Intradiscal Biologics for the treatment of Chronic Discogenic Low Back Pain.

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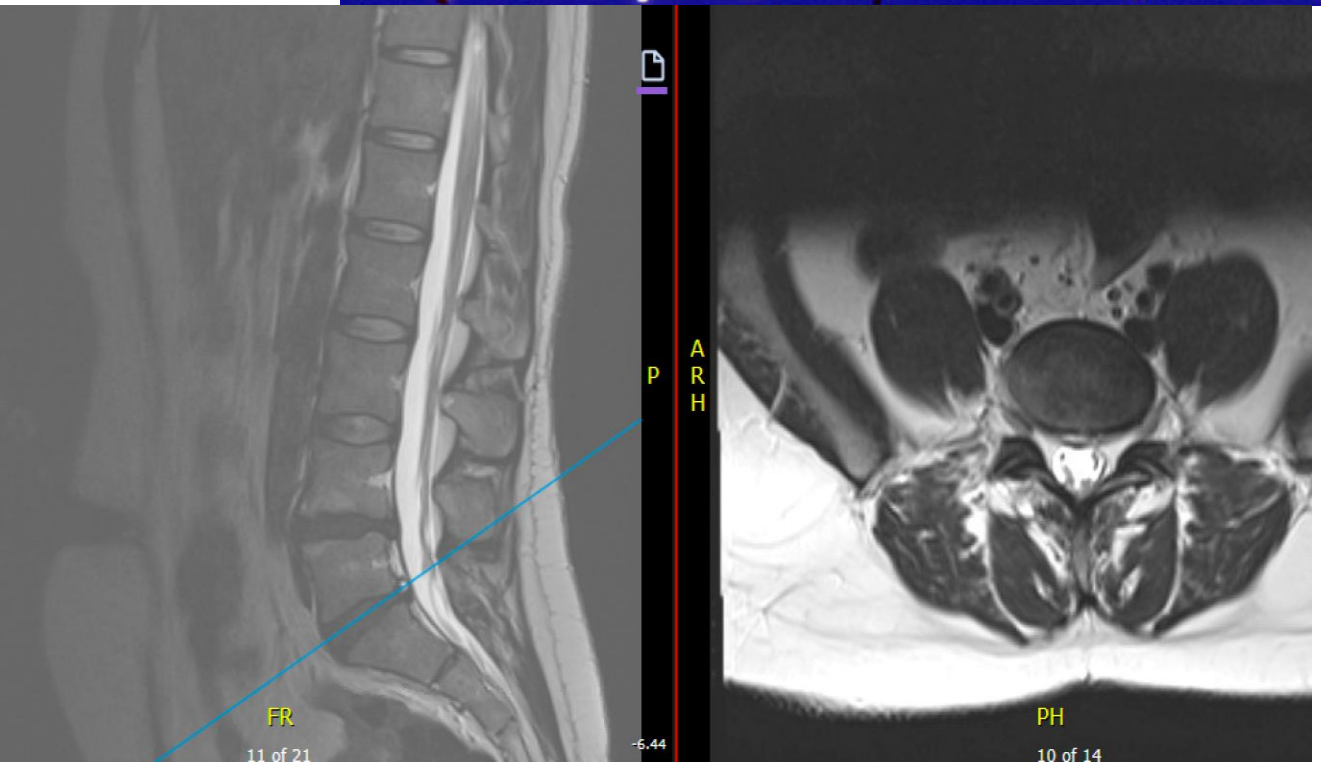
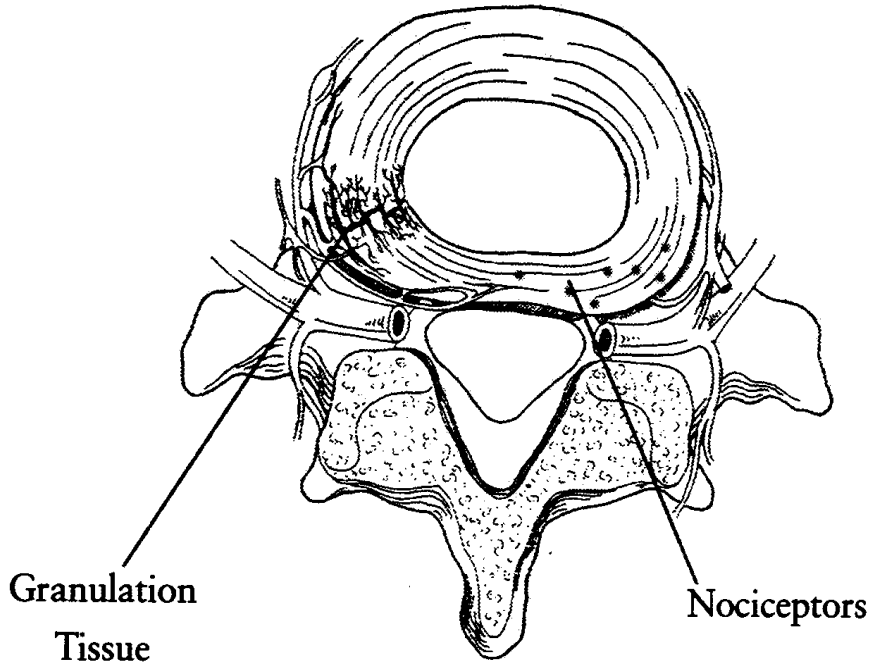
Disc Degeneration vs. Discogenic Pain





