee OA	Biological: very small embryonic-like stem cell	China	NCT03975101
Evaluating Safety and Efficacy of Mesenchymal Stem Cells From Umbilical Cord	Knee OA	Drug: mesenchymal stem cells from umbilical cord	China	NCT03358654
A Study Evaluating the Efficacy of a Single Injection Autologous Adipose Derived Mesenchymal Stromal Cells in Patients With Knee Osteoarthritis	Knee OA	Biological: Injection (2x106 ASC/5ml).|Biological: Injection (10x106 ASC/5ml).|Other: Placebo	France	NCT02838069
Transplantation of Bone Marrow Stem Cells Stimulated by Proteins Scaffold to Heal Defects Articular Cartilage of the Knee	Knee OA	Procedure: Transplantation of Bone Marrow Stem Cells Activated in Knee Arthrosis	France	NCT01159899
Safety and Efficacy of Autologous Bone Marrow Stem Cells for Treating Osteoarthritis	Knee OA	Other: Autologous bone marrow stem cells	India	NCT01152125
Mesenchymal Stem Cells Enhanced With PRP Versus PRP In OA Knee	Knee OA	Biological: Mesenchymal stem cell suspension|Biological: PRP	India	NCT01985633
Implantation of Allogenic Mesenchymal Stem Cell From Umbilical Cord Blood for Osteoarthritis Management	Knee OA	Drug: Hyaluronic Acid|Biological: Umbilical Cord Mesenchymal Stem Cell|Biological: Recombinant Human Somatropin	Indonesia	NCT03800810

Title	Conditions	Interventions	Country	Trial Number
Stem Cell Transplantation for the Treatment of Knee Osteoarthritis	Knee OA	Biological: Autologous Stem Cell Transplantation	Iran	NCT00550524
The Effects of Stromal Vascular Fraction and Mesenchymal Stem Cells as Intra-articular Injection in Knee Joint Osteoarthritis	Knee OA	Biological: Mesenchymal stem cell|Biological: Placebo	Iran	NCT03164083
