

## Appendix A. Inclusion Criteria and Search Strategy

**Appendix Table A1. PICO inclusion/exclusion criteria: Intervertebral disc repair**

Study Component	Inclusion	Exclusion
<b>Participants</b>	<ul style="list-style-type: none"> <li>• Adult patients with symptomatic cervical or lumbar DDD or disc prolapse presenting for initial treatment</li> </ul>	<ul style="list-style-type: none"> <li>• Skeletally immature patients</li> <li>• History of tumor implantation at the site</li> <li>• Infection</li> <li>• Patients with SCI</li> <li>• Patients with any prior surgery (e.g., fusion) and/or revision surgery at the index level</li> </ul>
<b>Intervention</b>	<ul style="list-style-type: none"> <li>• Mesenchymal Cells, either bone or adipose-derived (in any type of preparations and concentrations) or other “stem” cells injected into the disc; chondrocytes.</li> </ul>	<ul style="list-style-type: none"> <li>• Adjunctive treatments (e.g. spinal steroid injections, PRP)</li> <li>• Surgical procedures in addition to stem cell treatment (e.g. fusion)</li> </ul>
<b>Comparator(s)</b>	<ul style="list-style-type: none"> <li>• Conservative care (including pharmacological care, physical therapy, rehabilitation, etc.)</li> <li>• Disc-preserving injection treatments including steroid injection (outside of the disc), platelet-rich plasma (PRP), etc.</li> <li>• Surgical treatment (e.g. for disc prolapse)</li> </ul>	
<b>Outcomes</b>	<p><b>Primary Outcomes:</b> Validated measures for</p> <ul style="list-style-type: none"> <li>• Function</li> <li>• Pain</li> </ul> <p><b>Secondary or intermediate outcomes</b></p> <ul style="list-style-type: none"> <li>• HRQoL (validated measures)</li> <li>• Radiographic outcomes (disc height and motion segment preservation)</li> <li>• Symptomatic Adjacent Segment Pathology (ASP)</li> </ul> <p><b>Adverse events, harms, complications</b></p> <ul style="list-style-type: none"> <li>• Peri-procedural complications</li> <li>• Need for subsequent treatment (including surgical intervention)</li> </ul> <p><b>Economic Outcomes</b> (e.g. ICER or other measures of comparative cost effectiveness)</p>	<ul style="list-style-type: none"> <li>• Non-clinical outcomes</li> <li>• Radiographic outcomes other than disc height and motion</li> </ul>
<b>Study Design</b>	<ul style="list-style-type: none"> <li>• Comparative studies (RCTs, cohort studies with concurrent controls) to address efficacy, effectiveness and safety, with a focus on those with least risk of bias</li> <li>• For Key Question 3, studies that are sufficiently powered to detect treatment modification</li> <li>• Well-designed prospective case series of <math>\geq 20</math> patients (<i>if</i> no comparative studies identified)</li> </ul>	<ul style="list-style-type: none"> <li>• In vitro studies, animal studies</li> <li>• Case reports</li> <li>• If included, case series with &lt;10 patients</li> <li>• Comparative studies with &lt;10 patients per treatment group</li> </ul>

	<ul style="list-style-type: none"> <li>• Full economic studies (e.g. ICER, other measure of comparative cost effectiveness)</li> </ul>	
<b>Publication</b>	<ul style="list-style-type: none"> <li>• Studies published in English in peer reviewed journals, publically published HTAs or available FDA reports</li> </ul>	<ul style="list-style-type: none"> <li>• Abstracts, editorials, letters</li> <li>• Duplicate publications of the same study which do not report on different outcomes</li> <li>• Single reports from multicenter trials</li> <li>• Studies reporting on the technical aspects of biologics use in fusion surgery</li> <li>• White papers</li> <li>• Narrative reviews</li> <li>• Articles identified as preliminary reports when results are published in later versions</li> </ul>
<b>Time</b>	<ul style="list-style-type: none"> <li>• Intended focus on outcomes with at least 12 months follow up</li> </ul>	<ul style="list-style-type: none"> <li>• None</li> </ul>

#### Updated Search Strategy

Dates: Inception through 10-31-2018

	<b>Search terms</b>	<b>Citations</b>
	<b>Cervical</b>	
1.	Neck Pain [MeSH] OR Cervical Vertebrae [MeSH] OR "cervical vertebrae" [TIAB] OR cervical [TIAB]	217,179
2.	Intervertebral Disc* [TIAB] OR intradiscal [TIAB] OR Disc* [TIAB] OR Disk* [TIAB] OR Intervertebral Disc [Mesh] OR Intervertebral Disc Degeneration [mesh] OR Intervertebral Disc Degen* [TIAB] OR degen* disc [TIAB] OR intervertebral disc disease [TIAB] OR degen* disc disease [TIAB] OR Degen* intervertebral disc [TIAB] OR disc prolapse [TIAB] OR disc prolapse [mesh]	4992
3.	#1 AND #2	<b>526</b>
4.	"Transplantation, Autologous"[Mesh] OR Regenerative Medicine [mesh] OR Stem cells [Mesh] OR Mesenchymal Stem Cells [Mesh] OR mesenchymal stem cell transplantation [Mesh] OR stem cell transplantation [Mesh] OR adult stem cells [mesh] OR Multipotent Stem Cells [Mesh] OR "Hematopoietic Stem Cells"[Mesh] OR chondrocytes [Mesh] OR Osteoblasts [Mesh]	323048
5.	Cell therapy [TIAB] OR Autologous cell therapy [TIAB] OR disc regen* [TIAB] OR disc repair [TIAB] OR intervertebral disc repair [TIAB] OR intervertebral disc injection [TIAB] OR stem cell [TIAB] OR progenitor cell [TIAB] OR stromal cell [TIAB] OR bone marrow [TIAB] OR bone marrow aspirat* [TIAB] OR Bone marrow concentrate [TIAB] OR mesenchymal cell [TIAB] OR multipotent stromal cells [TIAB] OR adipose tissue-derived cell* [TIAB] OR adipose-derived cell* [TIAB] OR Lipoaspirate [TIAB] OR disc cell [TIAB] OR nucleus pulposus cell [TIAB] OR "stromal vascular fraction" [TIAB] OR chondrocytes [TIAB]	48

	OR Osteoblasts [TIAB] "notochordal cells" [TIAB]	
6.	#4 OR #5	<b>323076</b>
7.	#3 AND #6	<b>21</b>

	<b>Search terms</b>	<b>Citations</b>
	<b>Lumbar</b>	
1.	Lumbar Vertebrae [MeSH] OR "Lumbar Vertebrae" [TIAB] OR thoracolumbar[TIAB] OR "Low Back Pain" [TIAB] OR Lumbar [TIAB]	217,179
2.	Intervertebral Disc* [TIAB] OR intradiscal [TIAB] OR Disc* [TIAB] OR Disk* [TIAB] OR Intervertebral Disc [Mesh] OR Intervertebral Disc Degeneration [mesh] OR Intervertebral Disc Degen* [TIAB] OR degen* disc [TIAB] OR intervertebral disc disease [TIAB] OR degen* disc disease [TIAB] OR Degen* intervertebral disc [TIAB] OR disc prolapse [TIAB] OR disc prolapse [mesh]	4992
3.	#1 AND #2	<b>2598</b>
4.	"Transplantation, Autologous"[Mesh] OR Regenerative Medicine [mesh] OR Stem cells [Mesh] OR Mesenchymal Stem Cells [Mesh] OR mesenchymal stem cell transplantation [Mesh] OR stem cell transplantation [Mesh] OR adult stem cells [mesh] OR Multipotent Stem Cells [Mesh] OR "Hematopoietic Stem Cells"[Mesh] OR chondrocytes [Mesh] OR Osteoblasts [Mesh]	323,048
5.	Cell therapy [TIAB] OR Autologous cell therapy [TIAB] OR disc regen* [TIAB] OR disc repair [TIAB] OR intervertebral disc repair [TIAB] OR intervertebral disc injection [TIAB] OR stem cell [TIAB] OR progenitor cell [TIAB] OR stromal cell [TIAB] OR bone marrow [TIAB] OR bone marrow aspirat* [TIAB] OR Bone marrow concentrate [TIAB] OR mesenchymal cell [TIAB] OR multipotent stromal cells [TIAB] OR adipose tissue-derived cell* [TIAB] OR adipose-derived cell* [TIAB] OR Lipoaspirate [TIAB] OR disc cell [TIAB] OR nucleus pulposus cell [TIAB] OR "stromal vascular fraction" [TIAB] OR chondrocytes [TIAB] OR Osteoblasts [TIAB] "notochordal cells" [TIAB]	48
6.	#4 OR #5	<b>323076</b>
7.	#3 AND #6	
8.	#7 NOT ( in vitro [TIAB] OR animal* [TIAB] OR rat* [TIAB] OR mouse [TIAB] OR mice [TIAB] OR canine [TIAB] OR dog* [TIAB] OR goat* [TIAB] OR primate* [TIAB] OR ape* [TIAB] OR rabbit* [TIAB] )	<b>153</b>
9.	Filters: Humans, English	<b>119</b>

## Appendix B. Risk of Bias Assessment for Individual Studies

Appendix Table B1. Criteria for risk of bias assessment

Risk of Bias Description	Studies of Therapy	
	Study design	Criteria
<p><b>Low risk:</b></p> <p>Study adheres to commonly held tenets of high quality design, execution and avoidance of bias</p>	Good quality RCT	<ul style="list-style-type: none"> <li>• Random sequence generation</li> <li>• Allocation concealment</li> <li>• Intent-to-treat analysis</li> <li>• Blind or independent assessment for author's primary important outcomes*</li> <li>• Co-interventions applied equally</li> <li>• F/U rate of 80%+ and &lt;10% difference in follow-up between groups</li> <li>• Controlling for possible confounding†</li> </ul>
<p><b>Moderately low risk:</b></p> <p>Study has potential for some bias; study does not meet all criteria for a good quality RCT, but deficiencies not likely to invalidate results or introduce significant bias</p>	Moderate quality RCT	<ul style="list-style-type: none"> <li>• Violation of one or two of the criteria for good quality RCT</li> </ul>
	Good quality cohort	<ul style="list-style-type: none"> <li>• Blind or independent assessment in a prospective study, or use of reliable data‡ in a retrospective study</li> <li>• Co-interventions applied equally</li> <li>• F/U rate of 80%+ and &lt;10% difference in follow-up between groups</li> <li>• Controlling for possible confounding†</li> </ul>
<p><b>Moderately High risk:</b></p> <p>Study has significant flaws in design and/or execution that increase potential for bias that may invalidate study results</p>	Poor quality RCT	<ul style="list-style-type: none"> <li>• Violation of three or more of the criteria for a good quality RCT</li> </ul>
	Moderate or poor quality cohort	<ul style="list-style-type: none"> <li>• Violation of any of the criteria for good quality cohort</li> </ul>
	Case-control	<ul style="list-style-type: none"> <li>• Any case-control design</li> </ul>
<p><b>High risk:</b></p> <p>Study has significant potential for bias; lack of comparison group precludes direct assessment of important outcomes</p>	Case series	<ul style="list-style-type: none"> <li>• Any case series design</li> </ul>

\* Outcome assessment is independent of healthcare personnel, investigator or patient judgment.

† Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups. RCTs get credit if there is a similar distribution of baseline characteristics between groups but must also control for confounding if distribution is not similar.

‡ Reliable data are data such as mortality or re-operation

**Appendix Table B2. Risk of Bias for Comparative Trials of Intervertebral Disc Repair**

Methodological Principle	Noriega 2017	Tschugg 2016 <sup>‡</sup>
<b>Study design</b>		
Randomized controlled trial	■	■
Prospective Cohort Study		
Retrospective Cohort Study		
Prospective Case Series		
Retrospective Case Series		
Random sequence generation*	Yes	Yes
Concealed allocation*	Yes	No
Intention-to-treat*	Yes	No
Independent/blind assessment	No (patient-reported) Yes (radiographic) <sup>§</sup>	No
Complete follow-up of $\geq 80\%$	Unclear**	Yes
<10% difference in follow-up between groups	Yes	No
Controlling for possible confounding <sup>†</sup>	Unclear <sup>††</sup>	No
<b>Risk of Bias</b>	<b>Moderately High</b>	<b>Moderately High</b>

\*Applies only to randomized controlled trials

<sup>†</sup>Groups must be comparable on baseline characteristics or evidence of control for confounding present

<sup>‡</sup>Tschugg presents only preliminary safety results of an ongoing trial.

<sup>§</sup>Patient-reported outcomes cannot be 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.

<sup>††</sup> Group population characteristics were not reported separately. No table of baseline demographics by group provided.

**Appendix Table B3. Risk of Bias for Case Series of Intervertebral Disc Repair**

Methodological Principle	Centeno 2017	Coric 2013	Haufe 2006	Kumar 2017	Orozco 2011	Pettine 2015, 2016, 2017
<b>Study design</b>						
Randomized controlled trial						
Prospective Cohort Study						
Retrospective Cohort Study						
Prospective Case Series		■	■			■
Retrospective Case Series	■			■	■	
Random sequence generation*	N/A	N/A	N/A	N/A	N/A	N/A
Concealed allocation*	N/A	N/A	N/A	N/A	N/A	N/A
Intention-to-treat*	N/A	N/A	N/A	N/A	N/A	N/A
Independent/blind assessment	No	No	No	Unclear §	No	No (patient-reported) Yes (radiographic) ‡
Complete follow-up of ≥80%	Yes (clinical) No (radiographic)**	Unclear††	Unclear††	Unclear††	Unclear††	Unclear††
Controlling for possible confounding†	N/A	N/A	N/A	N/A	N/A	N/A
<b>Risk of Bias</b>	<b>High</b>	<b>High</b>	<b>High</b>	<b>High</b>	<b>High</b>	<b>High</b>

N/A, not applicable

\*Applies only to randomized controlled trials

†Groups must be comparable on baseline characteristics or evidence of control for confounding present.

‡ Radiological assessments were conducted by a blinded assessor. All other aspects were unblinded.

§ Although authors describe the study as an ‘open-label’ study, they also indicate that patients and providers were blinded.

\*\* Based on their primary outcome (SANE) they achieved 90%. For all other clinical and radiographic outcomes they did not achieve >80%.

†† Percent f/u cannot be determined as number of eligible patients, loss to follow-up, and/or patient selection criteria were not adequately described; potential for selection bias is of concern.

### Appendix C. List of current on-going trials

Trial ID: NCT02529566

Title: Human Autograft Mesenchymal Stem Cell Mediated Stabilization of The Degenerative Lumbar Spine

Status: Estimated Completion in July 2018

<https://clinicaltrials.gov/ct2/show/record/NCT02529566>

Trial ID: CT01513694

Title: Clinical Trial Phase I / II Prospective, Open, Non-randomized for Treatment of Lumbar Intervertebral Degenerative Disc Disease With Posterolateral Instrumented and Autologous Mesenchymal Stem Cells

Status: Recruitment Completed, Status Unknown

<https://clinicaltrials.gov/ct2/show/NCT01513694>

Trial ID: NCT01290367

Title: A Prospective, Double Blind, Controlled Study Evaluating Safety and Preliminary Efficacy of a Single Injection of Adult Mesenchymal Precursor Cells (MPCs) Combined With Hyaluronan in Subjects With Chronic Discogenic Lumbar Back Pain

Status: Recruitment Completed, not yet Published

<https://clinicaltrials.gov/ct2/show/record/NCT01290367>

Trial ID: NCT03347708

Title: Study to Evaluate the Safety and Preliminary Efficacy of IDCT, a Treatment for Symptomatic Lumbar Intervertebral Disc Degeneration

Status: Recruiting

<https://clinicaltrials.gov/ct2/show/record/NCT03347708>

Trial ID: NCT03461458

Title: Autologous, Culture-Expanded Mesenchymal Stromal Cells for Degenerative Disc Disease

Status: Recruiting

<https://clinicaltrials.gov/ct2/show/NCT03461458>

Trial ID: NCT03347708

Title: A Prospective, Randomized, Double-Blinded, Vehicle- and Placebo-Controlled, Multicenter Study to Evaluate the Safety and Preliminary Efficacy of IDCT in Subjects With Single-Level, Symptomatic Lumbar Intervertebral Disc Degeneration

Status: Not yet recruiting, estimated November 2020 study completion

<https://clinicaltrials.gov/ct2/show/record/NCT03347708>

Trial ID: NCT01771471

Title: A Study Comparing the Safety and Effectiveness of Cartilage Cell Injected Into the Lumbar Disc as Compared to a Placebo

Status: Terminated

<https://clinicaltrials.gov/ct2/show/NCT01771471>

Trial ID: NCT02379689

Title: Efficacy of Intradiscal Injection of Viable Placental Tissue Extract in Subjects With One or Two Level, Symptomatic Lumbar Intervertebral Disc Degeneration

Status: Unknown

<https://clinicaltrials.gov/ct2/show/NCT02379689>

Trial ID: NCT02440074

Title: Lumbar Degenerative Disc Disease Treatment With Bone Marrow Autologous Mesenchymal Stem Cells (MSV)

Status: Withdrawn (Not funded, Administrative formalities not completed)

<https://clinicaltrials.gov/ct2/show/record/NCT02440074>

Trial ID: NCT01643681

Title: Safety and Efficacy of Autologous Adipose Tissue Derived Mesenchymal Stem Cells Transplantation in Patient With Lumbar Intervertebral Disc Degeneration

Status: Unknown

<https://clinicaltrials.gov/ct2/show/record/NCT01643681>



## Appendix D. Detailed data abstraction

Appendix Table D1. Study Characteristics and Demographics for studies evaluating the use of Allogenic Cell Therapies for Lumbar Disc Regeneration

Author (year), Location, Study Design, RoB	Diagnosis, Inclusion/Exclusion Criteria	Intervention, Comparator	Demographics	F/U	Outcomes	Funding, COI
<p><b>Noriega 2017</b></p> <p>Spain, Randomized Controlled Trial</p> <p><i>Moderately High</i></p>	<p>Diagnosis: Degenerative Disc Disease (radiculopathy, myelopathy NR)</p> <p><b>Inclusion:</b> 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 of disc height &gt;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</p>	<p><u>Allogenic MSC group (n=12)</u></p> <p>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</p> <p><b>Cell Type:</b> MSCs  <b>Cell Source:</b> allogenic (5 donors)  <b>Cell Preparation:</b>            -donors: n = 5, 4 men and 1 woman)            -bone marrow volume: 105±5 mL,            -Mean Number mononuclear cells obtained: 1.23 ± 0.25X 10<sup>9</sup>            -mean±SD expansion time: 27±2 days, suspended in Ringer-lactate at 12.5X10<sup>6</sup> cells/mL            -viability greater than</p>	<p><u>Total, Mean (SD)</u>            N=24            Male: 71%            Mean Age(SD): 38(2)            Levels Treated, n:            -L1-2: 1            -L2-3: 1            -L3-4: 3            -L4-5: 18            -L5-S1: 15            Comorbidities, %:            -tobacco use: NR            -Prior Surgery: NR</p>	<p>1 week (100%, 100%),            3 mos (100%, 100%),            6 mos (100%, 100%),            12 mos (100%, 100%)</p> <p>F/U percentages based on those randomized, information on total eligible patients was not available.</p>	<ul style="list-style-type: none"> <li>▪ ODI</li> <li>▪ VAS</li> <li>▪ SF-12</li> <li>▪ Radiographic Measures (Disc Height)</li> <li>▪ Adverse Events</li> </ul>	<p>Funding: Financial support from the Red de Terapia Celular (RD12/0019/0036, RD12/0019/0001 and RD16/0011/0003), Instituto de Salud Carlos III, Ministerio de Economía y Competitividad, and the Centro en Red de Medicina Regenerativa de Castilla y León i</p> <p>COI: Authors declared no COI.</p>

	<p>consent of the patient; in fertile women, negative pregnancy test result, agreement to adequate contraceptive methods</p> <p><u>Exclusion:</u> 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/m<sup>2</sup>) greater than 35 (obesity grade II); breastfeeding; Neoplasia; Immunosuppression; Hypersensitivity to amide-type local anaesthetics or other known contraindications or interactions of mepivacaine; Participation in another clinical trial or treatment with another investigational product &lt;30 days before inclusion in the study; other conditions that may, according to medical criteria, discourage participation in the study.</p>	<p>98%±1%</p> <p><b>Cell Expansion:</b> Yes <b>Cell Concentration:</b> 25x10<sup>6</sup> MSC in 2 mL of saline/disc <b>Cell Delivery:</b> percutaneous injection into symptomatic disc <b>Anesthetic Use:</b> local anesthesia (type NR)</p> <p><u>Sham Control Group (n=12)</u> 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.</p> <p><b>Cointerventions:</b> None</p>				
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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 Assessment 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

**Appendix Table D2. Study Characteristics and Demographics for studies evaluating the use of Autologous Stem Cells for Lumbar Disc Regeneration**