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Discogenic Pain

57 biopsy samples of anterior L3 to L5 intervertebral discs obtained during combined anterior/ posterior fusion surgery for chronic (>12 months) back pain
Confirmed in growth of unmyelinated nerve tissue into annulus fissures

The Lancet, 1997; 350: 178-81, A J Freemont, T E peacock, P Goupille, J A Hoyland, J O'Brian, M I V Jayson

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Nerve Elements in the Intervertebral Disc

	Perivascular small nerves		Myelinated large-caliber		Small free nerve fibers		Mechano-receptors	
	C	*DD*	*C*	*DD*	*C*	*DD*	*C*	*DD*
ALL	+	+	+	+	+	+	-	-
Transitional zone between ALL and AF	+	+	+	+	+	+	-	+ (4/10)
Outer zone AF (outer 1/3)	-	-	+	+	+	+	-	+ (1/10)
Inner zone AF (inner 2/3)	-	-	-	-	-	+ (8/10)	-	-
Nucleus pulposus	-	-	-	-	-	+ (2/10)	-	-

Coppes, et al. Spine 1997

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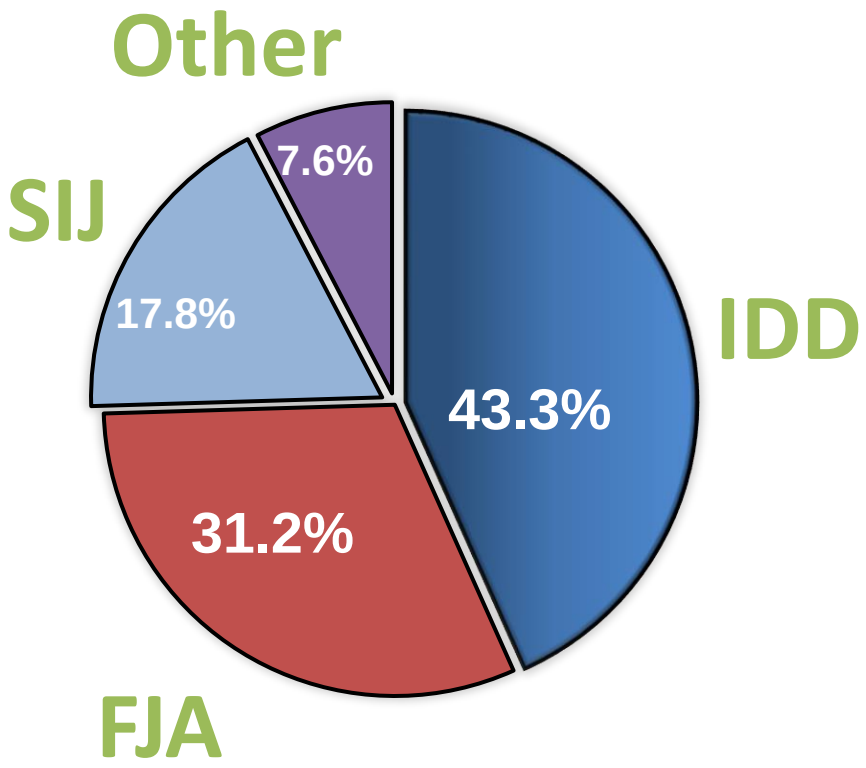
Prevalence of Source of CLBP



- IDD = degradation of nuclear matrix & development of annular fissures
- IDD is one of the most common cause of CLBP
- Prevalence lies between 30-50%

(Schwarzer A. Spine 1995)