Treatment for Knee Osteoarthritis With Injections of BMC at the Bone-cartilage Interface. Pilot Study	Knee OA	Biological: Injection of autologous concentrated bone marrow aspirate	Italy	NCT03110666
Evaluation of Effectiveness of Combined Intra-articular and Intra-osseus Injection VS a Single Intra-articular Injection of Bone Marrow Concentrate	Knee OA	Biological: Bone Marrow Concentrate	Italy	NCT03876795
Randomized Double-blind Study on the Treatment of Osteoarthritis of the Bilateral Knee: Autologous Bone Marrow Concentrate vs. Hyaluronic Acid	Knee OA	Biological: injection of autologous bone marrow concentrate|Biological: injection of hyaluronic acid.	Italy	NCT03110679
Subchondral and Intra-articular Application of Bone Marrow Concentrate for Knee Unicompartmental OA	Knee OA	Biological: Subchondral and intra-articular injection of BMC	Italy	NCT03790189
Use of Adipose Tissue Derived Mesenchymal Stem Cells for Knee Osteoarthrosis	Knee OA	Biological: Adipose tissue derived mesenchymal stem cell	Jordan	NCT02966951
Use of Wharton Jelly Derived Mesenchymal Stem Cells for Knee Osteoarthrosis	Knee OA	Biological: Wharton Jelly derived mesenchymal stem cell	Jordan	NCT02963727
Safety of Allogeneic Bone Marrow Derived Mesenchymal Stem Cells in Subjects With Osteoarthritis	Knee OA	Biological: Human allogeneic mesenchymal bone marrow derived stem cells	Mexico	NCT03602872
Autologous Stromal Vascular Fraction of Cells for Treatment of Knee Articular Cartilage Dystrophy	Knee OA	Procedure: Liposuction|Other: SVF isolation|Other: Intraarticular administration of autologous SVF	Russia	NCT02827851
Knee Osteoarthritis Treatment With Adipose-derived Stem Cells: Phase II Clinical Trial	Knee OA	Biological: Stem cells	Saudi Arabia	NCT03308006