Author (year), Location, Study Design, RoB	Diagnosis, Inclusion/Exclusion Criteria	Intervention, Comparator	Demographics	F/U	Outcomes	Funding, COI
<p><b>Centeno 2017</b></p> <p>USA, Single-Arm Registry Study, Retrospective Case Series</p> <p><i>High</i></p>	<p>Diagnosis: Degenerative Disc Disease (DDD), low back pain (chronicity NR) with radiculopathy</p> <p><u>Inclusion:</u> DDD patients with a posterior disc bulge confirmed on MRI, consistent with history+exam; Clinical diagnosis of radicular pain; Failed conservative treatment (i.e. physical therapy, modalities, and multiple medications); Failed interventional therapy (i.e. epidural steroid injections at the suspected level of the pain generator); Unwillingness</p>	<p><u>Bone Marrow Aspirate derived MSCs</u></p> <p>3 stage injection process; in main injection MSCs administered under local anesthesia (pre- and post-injections consisted of 3-5 cc of platelet lysate injectate)</p> <p><b>Cell Type:</b> MSCs  <b>Cell Source:</b> autologous, bone marrow  <b>Cell Preparation:</b> MSCs were cultured from 60cc of autologous bone marrow aspirate harvested per patient  <b>Cell Expansion:</b> Yes  <b>Cell Concentration:</b> -Avg. Cell Dose: 2.3X10<sup>7</sup></p>	<p>N=33  Male: 63.6%  Mean Age: 40.3(14.2) years  Mean BMI (kg/m<sup>2</sup>): 24.8 (2.8)</p> <p>Comorbidities, %:  - Smoking: NR  -Prior Surgery: NR</p> <p>Levels Treated:  -L4-5: NR  -L5-S1: 22/33  -&gt;1 injection: 4 patients</p>	<p>,3 mos, 6 mos, 12 mos, 18 mos, 24 mos, 36 mos, 48 mos, 60 mos, 72 mos (unclear)</p> <p>F/U % at all time frames cannot be determined from data given*</p>	<ul style="list-style-type: none"> <li>▪ NPRS</li> <li>▪ modified Single Assessment Numeric Evaluation (m-SANE)</li> <li>▪ Functional Rating Index (FRI)</li> <li>▪ IVD Posterior Dimension</li> <li>▪ Adverse Events</li> </ul>	<p>Funding: This research was funded by Regenerative Sciences, LLC and the Centeno-Schultz Clinic.</p> <p>COI: Lead author is a shareholder and director of Regenerative Sciences, LLC and president and owner of the Centeno-Schultz Clinic. Other authors reported no COI.</p>

	<p>to pursue surgical option.</p> <p><b>Exclusion:</b>  Patients with active non-corrected endocrine disorder potentially associated with symptoms (i.e. hypothyroidism, diabetes); Active neurologic disorder potentially associated with symptoms (i.e. peripheral neuropathy, multiple sclerosis); Severe cardiac disease; Pulmonary disease requiring medication usage; History of active neoplasm within past 5 years; Anemia; Prior therapeutic intradiscal injection (i.e. hyaluronic acid or Fibrin).</p>	<p>(range 1.73X10<sup>6</sup> to 4.5X10<sup>7</sup>)  1–3 mL of cultured MSCs  <b>Cell Delivery:</b>  percutaneous injection into symptomatic disc  <b>Anesthetic Use:</b> 1% Lidocaine</p>				
<p><b>Kumar 2017</b>  South Korea, Retrospective Case Series    <i>High</i></p>	<p>Diagnosis: Degenerative Disc Disease, Chronic (&gt;3 mos) axial discogenic low back pain (radiculopathy or myelopathy NR)</p> <p><b>Inclusion:</b>  both sexes; age 19-70 years; with <math>\geq 4/10</math> on VAS; disability level <math>\geq 30\%</math> on the ODI; failure to respond to conventional treatments including medication, intensive physical rehabilitation, and local anesthetic infiltration in facet joints or medial branches;</p>	<p><b>AT-MSCs</b>  Liposuction harvested adipose tissue, processed into MSCs, and transplanted into patients along with Hyaluronic Acid</p> <p><b>Cell Type:</b> Autologous, MSCs with Hyaluronic Acid  <b>Cell Source:</b> subcutaneous abdominal adipose tissue-derived (via liposuction)  <b>Cell Preparation:</b> Autologous MSCs were isolated from</p>	<p><b>Total, Mean (SD)</b>  N=10  Male: 60%  Mean Age: 43.5 years  Mean Disease Duration: 48.3 mos.  Levels Treated:  -L4-5: 9  -L5-S1 + L4-5: 1</p> <p>Comorbidities, %:  -hypertension: 20%  -Smoking History: 20%  -Prior Surgery: 0% (exclusion criteria)</p>	<p>1 mos, 3 mos, 6 mos, 9 mos, 12 mos (unclear)</p> <p>F/U % at all time frames cannot be determined from data given*</p>	<p>*ODI  *VAS  *Adverse Events  *Radiographic Outcomes (Disc Height)</p>	<p>Funding: This work was supported by the Korea Healthcare Technology Research &amp; Development Project, Ministry for Health &amp; Welfare Affairs, Republic of Korea (HI14C3245, HI16C0106, and HR16C0002).</p> <p>COI: NR</p>

	<p>moderate grade of IVD degeneration (Pfirrmann's grade III–IV at one or two levels based on T2-weighted MRI); and degenerative symptomatic discs confirmed by discography</p> <p><u>Exclusion:</u> 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 &gt; 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</p>	<p>adipose tissue and cultured for 3 weeks. <b>Cell Expansion:</b> Yes <b>Cell Concentration:</b> The first five consecutive subjects received a mixture of 0.5 ml of stem cell suspension (<math>2 \times 10^7</math> 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 (<math>4 \times 10^7</math> cells/disc) and 1 ml of Tissuefill® (1%). Cell viability ranged from 87.13 to 97.57% <b>Cell Delivery:</b> percutaneous injection into symptomatic disc <b>Anesthetic Use:</b> 1% buffered lidocaine</p>				
<p><b>Orozco 2011</b> Spain, Retrospective Case Series  <i>High</i></p>	<p>Diagnosis: Degenerative Disc Disease, chronic (not defined) low back pain</p> <p><u>Inclusion:</u> Patients with DDD with preserved annulus fibrosus, persistent low-back pain,</p>	<p><u>Autologous MSCs</u> MSCs derived from bone marrow harvested from the iliac crest.</p> <p><b>Cell Type:</b> MSCs <b>Cell Source:</b> autologous (bone marrow)</p>	<p>N=10 Male: 40% Mean Age(SD): 35(7) years Levels Treated: -L4-5: 20% -L5-S1: 60% -L4-5 &amp; L5-S1: 20%</p>	<p>3 mos, 6 mos, 12 mos (unclear)</p> <p>F/U % at time frames cannot be determined from data</p>	<ul style="list-style-type: none"> <li>▪ VAS (Lumbar Pain + Sciatic Pain)</li> <li>▪ ODI</li> <li>▪ SF-36</li> <li>▪ Radiographic Outcomes (Disc Height; Fluid</li> </ul>	<p>Funding: Advanced Therapies Program of the Spanish Ministerio de Sanidad, the Red de Terapia Celular grant RD06/0010/0000 of the Instituto</p>

	<p>non-responsive to conservative treatment; fibrous ring capable of holding the cell implantation, demonstrated by discography (stages 2, 3 and 4 of Adams); &gt;50% decrease in disc height by radiographic measure; absence of spinal infection; no significant alterations that contraindicates intervention</p> <p><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 stenosis, 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 m<sup>2</sup>) greater than 30.5 (obesity grade II; Pregnancy or breast-feeding; neoplasia; immunosuppression;</p>	<p><b>Cell Preparation:</b> bone marrow volume - 89±5 mL Number of mononuclear cells obtained - 794±34X10<sup>6</sup> Expansion time - 24±4days viability at application – 83%±5%</p> <p><b>Cell Expansion:</b> Yes <b>Cell Concentration:</b> 10±5X10<sup>6</sup> cells per disc <b>Cell Delivery:</b> percutaneous injection into symptomatic disc(s) <b>Anesthetic Use:</b> local anesthesia (NR)</p> <p><b>Cointerventions:</b> None</p>	<p>Comorbidities: - Smoking: NR -Prior Surgery: NR</p>	<p>given*</p>	<p>Content) ▪ Adverse Events</p>	<p>de Salud Carlos III, Ministerio de Ciencia e Innovación, and the Centro en Red de Medicina Regenerativa de Castilla y León.</p> <p>COI: None declared</p>
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	participation in other clinical trial or treated with investigational products;					
<p><b>Pettine 2015 [2016, 2017]</b></p> <p>USA, Prospective Case Series</p> <p><i>High</i></p>	<p>Diagnosis: Degenerative Disc Disease</p> <p><u>Inclusion:</u> Patients with centralized chronic low back pain that increased with activity and lasted <math>\geq 6</math> mos; undergone nonoperative (conservative) management for 3 mos 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 <math>&lt; 30\%</math> compared to an adjacent nonpathologic disc; pretreatment baseline ODI score of <math>\geq 30</math> on the 100-point scale; and pretreatment baseline low back pain of <math>\geq 40</math> mm on the 100 mm VAS. An intact annulus was not required to be in the study.</p> <p><u>Exclusion:</u> Patients with abnormal neurologic exam; symptomatic compressive pathology due to stenosis or herniation;</p>	<p><u><i>Autologous Bone Marrow Concentrate (BMC) Injection (n=26)</i></u> After injection, patients were prescribed pain medicine to be used as needed for 3 days and put on restricted physical activity for 2 weeks.</p> <p><b>Cell Type:</b> autologous, nonexpanded bone marrow concentrated cell, containing a variety of stem and progenitor cells including MSCs <b>Cell Preparation:</b> BMA(55 ml) was collected over acid citrate dextrose anticoagulant (5 ml) from the patient’s posterior iliac crest. <b>Cell Expansion:</b> No (centrifuged for 12 minutes after aspiration, prior to injection) <b>Cell Concentration:</b> 2–3 ml of BMC was used per symptomatic lumbar disc injection -Total Nucleated Cell count/ml in BMC: <math>121(\pm 11) \times 10^6</math> -viability greater than <math>98\% \pm 1\%</math> <b>Cell Delivery:</b></p>	<p>N= 26 Male: 42.3% Median Age(range): 40 (18-61) BMI: 26.6 (19-37)</p> <p>Comorbidities: -smoking: NR -prior surgery: NR</p>	<p>12 mos (unclear)</p> <p>F/U % at all time frames cannot be determined from data given*</p>	<ul style="list-style-type: none"> <li>▪ ODI</li> <li>▪ VAS</li> <li>▪ Adverse Events &amp; Subsequent Treatment</li> </ul>	<p>Funding: NR</p> <p>COI: Three authors are employees of the company that provided bone marrow concentration devices used in the study.</p>

	spondylolysis or any spondylolisthesis	percutaneous injection into symptomatic disc(s) <b>Anesthetic Use:</b> 1% buffered lidocaine				
<b>Hematopoietic Stem Cells</b>						
<b>Haufe 2006</b>  USA, Prospective Case Series  <i>High</i>	Diagnosis: Degenerative Disc Disease  <u>Inclusion:</u> NR  <u>Exclusion:</u> NR	<u><i>Hematopoietic Stem Cells (n=10)</i></u> 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.  <b>Cell Type:</b> Hematopoietic Stem Cells <b>Cell Source:</b> autologous (bone marrow aspirate) <b>Cell Preparation:</b> BMA extracted from pelvic crest -bone marrow volume: 5cc <b>Cell Expansion:</b> NR <b>Cell Concentration:</b> 1 cc of HSCs <b>Cell Delivery:</b> percutaneous injection into symptomatic disc <b>Anesthetic Use:</b> local anesthesia	<u>Total, Mean (SD)</u> N=10 Male: 50% Mean Age (range): NR (32-74) years Prior Surgery: NR	12 mos (unclear)  F/U % at all time frames cannot be determined from data given*	* VAS * Subsequent Treatment (Surgery)	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 Assessment 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