Retrospective chart review 378 cases
Laplante et al: Pain Physician 2012

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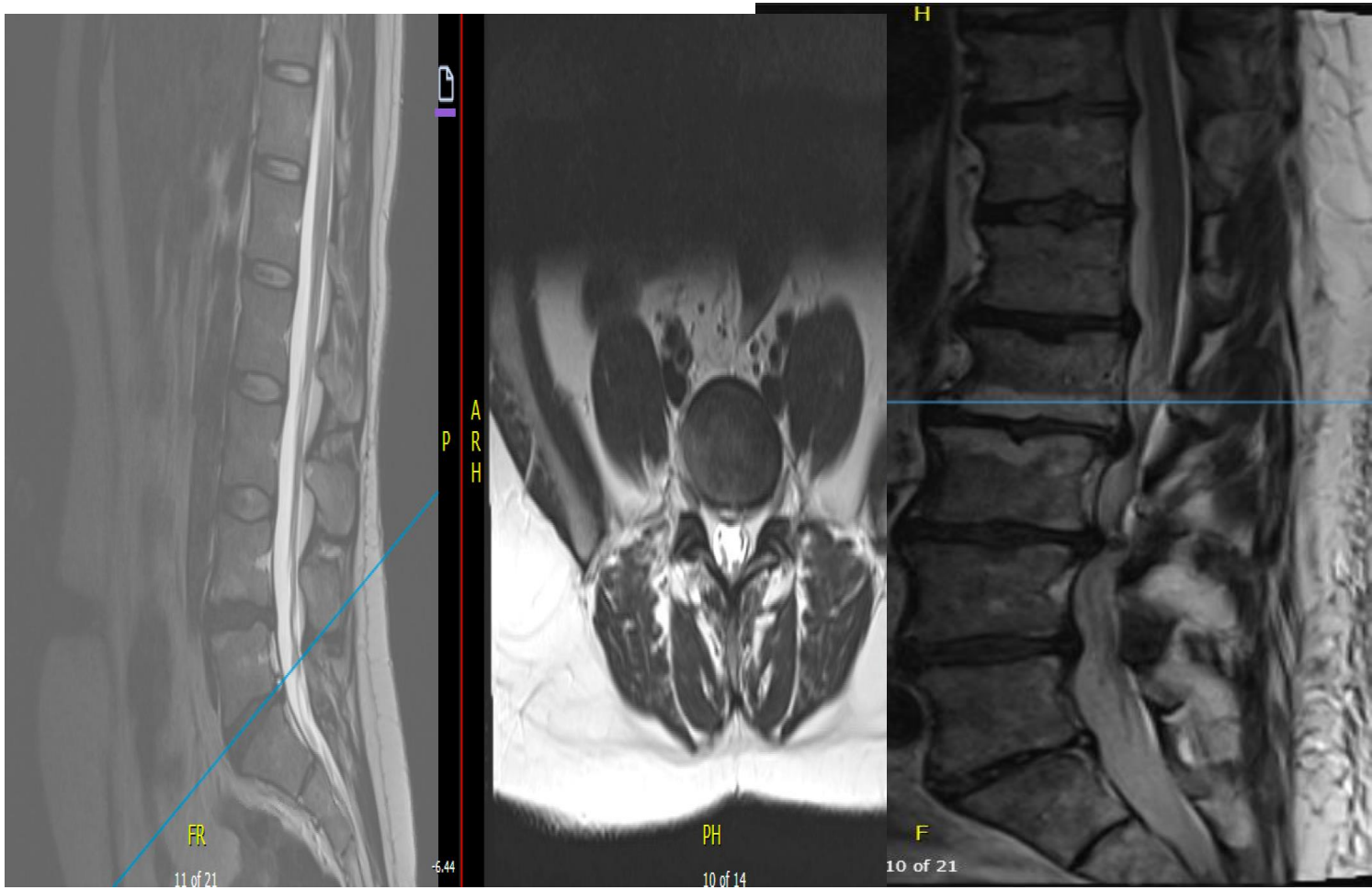
Lumbar Disc Degeneration

- Affects more than 16 million individuals in the U.S. every year [1]
- Is a leading cause of disability worldwide [2]
- Costs more than $100B per year in the U.S. alone [3]
- Is the primary reason for non-cancer opioid prescriptions [4]