Title	Conditions	Interventions	Country	Trial Number
The Evaluation of Safety and Effectiveness of Intraarticular Administration of Autologous Stromal-Vascular Fraction of Adipose Tissue Cells for Treatment of Knee Joint Arthrosis	Knee OA	Biological: Stromal-vascular fraction	Serbia	NCT04050111
A Phase 3 Study to Evaluate the Efficacy and Safety of JointStem in Treatment of Osteoarthritis	Knee OA	Biological: JOINTSTEM|Drug: saline	South Korea	NCT03990805
Follow-up Study for Participants Jointstem Clinical Trial	Knee OA	Drug: Jointstem	South Korea	NCT03509025
Evaluate Safety and Explore Efficacy of SMUP-IA-01 in Patients With Knee Osteoarthritis	Knee OA	Biological: SMUP-IA-01(low-dose)|Biological: SMUP-IA-01(mid-dose)|Biological: SMUP-IA-01(high-dose)	South Korea	NCT04037345
Treatment of Osteoarthritis by Intra-articular Injection of Bone Marrow Mesenchymal Stem Cells With Platelet Rich Plasma	Knee OA	Biological: 100 million Bone marrow mesenchimal stem cells|Biological: Platelet Rich plasma (PRGF)	Spain	NCT02365142
Clinical Investigation to Compare the Safety and Efficacy of Cellular Matrix to Those of OstenilÂ® Plus and to Those of PRP Only	Knee OA	Device: Cellular Matrix / A-CP HA|Device: OstenilÂ® Plus|Device: RegenKit-BCT-1	Switzerland	NCT02964143
Adipose-derived Stem Cells (ADSCs) for Knee Osteoarthritis	Knee OA	Biological: Elixcyte 8 ml|Device: Hya Joint Plus|Biological: Elixcyte 4 ml|Biological: Elixcyte 2 ml	Taiwan	NCT02784964
A Dose- Escalation Phase I Study to Evaluate Safety and Phase II Study to Evaluate Efficacy of GXCPC1 to Osteoarthritis	Knee OA	Drug: GXCPC1|Device: HA	Taiwan	NCT03943576