\* Percent F/U within studies could not be determined as number of eligible patients, loss to follow-up, and/or patient selection criteria were not adequately described; potential for selection bias is of concern.

**Appendix Table D3. Study Characteristics and Demographics for studies evaluating the use of Allogenic Chondrocytes for Lumbar Disc Regeneration**

Author (year), Location, Study Design, RoB	Diagnosis, Inclusion/Exclusion Criteria	Intervention, Comparator	Demographics	F/U	Outcomes	Funding, COI
<p><b>Coric 2013</b></p> <p>USA, Prospective Case Series</p> <p><i>High</i></p>	<p><u>Diagnosis:</u> single-level degenerative disc disease; low back pain (radiculopathy excluded)</p> <p><u>Inclusion:</u> Age 18-70; negative pregnancy test at the time of treatment, be actively practicing contraception or abstinence, be surgically sterilized, or be postmenopausal; Have central LBP aggravated by movement and or postural changes (standing/sitting); One Grade III or IV (Pfirrmann scale) lumbar disc without annular rupture; Have tried and failed at &gt;12 weeks of conservative</p>	<p><i>Nu-Qu Allogenic Juvenile Chondrocytes</i></p> <p>Fluoroscopically guided injection of culture multiplied juvenile chondrocytes</p> <p><b>Cell Type:</b> juvenile chondrocytes</p> <p><b>Cell Source:</b> allogenic (cadaveric donors)</p> <p><b>Cell Preparation:</b> Cadaver-harvested chondrocytes expanded in vitro prior to Intradiscal injection</p> <p><b>Cell Expansion:</b> Yes</p> <p><b>Cell Concentration:</b> 1-2 ml (mean injection 1.3 ml) of juvenile chondrocytes (approximately 10<sup>7</sup>)</p>	<p>N=15 Male: 60% Mean Age(range): 40 (19-47) years</p> <p>Smoking: NR Levels Treated: -L3-4: 2 -L4-5: 1 -L5-S1: 12 Prior Surgery: 0% (exclusion criteria)</p>	<p>1 mos, 3 mos, 6 mos, 12 mos</p> <p>F/U % at all time frames cannot be determined from data given</p>	<p>* ODI *NPRS *SF-36 *Radiographic Measures (MRI-Rated Improvement, Deterioration) *Adverse Events &amp; Subsequent Treatment</p>	<p>Funding: ISTO Technologies</p> <p>COI: Two authors have ties (as previous investigators for, and research and travel fund recipients) to the study sponsor. The lead author is a consultant for and owns stock in a number of biotechnology companies.</p>

	<p>management directed by licensed physician, chiropractor, and/or physical therapist. Treatment must include any or a combination of physical therapy, chiropractic care, or pain management (e.g. rest or activating physical therapy, heat, cold, electrical stimulation, ultrasound, manipulation, acupuncture, analgesics including narcotics with no history of abuse), antiinflammatory medication, radiofrequency treatments, and spinal injections, including epidural steroid and or anesthesia injections; Have been offered and have refused, for the duration of the clinical trial, the treatment alternatives of systemic steroid use, epidural and spinal injection of any kind, nerve ablation, and surgical intervention; Have agreed to refuse participation in another clinical trial for the duration of this study and have score on the NPRS of 4-8 and/or ODI <math>\geq</math> 40%.</p> <p><u>Exclusion:</u> current disc extrusion at any lumbar level; Severe</p>	<p>chondrocyte cells/mL -Minimum culture viability of 75%</p> <p><b>Cell Delivery:</b> percutaneous injection into symptomatic disc</p> <p><b>Anesthetic Use:</b> Local anaesthetic</p> <p><b>Cointerventions:</b> None</p>				
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<p>disc narrowing (<math>\geq 50\%</math> loss of disc height at the targeted level); Disc bulges or protrusions at any level resulting in radiculopathy; Type II or III Modic changes at any level; Type I Modic changes at any level other than the targeted level; Type I Modic changes at the treated level if the maximum height of the changes is 25% or more of the vertebral body height; Osteoporotic compression fracture at any vertebral level; Lumbar Scheurmann disease or endplate abnormality targeted level; Anterolisthesis or retrolisthesis <math>\geq 3</math> mm at any level; Moderate to severe or worse facet disease at any level of the lumbar spine; Facet effusion at any level of the lumbar spine; Moderate or severe central canal stenosis, Grade II or III lateral recess stenosis, or foraminal stenosis at any level; Spondylolysis or instability at any level; Lumbar coronal angulation <math>\geq 10^\circ</math>; Cauda equina syndrome; Extradiscal extravasation of contrast on discogram; Accepts <math>&lt; 1</math> ml of contrast on discogram;</p>					
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<p>Previous spine surgery or other invasive treatment of the study disc, with the exception of previous epidural steroid or anesthesia injection; Currently enrolled or have participated in another clinical trial for the treatment of intervertebral disc disease, or received a study drug or investigational biological agent for the treatment of intervertebral disc disease within the last 6 months; Participating or have participated in any another clinical study in the last 3 months; Currently experiencing chronic pain generating from any other source that (in the judgment of the investigator) may interfere with the evaluation of back pain, and or back pain related disability and/or physical well being; Radicular pain (as evidenced by nerve root tension signs) and/or radiculopathy; Infection at the planned treatment site; Exposure to TISSEEL within the previous 12 months; Exposure to aprotinin(Trasylol) within the previous 12</p>					
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	<p>mos; Allergy or hypersensitivity to aprotinin; Allergy or hypersensitivity to radiocontrast medium; BMI <math>\geq 40</math>; Pregnant or breastfeeding; Currently diagnosed with immunodeficiency of any cause; Receiving any immunosuppressant therapies; History of frequent infections, active infections, or recent infections (within 1 month prior to anticipated date of dosing); Taking anticoagulants other than low-dose aspirin, or have other known bleeding diatheses; Diagnosed with any uncontrolled comorbid disease including AIDS, diabetes, hepatic or renal disease, and cardiopulmonary disorders such as chronic obstructive pulmonary disease, myocardial infarction, and chronic heart failure; Active malignancy or history of malignancy (except basal or squamous cell cancer that has been fully excised); Abnormal urinalysis, complete blood count, or serum chemistry judged to be clinically significant by the investigator and/or Data</p>					
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	<p>Safety Monitoring Board; Significant illness (including metastasis of any type); Substantial risk for need of organ transplantation; Those who are judged by the investigator to have an exaggerated pain and/or behavioral response during and/or after discography; Those who use illegal drugs as evidenced on urine drug screening; History of alcoholism, medication, or drug abuse within the last 5 years, or presently consuming alcohol in excess of 14 drinks per week (a drink is defined as 360 ml of beer, 120 ml of wine, or 30 ml of hard liquor); Those with scores in the "Distressed" category on the Distressed and Risk Assessment Method, has a history of psychosis, or has any of the following: a personality disorder, poor motivation, emotional or intellectual issues including exaggerated or unreasonable behavioral response to pain that would likely make the candidate unreliable for the study, or any combination of these variables in the investigator's judgment that</p>					
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	should exclude a candidate and those for whom MRI is contraindicated					
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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 Assessment 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

#### Appendix Table D4. Study Characteristics and Demographics for studies evaluating the use of Autologous Chondrocytes for Lumbar Disc Regeneration

Author (year), Location, Study Design, RoB	Diagnosis, Inclusion/Exclusion Criteria	Intervention, Comparator	Demographics	F/U	Outcomes	Funding, COI
<p><b>Tschugg 2016</b></p> <p>Austria, ONGOING Randomized Controlled Trial, Phase I/II Interim Safety Results</p> <p><i>Moderately High</i></p>	<p>Diagnosis: Degenerative Disc Disease</p> <p><u>Inclusion:</u> Patients with Symptomatic Lumbar Disc Herniation who failed adequate conservative or interventional treatment; radiographically determined disk herniation at the treatment level that correlated with primary symptoms; no previous lumbar spine surgery; aged 18-60 years; German language proficiency.</p> <p><u>Exclusion:</u> Patients with MRI documented assoc.</p>	<p><u>Autologous Disc Chondrocyte Transplantation with Novocart Disc Plus(n=12)</u></p> <p>90 days following sequestration of herniated disc, autologous IVD cells were transplanted from one IVD into another alongside a multicomponent polymerizing gel (NOVOCART Disk Plus)</p> <p><b>Cell Type:</b> NDisk+ is polymerizing gel with two components, component A (modified albumin, hyaluronic acid, and liquid matrix of autologous IVD cells dissolved in cell</p>	<p>N=24 Male: 58.3% Mean Age (SD): 42.5 (8.3) Mean BMI (kg/m<sup>2</sup>): 24.5</p> <p>Comorbidities, %: -tobacco use: 37.5% - Prior Surgery: 0% (exclusion criteria)</p>	1.5 mos (75%)	*Adverse Events	<p>Funding: Open access funding provided by University of Innsbruck and Medical University of Innsbruck. The study is funded by the federal ministry of education and research.</p> <p>COI: TETEC AG, a shared company of B Braun Aesculap, Tuttlingen, Germany sponsors this study and this publication. The departments</p>