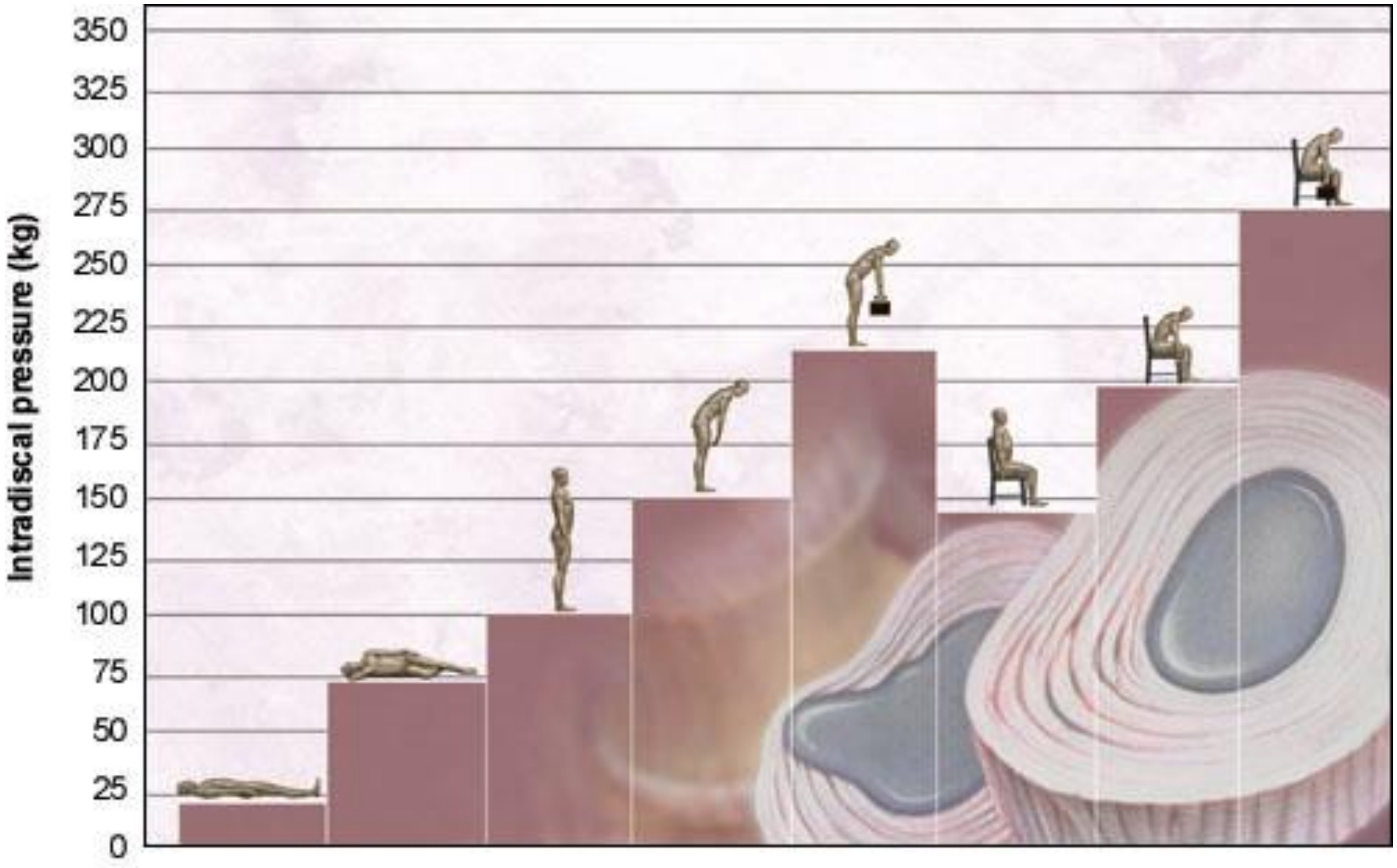
1. Ravindra VM et al. "Degenerative lumbar spine disease: Estimating global incidence and worldwide volume." *Global Spine Journal* 2018.
2. Hoy D et al. "The global burden of low back pain." *Ann. Rheum Dis.* 2014.
3. Davis AD et al. "Where the United States spends its spine dollars." *Spine* 2012.
4. Ringwalt et al. "Differential prescribing of opioid analgesics." *Pain Res Manag* 2014.

Discogenic Pain Criteria:

- Lumbar spine pain > 6 months
- Sitting intolerance.**
- Increased pain with bending forward and compression**.
- Pain is less with lying down or hip extension
- No radicular leg pain
- Pain with Sustained Hip Flexion**
- Normal neurologic exam
- Straight leg raising negative
- MRI: Dark disc with no nerve compression
- Positive provocative discography**



Intradiscal Pressure at Various Body Positions



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Location of Low Back Pain

Original Research

Does the Location of Low Back Pain Predict Its Source?

Michael J. DePalma, MD, Jessica M. Ketchum, PhD, Brian S. Trussell, MD, Thomas R. Saullo, MD, Curtis W. Slipman, MD

Table 2. *Contingency tables of presence/absence of midline and paramidline LBP vs positive/negative diagnoses for IDD, FJP, and SIJP*

	IDD			FJP			SIJP		
	Yes	No	Total	Yes	No	Total	Yes	No	Total
Midline LBP									
Present	68	25	93	8	85	93	4	89	93
Absent	3	74	77	44	33	77	27	50	77
Total	71	99	170	52	118	170	31	139	170
Paramidline LBP									
Present	35	68	103	38	65	103	24	79	103
Absent	17	7	24	2	22	24	1	23	24
Total	52	75	127	40	87	127	25	102	127

LBP = low back pain; IDD = internal disk disruption; FJP = facet joint pain; SIJP = sacroiliac joint pain.

PM&R
1934-1482/11/$36.00
Printed in U.S.A.