Allogeneic Bone Marrow MSC Therapy for Knee Osteoarthritis	Knee OA	Biological: ChondrochymalÂ®	Taiwan	NCT03589287
Mesenchymal Stem Cell Treatment for Primary Osteoarthritis Knee	Knee OA	Drug: Adipose-Derived Mesenchymal Stem Cells	Taiwan	NCT02544802
BMAC in Severe Hip or Knee Osteoarthritis Awaiting Arthroplasty	Knee & Hip OA	Biological: Bone Mineral Aspirate Concentrate (BMAC)	Canada	NCT03908827
BMA vs Cortisone for Glenohumeral Osteoarthritis	Shoulder OA	Drug: Cortisone|Biological: Bone Marrow Aspirate	Canada	NCT03580148

Title	Conditions	Interventions	Country	Trial Number
Bone Marrow Aspirate Concentrate Use in Hip Osteoarthritis	Hip OA	Procedure: BMAC/PRP Injection|Procedure: Cortisone Injection	Canada	NCT03410355
The Combined Use of PRP With Lipoaspirate and/or Bone Marrow Aspirate in Osteoarthritis	OA	Biological: Autologous cell therapy	Canada	NCT03984461
Intra-Articular Autologous Bone Marrow Mesenchymal Stem Cells Transplantation to Treat Mild to Moderate Osteoarthritis	OA	Drug: Hyaluronic Acid|Biological: Autologous bone marrow-derived mesenchymal stem cells	Malaysia	NCT01459640
Adipose-derived Mesenchymal Stem Cells in Osteoarthritis	OA	Biological: Intra-articular injection of ADMSC	Poland	NCT03869229
Wharton's Jelly-derived Mesenchymal Stem Cells in Osteoarthritis	OA	Biological: Intraarticular injection of WJMSC	Poland	NCT03866330
Tendon and Ligament Conditions				
Treatment of Tendon Injury Using Mesenchymal Stem Cells	Lateral Epicondylitis	Biological: ALLO-ASC(allogeneic adipose derived mesenchymal stem cell) injection	South Korea	NCT01856140
Treatment of Intractable Common Extensor Tendon Injury Using Mesenchymal Stem Cells (Allo-ASC)	Lateral Epicondylitis	Biological: High concentration of Allo-ASC|Biological: Low concentration of Allo-ASC|Drug: Fibrin glue|Drug: Normal saline	South Korea	NCT03449082