	<p>lumbar disease such as spinal stenosis, spondylolisthesis, or fracture; extensive damage to annulus fibrosus, or significant comorbidities were excluded from the study.</p>	<p>culture medium supplemented with human serum, chondroitin sulfate, insulin, BMP-2, ascorbate) and component B (bis thio polyethylene glycol).  <b>Cell Source:</b> autologous (IVD)  <b>Cell Preparation:</b> After disk tissue extraction, tissues were transferred for manufacturing of NDisk Product. Injections were made 90 days after sequestrectomy.  <b>Cell Concentration:</b>  -Mean Injection Volume 1.19 mL  <b>Cell Delivery:</b> percutaneous injection into symptomatic disc  Anesthetic Use: general endotracheal anesthesia  <b>Levels Treated, %:</b>  -L3-4: 8.3%  -L4-5: 25%  -L5-S1: 66.6%</p> <p><i><u>Autologous Disc Chondrocyte Transplantation with Novocart Disc Basic (n=8)</u></i></p> <p>Identical procedure except NDisk basic features fewer additional components than Novocart Disk Plus.</p>				<p>received grant support to perform the study. Two authors are employees of the sponsor.</p>
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		<p><b>Cell Type:</b> In NDisc basic component A is a liquid matrix composed of cell culture medium, modified albumin, and hyaluronic acid but the cell suspension is replaced by an aliquot of cell culture medium without additives, while component B remains the same (bis thio polyethylene glycol)</p> <p><b>Levels Treated, %:</b></p> <p>-L3-4: 0%</p> <p>-L4-5: 25%</p> <p>-L5-S1: 75%</p> <p><b>Cointerventions:</b> None reported</p>				
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AT-MSCs, autologous mesenchymal stem cells; BMA, Bone marrow aspirate; BMC, Bone Marrow Concentrate; BMI, body mass index; cc, cubic centimeters; BMP, bone morphogenetic protein; 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 Assessment 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

**Appendix Table D5. Data Abstraction for Studies Evaluating of Allogenic Stem Cells for Lumbar Disc Repair**

Author (year), Intervention, Location, Study Design, RoB	Primary Outcomes-Function	Primary Outcomes-Pain	Secondary or Intermediate Outcomes	Radiographic Outcomes	Adverse Events, Harms, Complications
<p><b>Noriega 2017*</b>, N=24</p> <p>Allogenic MSCs vs Sham</p> <p>Spain, Randomized Controlled Trial</p> <p><i>Moderately High</i></p>	<p><i>Allogenic MSCs vs Sham</i></p> <p><b>Oswestry Disability Index Scale (ODI; 0-100%, higher scores indicate greater disability )</b></p> <p><u>Mean, ±SD (n=12, 12 across all time periods):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 34±23 vs 24±14</li> <li>• 1 wk: 27±17 vs 20±16</li> <li>• 3 mos: 16±20 vs 25±15</li> <li>• 6 mos: 20±24 vs 30±20</li> <li>• 12 mos: 22±24 vs 34±25</li> </ul>	<p><i>Allogenic MSCs vs Sham</i></p> <p><b>Lumbar Pain Visual Analogue Scale (VAS; 0-100%, higher scores indicate severity of pain)</b></p> <p><u>Mean±SD (n=12, 12 across all time periods):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 67±26 vs 62±23</li> <li>• 1 wk: 63±26 vs 45±25</li> <li>• 3 mos: 43±30 vs 46±27</li> <li>• 6 mos: 40±29 vs 51±29</li> <li>• 12 mos: 47±36 vs 47±28</li> </ul>	<p><i>Allogenic MSCs vs Sham</i></p> <p><b>Short Form-12 Quality of Life (SF-12; 0-100% high scores indicate improved quality of life)</b></p> <p><u>Physical Component Score, Mean±SE (n=12, 12 across all time periods):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 39±2 vs 40±3</li> <li>• 1 wk: 39±2 vs 43±3</li> <li>• 3 mos: 47±3 vs 43±3</li> <li>• 6 mos: 46±3 vs 39±3</li> <li>• 12 mos: 45±3 vs 42±3</li> </ul> <p><u>Mental Component Score, Mean±SE (n=12, 12 across all time periods):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 46±3 vs 52±3</li> <li>• 1 wk: 47±3 vs 50±2</li> <li>• 3 mos: 50±2 vs 46±3</li> <li>• 6 mos: 52±2 vs 48±3</li> <li>• 12 mos: 48±3 vs 50±3</li> </ul>	<p><i>Allogenic MSCs vs Sham</i></p> <p><b>Disc Height Decrease in millimeters in Affected Discs, Mean±SE:</b></p> <ul style="list-style-type: none"> <li>• Overall: 0.04±0.19 (n=17 discs) vs 0.38±0.19 (n=16 discs); difference NS</li> </ul>	<p><i>Allogenic MSCs vs Sham</i></p> <p><b>Adverse Events</b></p> <p><u>Proportion of Participants who experienced minor pain requiring NSAIDs, (n/N)</u></p> <ul style="list-style-type: none"> <li>• 25% (3/12) vs 66.6% (8/12)</li> </ul> <p><u>Proportion of Participants who experienced pain requiring opioids, (n/N)</u></p> <ul style="list-style-type: none"> <li>• 8.3% (1/12) vs 8.3% (1/12)</li> </ul> <p><u>Number of Serious Adverse Events, (n/N)</u></p> <ul style="list-style-type: none"> <li>• 0 vs 0</li> </ul>

mos, months; MSCs, mesenchymal stem cells; NS, not significant; ODI, Oswestry Disability Index; SD, standard deviation; SE, standard error; SF-12, Short Form 12 Quality of Life; VAS, visual analogue scale; wk, weeks;

\* Footnote: This study notes Mean and “DS”, which we interpreted as “Standard Deviation;” although no footnote clarifies this specifically, the study is from Spain and standard deviation is noted as “desviación estándar” in Spanish.

**Appendix Table D6. Data Abstraction for Studies Evaluating the use of Autologous Stem Cells for Lumbar Disc Repair**

Author (year), Intervention, Location, Study Design, RoB	Primary Outcomes-Function	Primary Outcomes-Pain	Secondary or Intermediate Outcomes	Radiographic Outcomes	Adverse Events, Harms, Complications
<p><b>Centeno 2017, N=33</b></p> <p>Bone Marrow Aspirate-derived MSCs</p> <p>USA, Single-Arm Registry, Retrospective Case Series</p> <p><i>High</i></p>	<p><b>Functional Rating Index (FRI; 0-100, where 0 = functionally independent and 100 = severe disability)</b></p> <p><u>Mean Change Improvement from Baseline±SD (n=16 unless otherwise noted):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 61±NR</li> <li>• 1 mos: 19±NR</li> <li>• 3mos: 20±NR, p&lt;0.05 (n=NR)</li> <li>• 6 mos: 17±NR</li> <li>• 12 mos: 4.9±NR (n=6)</li> <li>• 18 mos: 17±NR</li> <li>• 24 mos : 17±NR</li> <li>• 36 mos: 12±NR</li> <li>• 48mos: 19±NR</li> <li>• 60mos: 35±NR, p&lt;0.05 (n=4)</li> <li>• 72 mos: 30±NR</li> </ul> <p><b>modified Single</b></p>	<p><b>Numeric Pain Rating Scale (NPRS; 0-10, 0 = no pain and 10 = worst possible pain)</b></p> <p><u>Mean Change from Baseline ±SD (n=25 across all time periods):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 5.2±NR</li> <li>• 1 month: 1.5±NR</li> <li>• 3mos: 1.6±NR, p&lt;0.05</li> <li>• 6 mos: 1.4±NR</li> <li>• 12 mos: 0.6±NR</li> <li>• 18 mos: 2±NR</li> <li>• 24 mos : 1.2±NR</li> <li>• 36 mos: 2 ±NR, p&lt;0.1</li> <li>• 48 mos: 2.5±NR, p&lt;0.05</li> <li>• 60 mos: 3.7 (NR), p&lt;0.05</li> <li>• 72 mos: 3.3 (NR), p&lt;0.1</li> </ul>	<p>NR</p>	<p><b>Posterior IVD Bulge Size Reduction at Post Treatment MRI</b></p> <p><u>Proportion of Participants with Decrease in Disc Bulge Size (n/N):</u></p> <ul style="list-style-type: none"> <li>• Post Treatment: 85% (17/20)</li> </ul> <p><u>Proportion of Patients with Post-treatment Reductions in Disc Bulge Size by threshold amount of reduction. % (n/N) †</u></p> <ul style="list-style-type: none"> <li>• &gt;0%: 85% (17/20)</li> <li>• &gt;5%: 70% (14/20)</li> <li>• &gt;10%: 58% (12/20)</li> <li>• &gt;15%: 50% (10/20)</li> <li>• &gt;20%: 45% (9/20)</li> <li>• &gt;25%: 40% (8/20)</li> <li>• &gt;30%: 40% (8/20)</li> <li>• &gt;35%: 30% (6/20)</li> </ul>	<p><b>Adverse Events</b></p> <p><u>Proportion Reporting Complaints, (n/N)</u></p> <ul style="list-style-type: none"> <li>• 27% (9/33)</li> </ul> <p><u>Proportion with Complaints deemed as Treatment-Related Adverse Event*, (n/N)</u></p> <ul style="list-style-type: none"> <li>• Pain-Related: 9.0% (3/33)</li> <li>- 1 case of Large Herniated Nucleus Pulposus (HNP)</li> <li>- 0 cases of Discitis</li> </ul> <p><u>Proportion with Serious Adverse Events, (n/N)</u></p> <ul style="list-style-type: none"> <li>• 0% (0/33)</li> </ul> <p><b>Subsequent Treatment</b></p>