Vol. 3, 33-39, January 2011
DOI: 10.1016/j.pmrj.2010.09.006

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Low Back Pain with Sustained Hip Flexion

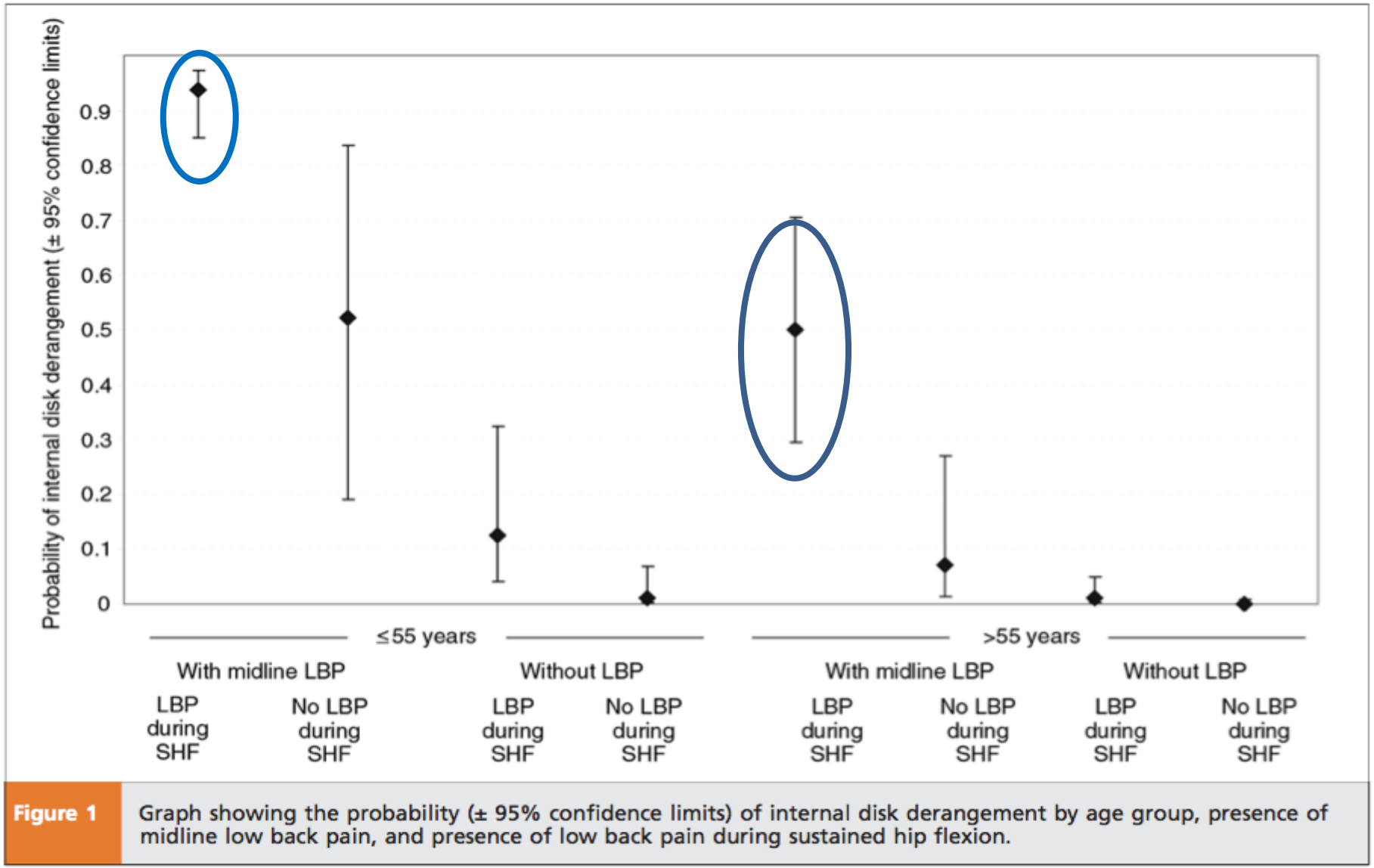

Figure 1 Graph showing the probability (± 95% confidence limits) of internal disk derangement by age group, presence of midline low back pain, and presence of low back pain during sustained hip flexion.