Treatment of Tendon Disease Using Autologous Adipose-derived Mesenchymal Stem Cells	Rotator Cuff Tear &Lateral Epicondylitis	Biological: Autologous adipose-derived MSCs|Drug: Compound betamethasone	China	NCT03279796
Autologous Stem Cells in Achilles Tendinopathy	Achilles Tendinitis	Biological: Autologous Mesenchymal Stem Cells	UK	NCT02064062
Treatment of Refractory Patellar Tendinopathy With Mesenquimal Trunk Cells. Comparative Study With PRP.	Patellar Tendinopathy	Procedure: mesenchymal stem cells|Procedure: Pure platelet-rich plasma	Spain	NCT03454737
Effectiveness and Safety of Autologous ADRC for Treatment of Anterior Cruciate Ligament Partial Rupture	Anterior Cruciate Ligament Partial Rupture	Procedure: Liposuction|Device: ADRC isolation|Procedure: Arthroscopic surgery|Other: Intraarticular administration of autologous ADRC	Russia	NCT02469792
Degenertive Disc Disase				

Title	Conditions	Interventions	Country	Trial Number
Autologous Adipose Derived Stem Cell Therapy for Intervertebral Disc Degeneration	DDD	Other: autologous adipose derived mesenchymal stem cell	South Korea	NCT02338271
Rotator Cuff				
Mesenchymal Stem Cells in Rotator Cuff Repair	Rotator Cuff Tear|Tendon Injuries|Mesenchymal Stem Cell	Biological: Mesenchymal stem cell|Procedure: Rotator cuff repair	Brazil	NCT03362424
Clinical Study on Mesenchymal Stem Cells Used in the Reconstruction Surgery of the Supraspinatus Muscle Lesions	Rotator Cuff Tear	Biological: mesenchymal stem cells|Procedure: without mesenchymal stem cells	Czech Republic	NCT03068988