	<p><b>Assessment Numeric Evaluation (SANE; - 100% worsened to 100% improved, with pre-treatment baseline at 0% )</b>  <u>Mean SANE Score ±SD</u>  (n=30 across all time periods):</p> <ul style="list-style-type: none"> <li>• 1 mos: 42±NR</li> <li>• 3 mos: 47±NR</li> <li>• 6 mos: 51±NR</li> <li>• 12 mos: 45±NR</li> <li>• 18 mos: 51±NR</li> <li>• 24 mos : 43±NR</li> <li>• 36 mos: 60±NR</li> <li>• 48 mos: 57±NR</li> <li>• 60 mos: 56±NR</li> <li>• 72 mos: 53±NR</li> </ul> <p><u>Proportion &gt;0% Improvement, (n/N) †</u></p> <ul style="list-style-type: none"> <li>• 1 mos: 100% (5/5)</li> <li>• 3mos: 84% (16/19)</li> <li>• 6 mos: 80% (12/15)</li> <li>• 12 mos: 84% (11/13)</li> <li>• 18 mos: 83% (10/12)</li> <li>• 24 mos : 72% (5/7)</li> <li>• 36 mos: 90% (9/10)</li> <li>• 48 mos: 84% (11/13)</li> <li>• 60 mos: 80% (8/10)</li> <li>• 72 mos: 67% (6/9)</li> </ul> <p><u>Reported ≥50% Improvement</u></p> <ul style="list-style-type: none"> <li>• Last Followup: 50.4% (n=NR)</li> </ul> <p><u>Reported &gt;0% Improvement</u></p>				<p><u>Proportion who Progressed to Spine Surgery at a later date , (n/N)</u></p> <ul style="list-style-type: none"> <li>• 6.0% (2/33)</li> </ul>
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	<ul style="list-style-type: none"> <li>• 36 mos: 90% (n=NR)</li> </ul>				
<p><b>Kumar 2017, N=11</b></p> <p>Autologous Mesenchymal Stem Cells &amp; Hyaluronic Acid</p> <p>South Korea, Single-Arm, Retrospective Case Series</p> <p><i>High</i></p>	<p><b>Oswestry Disability Scale(ODI; 0-100%, higher scores indicate greater disability)</b></p> <p><u>Mean±SD (n=10 across all time periods):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 42.8±15.03</li> <li>• 1 month: 31.2±13.86, p=0.002</li> <li>• 3 mos: 31.7±14.22, p=0.01</li> <li>• 6 mos: 21.3±7.42, p=0.002</li> <li>• 12 mos: 16.8±9.77, p=0.002</li> </ul> <p><u>Proportion of Patients who Achieved Treatment Success (≥50% reduction in VAS &amp; ODI compared to pretreatment, (n/N):</u></p> <ul style="list-style-type: none"> <li>• 6 mos: 70% (7/10)</li> <li>• 12 mos: 60% (6/10)</li> </ul>	<p><b>Visual Analogue Scale (VAS; 0-10, higher scores indicate severity of pain)</b></p> <p><u>Mean±SD (n=10 across all time periods):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 6.5±1.27</li> <li>• 1 month: 4.6±1.07, p=0.01</li> <li>• 3 mos: 4.3±1.63, p=0.02</li> <li>• 6 mos: 3.2±1.40, p=0.004</li> <li>• 12 mos: 2.9±1.66m p=0.002</li> </ul>	NR	<p><b>X-Ray Imaging</b></p> <p><u>Disc Height Decrease in Affected Disc:</u></p> <ul style="list-style-type: none"> <li>• 12 mos: No decrease</li> </ul>	<p><b>Adverse Events</b></p> <p><u>Treatment-Related Adverse Events:</u> None reported.</p> <p><u>Treatment-Related Serious Adverse Events:</u> None reported.</p>
<p><b>Orozco 2011, N=10</b></p> <p>Autologous Mesenchymal Stem Cells</p> <p>Spain, Single Arm Retrospective Case Series</p>	<p><b>Oswestry Disability Scale(ODI; 0-100%, higher scores indicate greater disability)</b></p> <p><u>Mean ±SE (n=10 across time periods):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 25.0±4.1</li> </ul>	<p><b>Visual Analogue Scale (VAS; 0-100%, higher scores indicate severity of pain)</b></p> <p><u>Lumbar Pain, Mean ±SE (n=10 across time periods):</u></p>	<p><b>Short Form-36 Quality of Life (SF-36; 0-100%)</b></p> <p><u>Physical Component Score Mean±SE (n=NR across time periods):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 12.7±3.7</li> </ul>	<p><b>Disc Height in millimeters in Affected Disc Segments, Mean±SE (n/N):</b></p> <ul style="list-style-type: none"> <li>• Baseline: 9.86±0.57</li> <li>• 6 mos: 9.81±0.55</li> <li>• 12 mos: 9.84±0.63</li> </ul>	<p><b>Adverse Events</b></p> <p><u>Treatment-Related Adverse Events:</u> NR</p> <p><u>Treatment-Related Serious Adverse Events:</u> None reported.</p>

<p><i>High</i></p>	<ul style="list-style-type: none"> <li>• 3 mos: 13.0±3.2, p&lt;0.05</li> <li>• 6 mos: 9.4±2.7, p&lt;0.01</li> <li>• 12 mos 7.4±2.3, p&lt;0.001</li> </ul>	<ul style="list-style-type: none"> <li>• Baseline: 68.9±3.3</li> <li>• 3 mos: 26.5±5.6, p&lt;0.001</li> <li>• 6 mos: 21.6±6.0, p&lt;0.001</li> <li>• 12 mos: 20.0±6.5, p&lt;0.001</li> </ul> <p><u>Sciatic Pain, Mean ±SE (n=6 across all time periods): ‡</u></p> <ul style="list-style-type: none"> <li>• Baseline: 37.0±9.3</li> <li>• 3 mos: 24.3±12.6, p=NS</li> <li>• 6 mos: 7.8 ±6.9, p&lt;0.001</li> <li>• 12 mos: 5.3±5.1, p&lt;0.001</li> </ul>	<ul style="list-style-type: none"> <li>• 12 mos: 24.8±3.9, p&lt;0.05</li> </ul> <p><u>Mental Component Score Mean±SE (n=NR across time periods):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 54.1±10.6</li> <li>• 12 mos: 49.7±10.5, p=0.77</li> </ul>		
<p><b>Pettine 2015 [2016, 2017], N=26</b></p> <p>Autologous Bone Marrow Concentrate</p> <p>USA, Single Arm Prospective Case Series</p> <p><i>High</i></p>	<p><b>Oswestry Disability Scale(ODI; 0-100%, higher scores indicate greater disability)</b></p> <p><u>ODI Score, Mean±SE (n=26 across time periods):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 56.5±NR</li> <li>• 3 mos: 22.8±NR, p&lt;0.0001</li> <li>• 6 mos: 24.4±NR, p&lt;0.0001</li> <li>• 12 mos: 25.0±NR, p&lt;0.0001</li> </ul> <p><u>% Reduction in ODI Score (n=26 across time periods):</u></p> <ul style="list-style-type: none"> <li>• 3 mos: 58.1%</li> <li>• 6 mos: 55.5%</li> </ul>	<p><b>Visual Analogue Scale (VAS; 0-100, higher scores indicate severity of pain)</b></p> <p><u>VAS Score, Mean±SE (n=26 across time periods):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 79.3±NR</li> <li>• 3 mos: 29.2±NR, p&lt;0.0001</li> <li>• 6 mos: 26.3±NR, p&lt;0.0001</li> <li>• 12 mos: 33.2.±NR, p&lt;0.0001</li> </ul> <p><u>% Reduction in VAS Score (n=26 across time periods):</u></p>	<p>NR</p>	<p>NR</p>	<p><b>Adverse Events</b></p> <p><u>Treatment-Related Adverse Events:</u> None reported.</p> <p><u>Treatment-Related Serious Adverse Events:</u> None reported.</p> <p><b>Subsequent Treatment</b></p> <p><u>Proportion of Patients who Elected to Undergo a Second BMC Injection</u></p> <ul style="list-style-type: none"> <li>• 6 mos: 7.7% (2/26)</li> </ul> <p><u>Proportion of Participants who</u></p>

	<ul style="list-style-type: none"> <li>• 12 mos: 56.8%</li> </ul> <p><i>Data from Surgery Survivors</i></p> <p><u>% Reduction in ODI among patients who did not Progress to Surgery (n=21 across time periods):</u></p> <ul style="list-style-type: none"> <li>• 3 mos: 65%</li> <li>• 6 mos: 66%,</li> <li>• 12 mos: 60%</li> <li>• 24 mos: 67%</li> </ul> <p><u>ODI Score Among Patients who did not Progress to Surgery within 24 mos, Mean±SE (n=21 across time periods):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 56.2±NR</li> <li>• 3 mos: 19.9±NR</li> <li>• 6 mos: 19.0±NR</li> <li>• 12 mos: 22.3±NR</li> <li>• 24 mos: 18.3±NR</li> </ul> <p><u>ODI Score Among Patients who did not Progress to Surgery within 36 mos, Mean±SE (n=20 across time periods):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 56.7±3.6</li> <li>• 36 mos: 17.5±3.2, p&lt;0.001</li> </ul>	<ul style="list-style-type: none"> <li>• 3 mos: 64.6%</li> <li>• 6 mos: 64.2%</li> <li>• 12 mos: 58.0%</li> </ul> <p><i>Data from Surgery Survivors</i></p> <p><u>% Reduction in VAS among patients who did Progress to Surgery (n=21 across time periods):</u></p> <ul style="list-style-type: none"> <li>• 3 mos: 67%</li> <li>• 6 mos: 77%</li> <li>• 12 mos: 66%</li> <li>• 24 mos: 72%</li> </ul> <p><u>ODI Score Among Patients who did not Progress to Surgery within 24 mos, Mean±SE (n=21 across time periods):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 81.5±NR</li> <li>• 3 mos: 27.0±NR</li> <li>• 6 mos: 18.7±NR</li> <li>• 12 mos: 28.1±NR</li> <li>• 24 mos: 22.9±NR</li> </ul> <p><u>VAS Score Among Patients who did not Progress to Surgery within 36 mos, Mean±SE (n=20 across time periods):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 82.1±2.6</li> <li>• 36 mos: 21.9±4.4, p&lt;0.001</li> </ul>		<p><u>Progressed to Spine Surgery at a later date, (n/N)</u></p> <ul style="list-style-type: none"> <li>• 12 mos: 7.7% (2/26)</li> <li>• 24 mos: 19.2% (5/26)</li> <li>• 36 mos: 23.1% (6/26)</li> </ul>
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<i>Hematopoietic Stem Cells</i>					
<b>Haufe 2006, N=10</b>	NR	<b>Visual Analogue Scale (VAS; 0-10, 0 = no pain and 10 = worst possible pain)</b>	NR	NR	<b>Subsequent Treatment</b>
Hematopoietic Stem Cells					<u>Proportion of Participants who Progressed to Spine Surgery at a later date, (n/N)</u>
USA, Single-Arm, Prospective Case Series		<u>Proportion with VAS Pain Reduction, (n/N):</u> • 12 mos: 0% (0/10)			• Spinal Fusion: 75% (7/10) § • Artificial Disc Replacement: 10% (1/10)
<i>High</i>					

BMC, bone marrow concentrate; CFU-F, colony-forming unit-fibroblast; FRI, Functional Rating Index; IVD, Intervertebral Disc; mos., months; MRI, magnetic resonance imaging; mSANE, modified Single Assessment Numeric Evaluation; NPRS, numeric pain rating scale; NS, not significant; SE, standard error; SEM, standard error of the mean; wk(s), week(s);

\* What qualified as treatment related was not clearly defined by Centeno et al.