DePalma, Michael et al., PM&R 3(1), 2011

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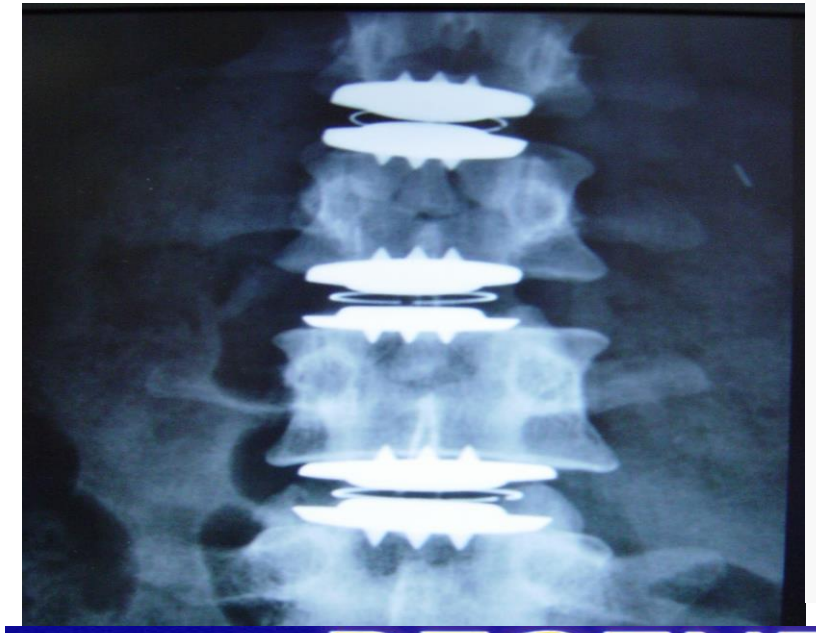
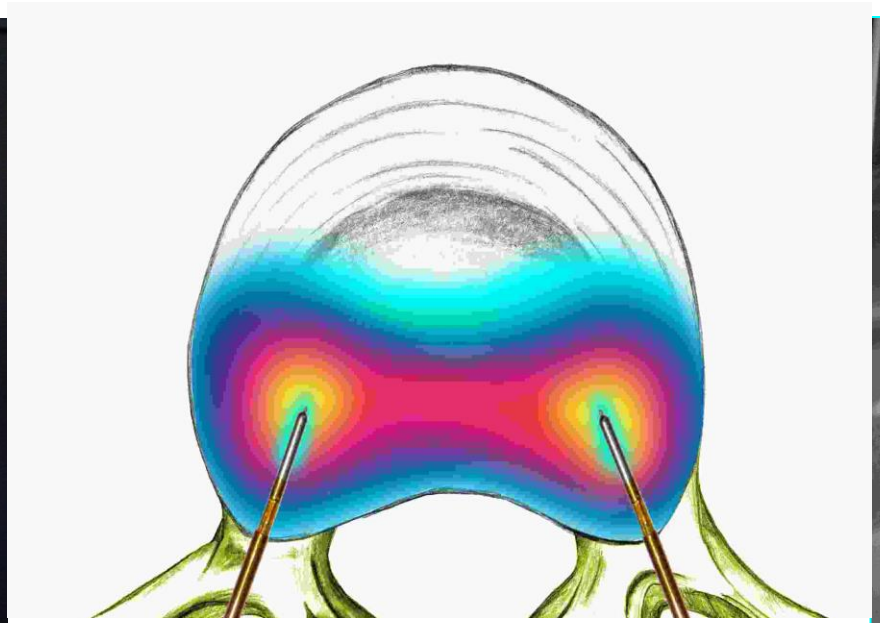
Current Treatment Options:

Replacement

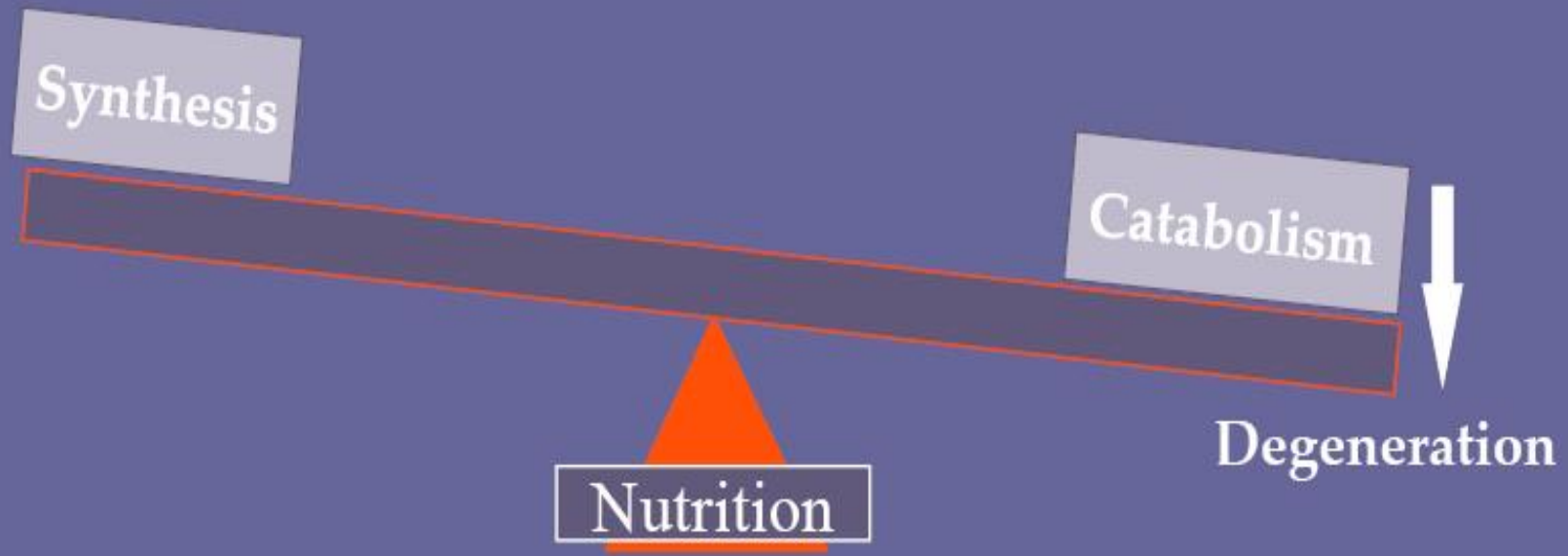


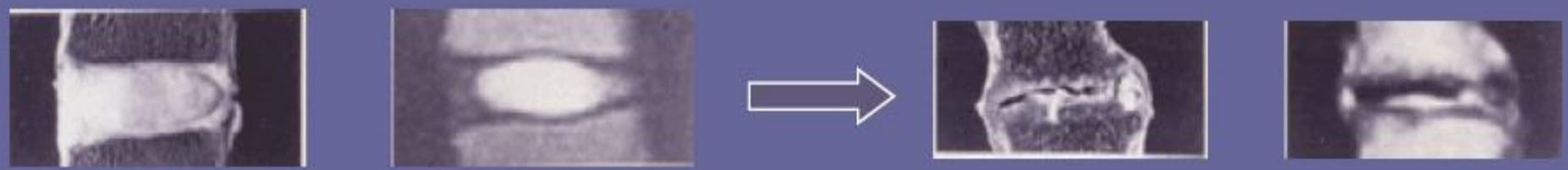
Ablation



Fusion

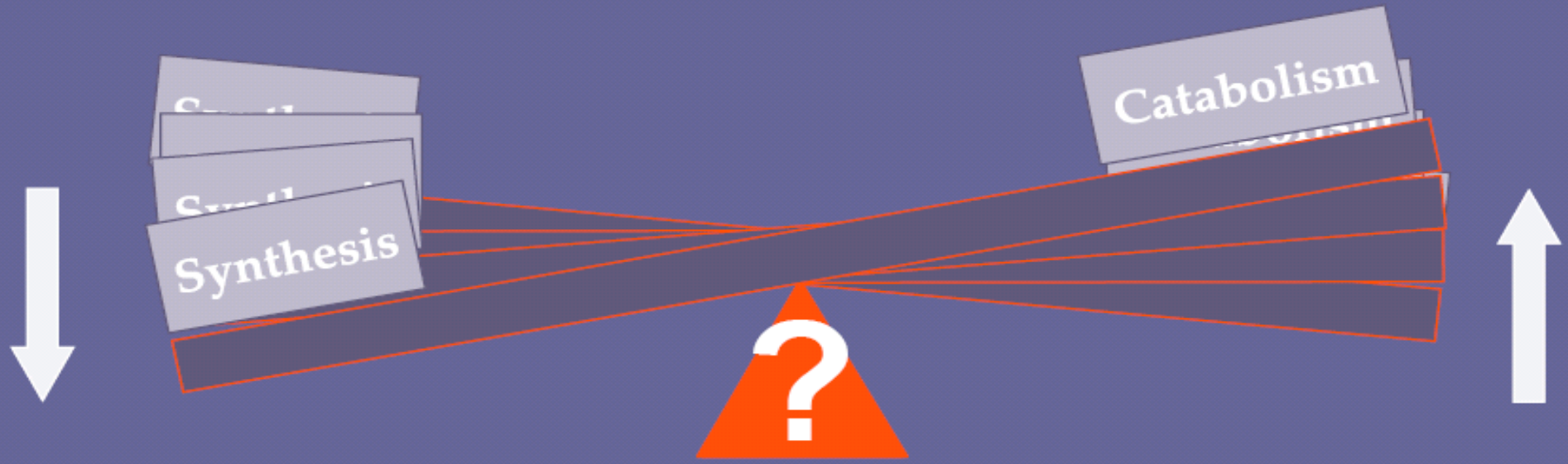
Imbalance
in proteoglycan synthesis / catabolism





Biologic Approaches to the Treatment of Degeneration Disc Disease

- **Intervene prior to end stage anatomic disease**
- **Address the underlying pathology**
- **Promote / Up-regulate Matrix Synthesis**
- **Inhibit Catabolic Processes**
- **Replace Lost Number of Cells to Increase Matrix**



Effectiveness of Intradiscal Regenerative Medicine Therapies for Long-Term Relief of Chronic Low Back Pain: A Systematic Review and Meta-Analysis

Study Design & Methods

- **Design:**
  - Systematic review and meta-analysis evaluating intradiscal injections for discogenic low back pain
- **Methods:**
  - **Data Sources:**
    - PubMed, Cochrane Library, U.S. National Guideline Clearinghouse, prior systematic reviews, and reference lists (1996–Sept 2024)
  - **Study Selection:**

- Included 8 RCTs (4 evaluating PRP, 4 evaluating MSCs) and 8 observational studies (4 assessing PRP, 4 assessing MSCs)

Manchikanti L, Knezevic E, Knezevic NN, Kaye AD, Atluri S, Sanapati MR, Pampati V, Hirsch JA. Effectiveness of Intradiscal Regenerative Medicine Therapies for Long-Term Relief of Chronic Low Back Pain: A Systematic Review and Meta-Analysis. Pain Physician. 2024 Dec;27(10):E995-E1032. PMID: 39688822.