Efficacy of Microfragmented Lipoaspirate Tissue in Arthroscopic Rotator Cuff Repair	Rotator Cuff Tears	Procedure: arthroscopic rotator cuff repair|Procedure: autologous micro-fragmented adipose tissue	Italy	NCT02783352
Treatment of Tendon Injury Using Allogenic Adipose-derived Mesenchymal Stem Cells (Rotator Cuff Tear)	Rotator Cuff Tear	Biological: allogenic adipose stem cell treatment	South Korea	NCT02298023
Mensenchymal Stem Cell (MSC) Included in OrthADAPT Membrane for Rotator Cuff Tears Repair	Rotator Cuff Tear	Biological: Mesenchymal Stem Cells (MSCs)|Biological: OrthADAPT	Spain	NCT01687777

APPENDIX H. Clinical Expert Peer Review

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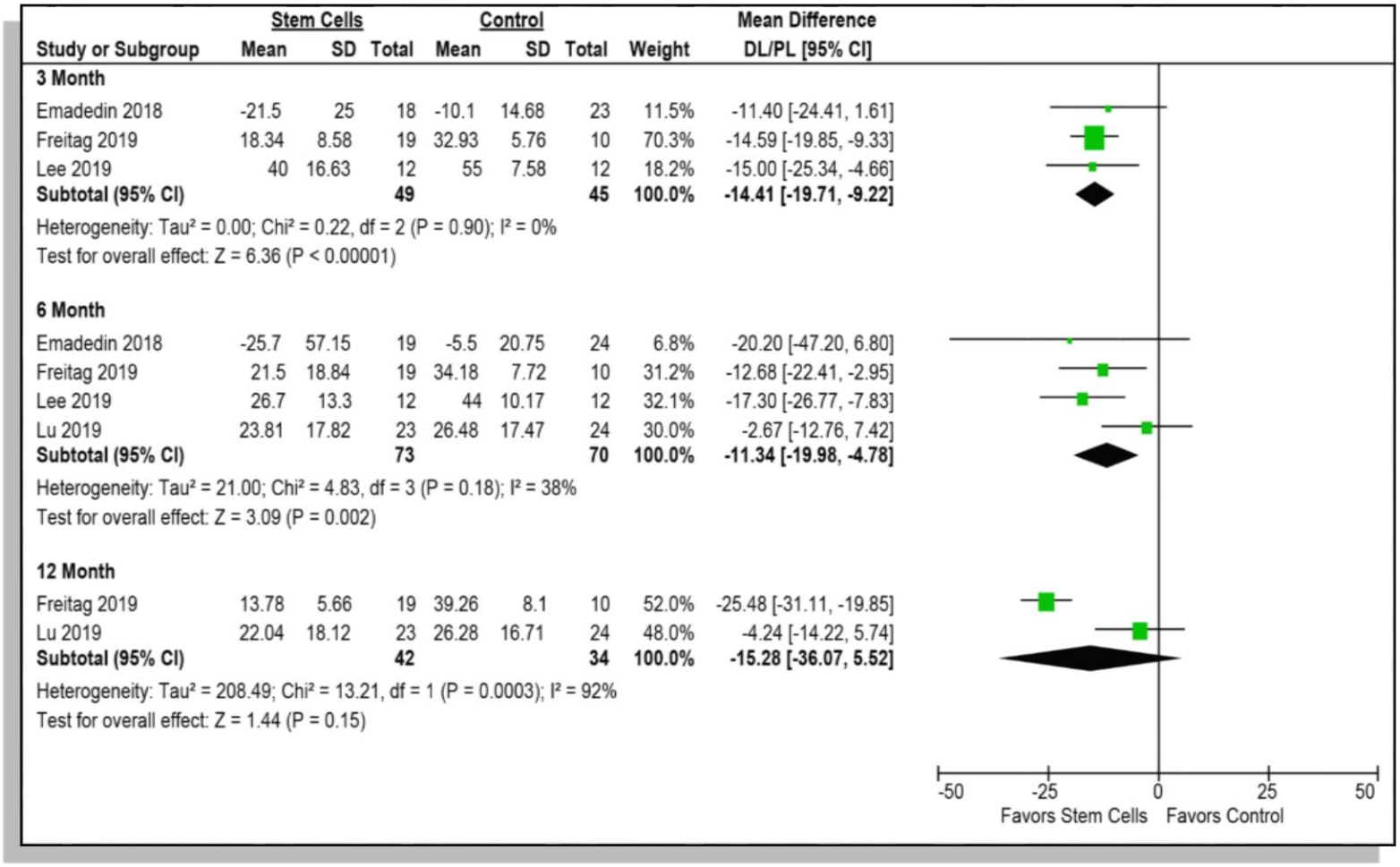
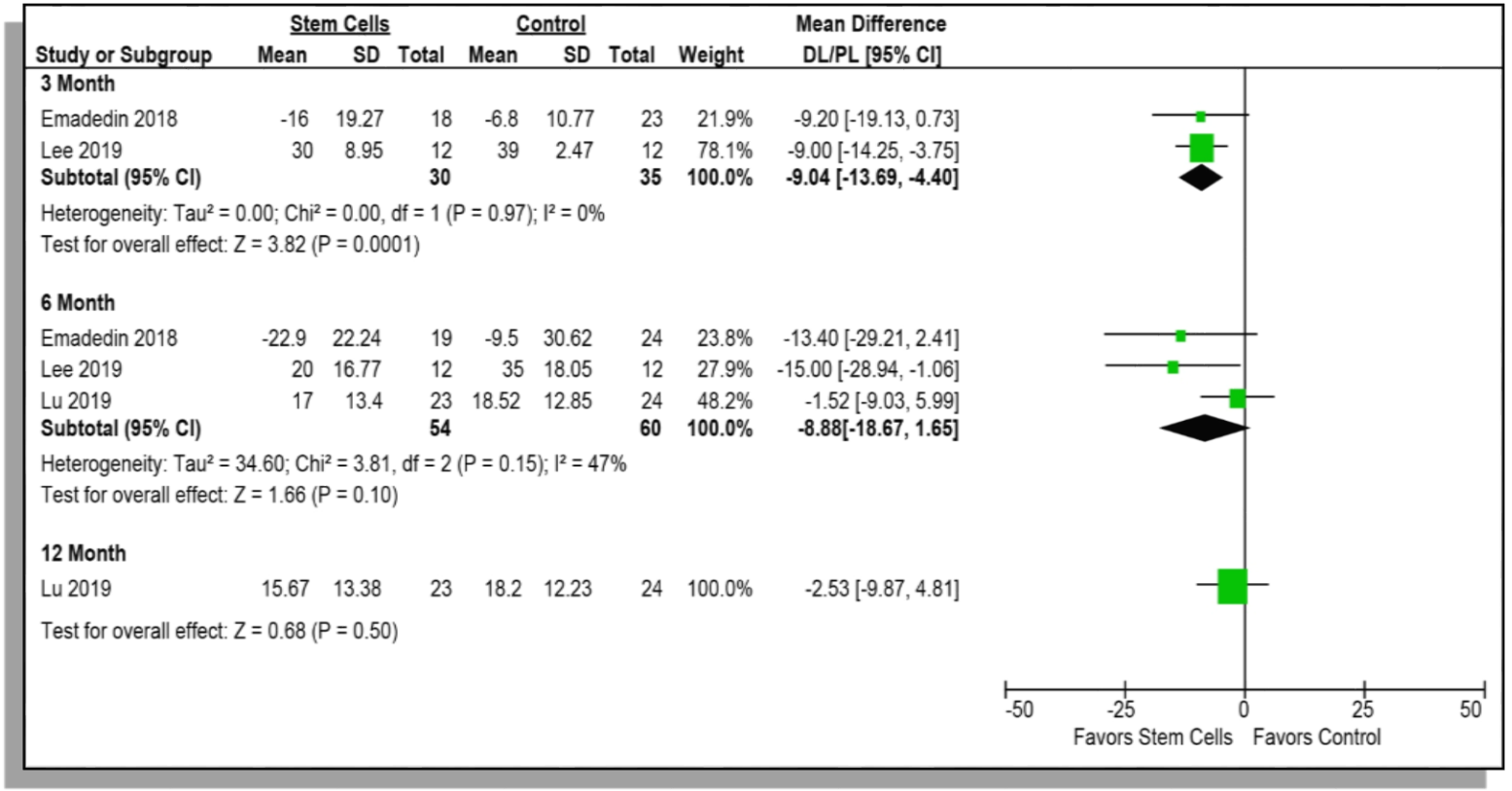
APPENDIX I. Sensitivity Analyses for outcomes from RCTs evaluating autologous, culture-expanded stem cell therapy for the treatment of knee OA

Appendix Figure I1. Autologous, culture-expanded stem cells for knee OA – sensitivity analysis of the WOMAC total follow-up scores from RCTs excluding Lamo-Espinosa 2016/2018.



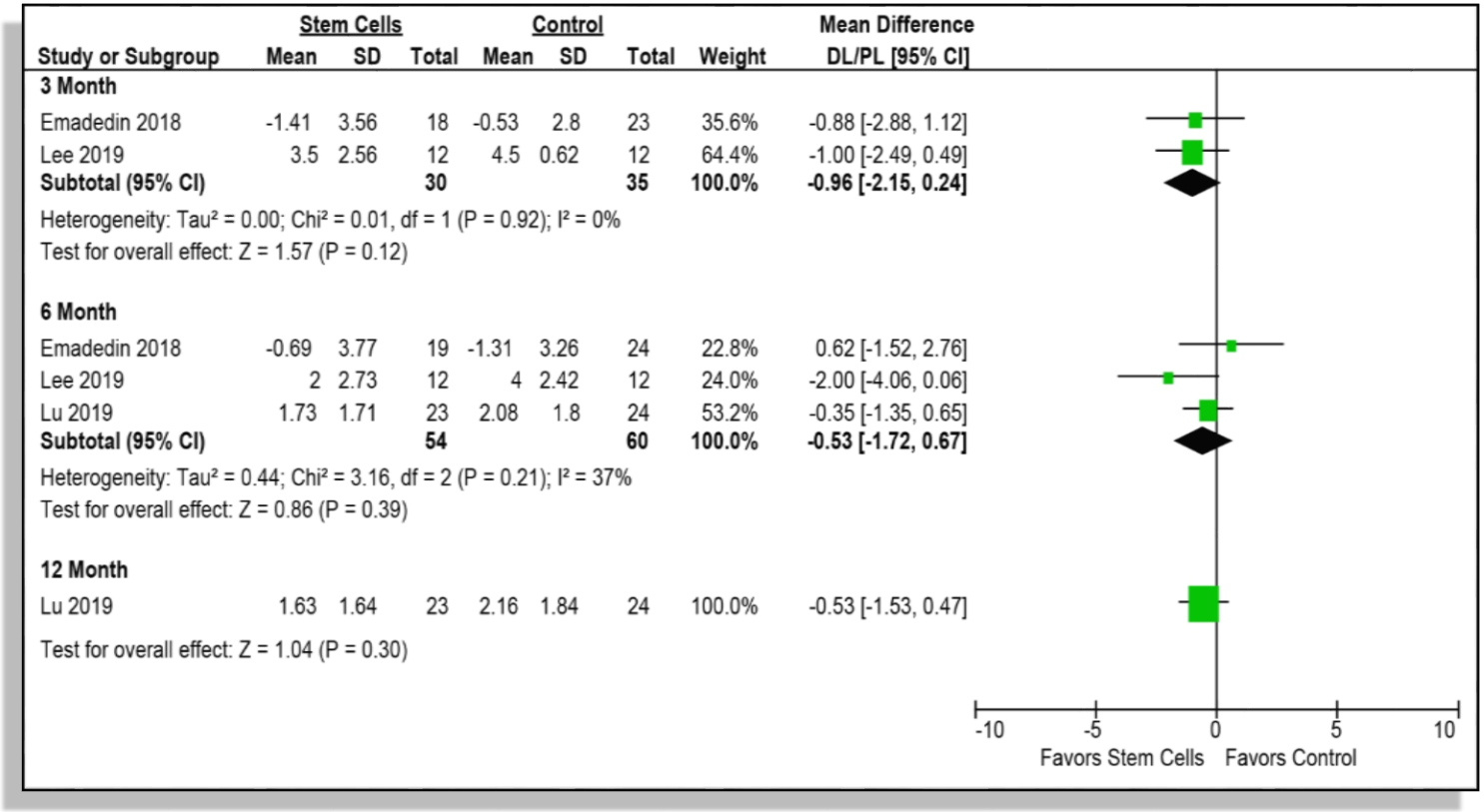
AD-MSC: adipose-derived mesenchymal stem cells; AD-MPC: adipose-derived mesenchymal progenitor cells; BM-MSC: bone marrow-derived mesenchymal stem cells; CI = confidence interval; HA = hyaluronic acid; Mod = moderately; OA = osteoarthritis; RoB = risk of bias; SD = standard deviation; UC = usual care (i.e., conservative care); WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Appendix Figure I2. Autologous, culture-expanded stem cells for knee OA – sensitivity analysis of the WOMAC physical function follow-up scores from RCTs excluding Lamo-Espinosa 2016/2018.