† Percentages and/or N's estimated from graphs

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

§ 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.

**Appendix Table D7. Data Abstraction for Studies Evaluating of Allogenic Chondrocytes for Lumbar Disc Repair**

<b>Author (year), Intervention, Location, Study Design, RoB</b>	<b>Primary Outcomes-Function</b>	<b>Primary Outcomes-Pain</b>	<b>Secondary or Intermediate Outcomes</b>	<b>Radiographic Outcomes</b>	<b>Adverse Events, Harms, Complications</b>
<b>Coric 2013, N=15</b>	<b>Oswestry Disability Scale(ODI; 0-100%, higher scores indicate greater disability )</b>	<b>Numeric Pain Rating Scale (NPRS; 0-10, 0 = no pain and 10 = worst possible pain)</b>	<b>Short Form-36 Quality of Life (SF-36; 0-100%)</b>	<b>Radiographic Outcomes*</b>	<b>Adverse Events †</b>
Allogenic Juvenile Chondrocytes			<u>Physical Component</u>	<u>Proportion of Patients who showed</u>	<u>Treatment-Related Adverse Events:</u> NR



<p>Prospective Case Series</p> <p><i>High</i></p>	<p><u>Mean ±SD (n=15 across all time periods):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 53.3±NR</li> <li>• 1 month: 27.6±NR</li> <li>• 3 mos: 27.1±NR</li> <li>• 6 mos: 26.9±NR</li> <li>• 12 mos: 20.3±NR, p&lt;0.0001 ‡</li> </ul> <p><u>Proportion of Patients who Achieved at least 30% ODI Improvement (n/N):</u></p> <ul style="list-style-type: none"> <li>• 12 mos: 92.9% (13/15)</li> </ul>	<p><u>Mean ±SD (n=15 across all time periods):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 5.7±NR (n=15)</li> <li>• 1 month: 3.9±NR (n=15)</li> <li>• 3mos: 3.5±NR (n=15)</li> <li>• 6 mos: 3.8±NR (n=15)</li> <li>• 12 mos: 3.1±NR, p=0.0025 ‡ (n=15)</li> </ul>	<p><u>Score, Mean±SD ( n=15 across all time periods):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 35.3±NR (n=15)</li> <li>• 1 month: 40.0±NR (n=15)</li> <li>• 3 mos: 43.1±NR (n=15)</li> <li>• 6 mos: 43.7±NR (n=15)</li> <li>• 12 mos: 46.9±NR, p=0.0002 ‡ (n=15)</li> </ul> <p><u>Mental Component Score, Mean±SD (n=15 across all time periods):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 48.5±NR</li> <li>• 1 month: 50.5±NR</li> <li>• 3 mos: 51.1±NR</li> <li>• 6 mos: 49.1±NR</li> <li>• 12 mos: 50.5±NR, p=0.64</li> </ul>	<p><u>Improvements in MRI Imaging, (n/N):</u></p> <ul style="list-style-type: none"> <li>• 6 mos: 77% (10/13)</li> </ul> <p><u>Proportion of Patients who showed No Improvements in MRI Imaging, (n/N):</u></p> <ul style="list-style-type: none"> <li>• 6 mos: 23% (3/13)</li> </ul>	<p><u>Proportion who experienced disc infections (n/N)</u></p> <ul style="list-style-type: none"> <li>• 0% (0/15)</li> </ul> <p><u>Proportion who experienced neurological deterioration (n/N)</u></p> <ul style="list-style-type: none"> <li>• 0% (0/15)</li> </ul> <p><u>Proportion of patients who experienced Serious or Unexpected Adverse Events:</u></p> <ul style="list-style-type: none"> <li>• 0% (0/15)</li> </ul> <p><b>Subsequent Treatment</b></p> <p><u>Proportion of Participants who Progressed to Spine Surgery at a later date, (n/N)</u></p> <ul style="list-style-type: none"> <li>• Total Disc Replacement by 12 mos: 20% (3/15)</li> </ul>
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BMC, bone marrow concentrate; CFU-F, colony-forming unit-fibroblast; FRI, Functional Rating Index; IVD, Intervertebral Disc; mos., months; MRI, magnetic resonance imaging; mSANE, modified Single Assessment Numeric Evaluation; NPRS, numeric pain rating scale; NS, not significant; SE, standard error; SEM, standard error of the mean; wk(s), week(s);

\* Coric et al. reported MRI-rated improvement or lack of improvement but did further specify criteria for these ratings.

† Coric et al. reported no “serious or unexpected adverse events”. They did not report whether there were expected treatment-related adverse events that did occur.

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

**Appendix Table D8. Data Abstraction for Studies Evaluating of Autologous Chondrocytes for Lumbar Disc Repair**

Author (year), Intervention, Location, Study Design, RoB	Primary Outcomes- Function	Primary Outcomes- Pain	Secondary or Intermediate Outcomes	Radiographic Outcomes	Adverse Events, Harms, Complications
<p><b>Tschugg 2016*, N=24</b></p> <p>Novocart Disc Plus vs Novocart Disc Basic</p> <p>Austria, Preliminary Safety Results Ongoing Prospective Randomized Controlled Trial</p> <p><i>Moderately High</i></p>	NR*	NR*	NR*	NR*	<p><i>NDisc+ vs NDisc Basic</i></p> <p><b>Adverse Events</b></p> <p><u>Proportion who experienced Treatment Emergent Adverse Events, (n/N)</u></p> <ul style="list-style-type: none"> <li>• 50% (6/12) vs 25% (2/8)</li> </ul> <p><u>Proportion of Participants who experienced Treatment- Related Adverse Events as determined by Investigator, (n/N)</u></p> <ul style="list-style-type: none"> <li>• 8.3% (1/12) vs 12.5% (1/8)</li> </ul> <p><u>Proportion who Experienced Serious Adverse Event, (n/N)</u></p> <ul style="list-style-type: none"> <li>• 8.3% (1/12) vs 0% (0/8)</li> <li>-Novocart Disk Plus patient experienced IVD Disk Protrusion (Serious Adverse event)</li> </ul>

IVD, Intervertebral Disc; mos., months; MRI, magnetic resonance imaging; NDisc+, Novocart Disc Plus; NDisc Basic, Novocart Disc Basic; NR, not reported;

\* Results for Primary and Secondary Outcomes were unpublished at the time of this review, only safety results were available.

**Appendix Table D9. Data Abstraction for Subpopulations Reported in Studies Evaluating the use of Autologous Stem Cells for Lumbar Disc Repair**

Author (year), Intervention, Location, Study Design, RoB	Primary Outcomes – Function*	Primary Outcomes – Pain*	Secondary or Intermediate Outcomes	Radiographic Outcomes	Adverse Events, Harms, Complications
<p><b>Pettine 2015 [2016, 2017], N=26</b></p> <p>Autologous Bone Marrow Concentrate</p> <p>USA, Single Arm Prospective Case Series</p> <p><i>High</i></p>	<p><i>Single vs Double Level</i></p> <p><b>Oswestry Disability Scale(ODI; 0-100%, higher scores indicate greater disability)</b></p> <p><u>ODI Score, Mean±SE (n=13, 13 across time periods):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 56.5±NR vs 55.5±NR</li> <li>• 3 mos: 18.4±NR, p&lt;0.0001 vs 27.4±NR, p&lt;0.005</li> <li>• 6 mos: 19.8±NR, p&lt;0.0001 vs 29.3±NR, p&lt;0.005</li> <li>• 12 mos: 26.2±NR, p&lt;0.005 vs 22.7±NR, p&lt;0.0001</li> </ul> <p>&lt;2000 CFU-F vs &gt;2000 CFU-F (MSCs) Concentration</p> <p><u>ODI Score, Mean±SE (n=9, 11 across time periods unless otherwise noted):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 54.2±NR vs 59.3±NR</li> <li>• 3 mos: 33.7±NR,</li> </ul>	<p><i>Single vs Double Level</i></p> <p><b>Visual Analogue Scale (VAS; 0-100, higher scores indicate severity of pain)</b></p> <p><u>VAS score, Mean±SE (n=13, 13 across time periods):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 78.5±NR vs 79.4±NR</li> <li>• 3 mos: 23.8±NR, p&lt;0.0001 vs 34.8±NR, p&lt;0.0001</li> <li>• 6 mos: 20.2±NR, p&lt;0.0001 vs 32.7±NR, p&lt;0.0001</li> <li>• 12 mos: 31.4±NR, p&lt;0.0001 vs 33.0±NR, p&lt;0.0001</li> </ul> <p>&lt;2000 CFU-F vs &gt;2000 CFU-F (MSCs) Concentration</p> <p><u>VAS Score, Mean±SE (n=9, 11 across time periods unless otherwise</u></p>	<p>NR</p>	<ul style="list-style-type: none"> <li>• NR</li> </ul>	<p>NR</p>

	<p>p&lt;0.01 vs 14.8±NR, p&lt;0.0001; p&lt;0.005</p> <ul style="list-style-type: none"> <li>• 6 mos: 36.3±NR vs 13.5±NR, p&lt;0.0001; p&lt;0.005</li> <li>• 12 mos: 26.3±NR, p&lt;0.005 vs 17.6±NR, p&lt;0.0001</li> <li>• 24 mos †: 24±NR, p=0.035 (n=5) vs 14.8±NR</li> <li>• 36 mos †: 29±NR, p=0.005, (n=5) vs 10±NR, p=0.005</li> </ul> <p><u>% Reduction in ODI Score, (n=9, 11 across time periods unless otherwise noted):</u></p> <ul style="list-style-type: none"> <li>• 3 mos: 41% vs 74%; p&lt;0.01</li> <li>• 6 mos: 40% vs 79%; p&lt;0.01</li> <li>• 12 mos: 48% vs 73%; p&lt;0.01</li> <li>• 24 mos: 51% (n=5 ‡) vs 74%'; p&lt;0.01 §</li> </ul> <p><i>Age ≤ 40 years vs Age &gt; 40 years</i></p> <p><u>ODI Score, Mean±SE (n=14, 12 across time periods):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 57.1±NR vs 55.8±NR</li> <li>• 3 mos: 18.2±NR, p&lt;0.0001 vs</li> </ul>	<p><u>noted):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 80.4±NR vs 82.0±NR</li> <li>• 3 mos: 46.4±NR, p&lt;0.005 vs 17.5±NR, p&lt;0.0001; p&lt;0.005</li> <li>• 6 mos: 36.7±NR, p&lt;0.005 vs 10.8±NR,</li> <li>•</li> <li>•</li> <li>•</li> <li>•</li> <li>•</li> <li>•</li> <li>•</li> <li>•</li> <li>•</li> <li>•</li> <li>•</li> <li>•</li> <li>•</li> <li>•</li> <li>• p&lt;0.0001; p&lt;0.01</li> <li>• 12 mos: 34.5±NR, p&lt;0.005 vs 25.5±NR, p&lt;0.0001</li> <li>• 24 mos: 30±NR, (n=5) vs 18±NR</li> <li>• 36 mos: 40±NR, p=0.001 (n=5) vs 10±NR, p=0.001</li> </ul> <p><u>% Reduction in VAS, (n=9, 11 across time periods unless otherwise noted):</u></p> <ul style="list-style-type: none"> <li>• 3 mos: 50% vs 79%; p&lt;0.01</li> <li>• 6 mos: 66% vs 88%; p&lt;0.01</li> <li>• 12 mos: 60% vs 70%; p&lt;0.01</li> <li>• 24 mos: 64% (n=5) vs 77% 'p&lt;0.01 §</li> </ul>			
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	<p>27.8±NR, p&lt;0.005</p> <ul style="list-style-type: none"> <li>• 6 mos: 20.6±NR, p&lt;0.0001 vs 28.5±NR, p&lt;0.005</li> <li>• 12 mos: 25.1±NR, p&lt;0.005 vs 24.8±NR, p&lt;0.005</li> </ul> <p><u>% Reduction in ODI Score (n=NR):</u></p> <ul style="list-style-type: none"> <li>• 3 mos: NR</li> <li>• 6 mos: NR</li> <li>• 12 mos: NR</li> <li>• 24 mos: NR</li> </ul>	<p><i>Age ≤ 40 years vs Age &gt; 40 years</i></p> <p><u>VAS Score, Mean±SE (n=14, 12 across time periods):</u></p> <ul style="list-style-type: none"> <li>• Baseline: 83.4±NR vs 74.8±NR</li> <li>• 3 mos: 24.6±NR, p&lt;0.0001 vs 34.2±NR, p&lt;0.005</li> <li>• 6 mos: 23.5±NR, p&lt;0.0001 vs 29.2±NR, p&lt;0.005</li> <li>• 12 mos: 32.3±NR, p&lt;0.0001 vs 34.5±NR</li> </ul> <p><u>% Reduction in VAS Score (n=NR):</u></p> <ul style="list-style-type: none"> <li>• 3 mos: NR</li> <li>• 6 mos: NR</li> <li>• 12 mos: NR</li> <li>• 24 mos: NR</li> </ul>			
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BMC, bone marrow concentrate; CFU-F, colony-forming unit-fibroblast; FRI, Functional Rating Index; IVD, Intervertebral Disc; mos., months; MRI, magnetic resonance imaging; mSANE, modified Single Assessment Numeric Evaluation; NPRS, numeric pain rating scale; NS, not significant; SE, standard error; SEM, standard error of the mean; wk(s), week(s);

\* First p-values are comparisons with baseline and second p-values are comparisons between groups.

† Data from ODI and VAS 24 months and 36 months follow-up for < & > 2000 CFU-F per mL were estimated from graph

‡ Four of the six patients who went on to receive surgery were from the <2000 CFU-F per mL subgroup and were excluded from subsequent follow-ups.

§ P values comparing follow-up scores to initial scores were all less than 0.001 and p values comparing >/<2,000 CFU-F/ml at each time point were all less than 0.01

**Appendix Table D10. Additional sub-group analysis: data of Patients who did not Progress to Surgery from Pettine 2015, 2016, & 2017**

Outcome Follow-up	Group A Mean (SD)	Group B Mean (SD)	p-value*
	<2000 CFU-F (n=9)	>2000 CFU-F (n=11)	
<b>Mean ODI</b>			
24 months	24±NR (n=5) †	14.8±NR	NR
36 months	29±NR (n=5) †	10±NR	NR
<b>% Reduction in ODI</b>	<b>% Δ from baseline</b>	<b>% Δ from baseline</b>	
3 months	41%	74%	p<0.01
6 months	40%	79%	p<0.01
12 months	48%	73%	p<0.01
24 months	51% (n=5)	74%	p<0.01
<b>Mean VAS</b>			
24 months	30±NR (n=5)	18±NR	NR
36 months	40±NR (n=5)	10±NR	NR
<b>% Reduction in VAS</b>	<b>% Δ from baseline</b>	<b>% Δ from baseline</b>	
3 months	50%	79%	p<0.01
6 months	66%	88%	p<0.01
12 months	60%	70%	p<0.01
24 months	64% (n=5)	77%	p<0.01

NR, not reported; ODI, Oswestry Disability Index; SD, standard deviation; VAS, visual analogue scale;

\* P-values are author reported unless otherwise noted.

† Four of the six patients who went on to receive surgery were from the <2000 CFU-F per mL subgroup and were excluded from subsequent follow-ups.

## Appendix E. Results summary tables: Cell therapy for IVD repair

**Appendix Table E1. Summary of RCT secondary outcomes data: Allogenic mesenchymal stem cells (expanded) versus sham treatment (Noriega 2017)**

Noriega 2017 RCT, Moderately High ROB Outcome Measure	F/U (months)	Allogenic MSC (n= 12) mean $\pm$ SD median (IQR)	Sham (n =12) mean $\pm$ SD median (IQR)	MD (95% CI)*	p-value*
<b>Quality of life</b>		<b>mean <math>\pm</math> SD†</b>	<b>mean <math>\pm</math> SD†</b>		
SF-36 PCS QoL (0-100 (best))	0 mos.	39 $\pm$ 6.9	40 $\pm$ 10.3	-1 (-8.42, 6.42)	0.7825
	3 mos.	47 $\pm$ 10.3	43 $\pm$ 10.3	4 (-4.7, 12.7)	0.3518
	6 mos.	46 $\pm$ 10.3	39 $\pm$ 10.3	7 (-1.7, 15.7)	0.1102
	12 mos.	45 $\pm$ 10.3	42 $\pm$ 10.3	3 (-5.7, 11.7)	0.4831
SF-36 MCS QoL (0-100 (best))	0 mos.	46 $\pm$ 10.3	52 $\pm$ 10.3	-6 (-14.7, 2.7)	0.1677
	3 mos.	50 $\pm$ 6.9	46 $\pm$ 10.3	4 (-3.4, 11.4)	0.2758
	6 mos.	52 $\pm$ 6.9	48 $\pm$ 10.3	4 (-3.4, 11.4)	0.2758
	12 mos.	48 $\pm$ 10.3	50 $\pm$ 10.3	-2 (-10.7, 6.7)	0.6390
<b>Disc height decrease</b>		<b><math>\Delta</math> vs baseline <math>\pm</math> SD†</b>	<b><math>\Delta</math> vs baseline <math>\pm</math> SD†</b>		
MRI Disc Height (mm)	NR	0.38 $\pm$ 0.66	0.04 $\pm$ 0.66	0.34 (-0.2, 0.9)	0.2202

CI = confidence interval; F/U = follow-up; IQR = interquartile range; MCS = Mental Component Summary. ; MD = mean difference between treatments; mm = millimeter; mos = months; MRI = magnetic resonance imaging; MSCs = mesenchymal stem cells; NR = not reported; PCS =Physical Component Summary; QoL = Quality of Life; RCT = randomized controlled trial; ROB = risk of bias; SD = standard deviation;

\* Effect sizes calculated unless otherwise indicated for comparison of treatment groups based on 2 sample t-test for differences in means;

†Where standard errors (SE) were reported, values were used to estimate standard deviation (SD): SD=SE\*SQRT(n)

**Appendix Table E2. Summary of case series secondary outcomes data (Coric 2013): Allogenic juvenile chondrocytes (expanded) for IVD repair in patients with low back pain and single level degenerative disc disease.**

Coric 2013 Case Series, High ROB Outcome Measure	F/U (months)	Allogenic chondrocytes (n= 15)	p-value across all time periods*
<b>Quality of life</b>		<b>Δ vs baseline</b>	
SF-36 PCS (0-100 (best))	0 mos.	35.3±NR	p=0.0002
	1 mos.	40.0±NR	
	3 mos.	43.1±NR	
	6 mos.	43.7± NR	
	12 mos.	46.9± NR	
SF-36 MCS (0-100 (best))	0 mos.	48.5± NR	p=0.64
	1 mos.	50.5± NR	
	3 mos.	51.1± NR	
	6 mos.	49.1± NR	
	12 mos.	50.5± NR	
<b>Radiographic (MRI)</b>		<b>% (n/N)</b>	
Improvement in disc contour or height	6 mos.	77% (10/13)	N/A

MCS = Mental Component Summary; mos = months; MRI = magnetic resonance imaging; N/A = Not applicable; NR = not reported; NS = not statistically significant; ODI = Oswestry Disability Index; PCS = Physical Component Summary;

\* P-values as reported by authors across follow-up periods



**Appendix Table E3. Summary of secondary outcomes from case series of autologous cells for IVD repair across common time frames**

Outcome Measure	Mesenchymal Cell Origin, Intervention	Author (year)	n	Mean ± SD	p-value based on Δ vs baseline*	
<b>Quality of life</b>						
<b>SF-36 PCS (0-100 (best))</b>						
Baseline	BMA (Non-Exp.)	Orozco 2011	10	12.7± 11.7†	N/A	
12 months			10	24.8±12.3†	p<0.05	
<b>SF-36 MCS</b>						
Baseline	BMA (Non-Exp.)	Orozco 2011	10	54.1± 33.5†	N/A	
12 months			10	49.7± 33.2†	p = 0.77	
<b>Radiographic</b>				<b>Mean±SD</b>		
<b>MRI-assessed Disc height (mm)</b>						
Baseline	BMA (Non-Exp.)	Orozco 2011	10	9.86±1.8†	N/A	
6 months					9.8±1.7†	NS
12 months					9.84±2.0†	NS
<b>X-Ray-assessed Disc height</b>	Adipose MSCs (Exp.) + HA	Kumar 2017	10	No decrease	NS	
12 months						

BMA = bone marrow aspirate; Exp. = expanded cells; HA = hyaluronic acid; MCS = Mental Component Summary; mm = millimeter; MRI = magnetic resonance imaging; N/A = Not applicable; Non-Exp = non-expanded cells; NS = not statistically significant; PCS = Physical Component Summary; SD = standard deviation;

\* p-values as reported by authors

†Where standard errors (SE) were reported, values were used to estimate standard deviation (SD): SD=SE\*SQRT(n)