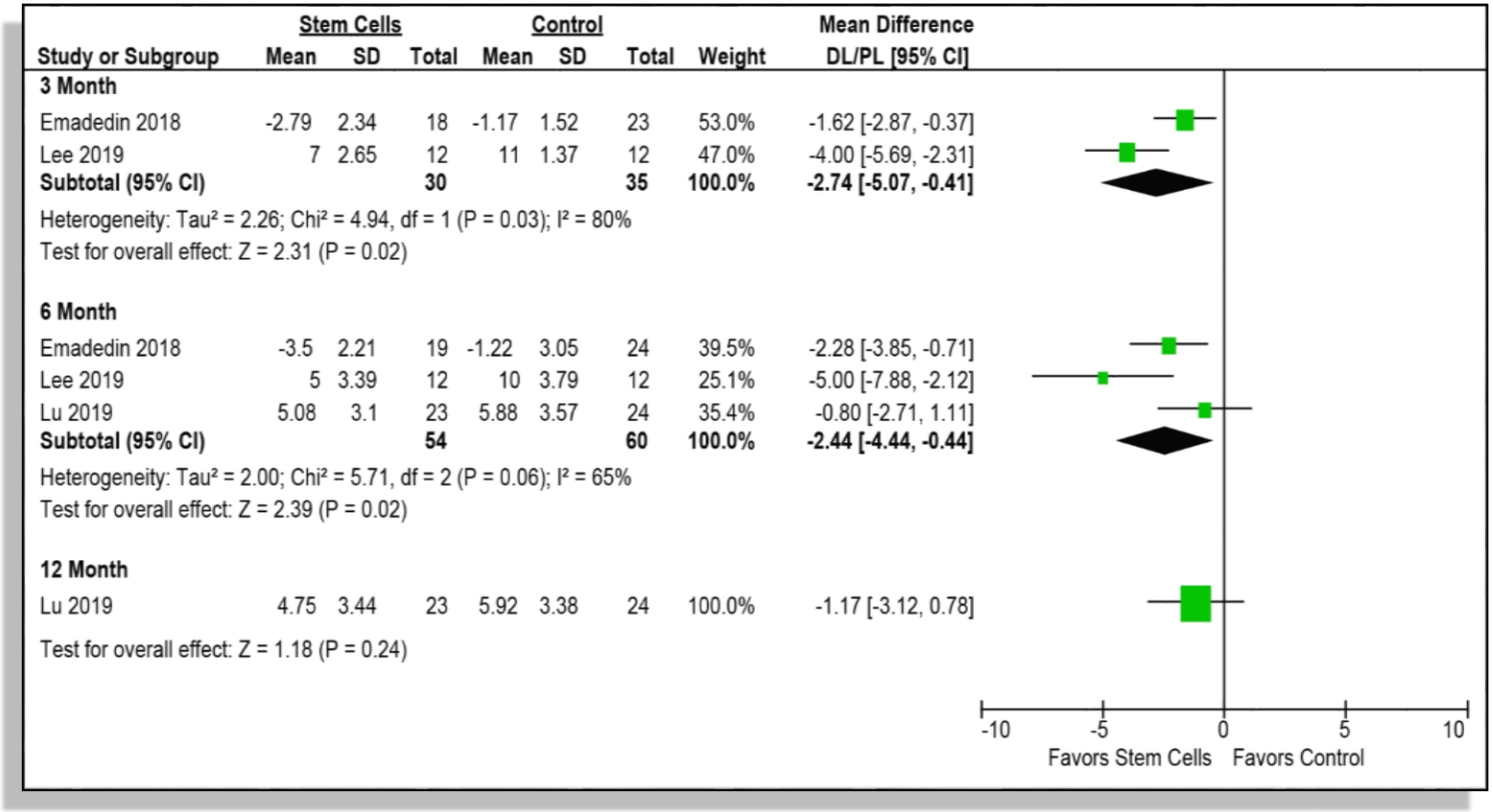
AD-MSC: adipose-derived mesenchymal stem cells; AD-MPC: adipose-derived mesenchymal progenitor cells; BM-MSC: bone marrow-derived mesenchymal stem cells; CI = confidence interval; HA = hyaluronic acid; Mod = moderately; OA = osteoarthritis; RoB = risk of bias; SD = standard deviation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Appendix Figure I3. Autologous, culture-expanded stem cells for knee OA – sensitivity analysis of the WOMAC stiffness follow-up scores from RCTs excluding Lamo-Espinosa 2016/2018.



AD-MSC: adipose-derived mesenchymal stem cells; AD-MPC: adipose-derived mesenchymal progenitor cells; BM-MSC: bone marrow-derived mesenchymal stem cells; CI = confidence interval; HA = hyaluronic acid; Mod = moderately; OA = osteoarthritis; RoB = risk of bias; SD = standard deviation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Appendix Figure I4. Autologous, cultured-expanded stem cells for knee OA – sensitivity analysis of the WOMAC pain follow-up scores from RCTs excluding Lamo-Espinosa 2016/2018.



AD-MSC: adipose-derived mesenchymal stem cells; AD-MPC: adipose-derived mesenchymal progenitor cells; BM-MSC: bone marrow-derived mesenchymal stem cells; CI = confidence interval; HA = hyaluronic acid; Mod = moderately; OA = osteoarthritis; RoB = risk of bias; SD = standard deviation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

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