Results:

- **Clinical Outcomes:**
  - ❖ Significant improvements observed in pain relief, physical function, and overall quality of life
- **Evidence Quality:**
  - ❖ Determined to be fair (Level III) with limited certainty and moderate recommendation strength
- **Limitations:**
  - ❖ Paucity of high-quality studies leading to moderate confidence in the evidence

Conclusion:

❖ This systematic review and single-arm meta-analysis suggest that intradiscal injections of MSCs and PRP may be effective in managing discogenic low back pain, supported by Level III evidence.

Manchikanti L, Knezevic E, Knezevic NN, Kaye AD, Atluri S, Sanapati MR, Pampati V, Hirsch JA. Effectiveness of Intradiscal Regenerative Medicine Therapies for Long-Term Relief of Chronic Low Back Pain: A Systematic Review and Meta-Analysis. Pain Physician. 2024 Dec;27(10):E995-E1032. PMID: 39688822.

The effectiveness of intradiscal biologic treatments for discogenic low back pain: a systematic review

Study Design & Methodology

- **Study Design:**
  - PRISMA-compliant systematic review focused on intradiscal biologic therapies for discogenic low back pain
- **Patient Sample**:
  - Patients diagnosed via provocation discography or clinical/imaging findings
- **Methodology:**
  - Comprehensive literature search in 2018 with an update in 2020
  - Interventions evaluated: Mesenchymal stem cells (MSC), Platelet-rich plasma (PRP), Microfragmented fat, amniotic membrane-based injectates and autologous conditioned serum

Schneider BJ, Hunt C, Conger A, Qu W, Maus TP, Vorobeychik Y, Cheng J, Duszynski B, McCormick ZL. The effectiveness of intradiscal biologic treatments for discogenic low back pain: a systematic review. Spine J. 2022 Feb;22(2):226-237. doi: 10.1016/j.spinee.2021.07.015. Epub 2021 Aug 2. PMID: 34352363.

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- **Results & Outcomes:** ***ref
  - Search yielded 3,063 articles → 37 full-text reviews → 12 studies met inclusion criteria
  - **Primary Outcome:** ≥50% pain relief at 6 months
  - **PRP:** Success rate of 54.8% (95% CI: 40%-70%)
  - **MSC:** Success rate of 53.5% (95% CI: 38.6%-68.4%), dropping to 40.7% in worst-case analysis (95% CI: 28.1%-53.2%)
  - **Functional Improvement:** ≥30% improvement in 74.3% of patients (95% CI: 59.8%-88.7%), worst-case at 44.1% (95% CI: 28.1%-53.2%)
- **Limitations/Shortfalls:**
  - Overall, very low quality of evidence
  - Notable methodological flaws in the single PRP randomized controlled trial and Negative findings in the single MSC trial
- **Conclusion:**
  - Limited observational support for intradiscal biologic agents in treating discogenic low back pain
  - Evidence (per GRADE system) for MSC and PRP remains very low quality

***Manchikanti L, Knezevic E, Knezevic NN, Kaye AD, Atluri S, Sanapati MR, Pampati V, Hirsch JA. Effectiveness of Intradiscal Regenerative Medicine Therapies for Long-Term Relief of Chronic Low Back Pain: A Systematic Review and Meta-Analysis. Pain Physician. 2024 Dec;27(10):E995-E1032. PMID: 39688822.

Why clinical trials in disc regeneration strive to achieve completion: Insights from publication status and funding sources

Study Design & Methodology

- **Objective:**
  - Analyze prospective clinical trials on cell-based treatments for chronic discogenic low back pain (LBP)
- **Methods:**
  - Systematic search for prospective trials in ClinicalTrials.gov focused on cell-based therapies for LBP due to intervertebral disc degeneration
  - Data extracted on:
    - Study design and recruitment
    - Experimental treatment modalities
    - Investigated outcomes
    - Current status, completion date, and publication status
    - Funding sources

Ambrosio L, Petrucci G, Russo F, Cicione C, Papalia R, Vadalà G, Denaro V. Why clinical trials in disc regeneration strive to achieve completion: Insights from publication status and funding sources. JOR Spine. 2024 May 24;7(2):e1329. doi: 10.1002/jsp2.1329. PMID: 38800643; PMCID: PMC11126785.

Results & Outcomes:

Trial Identification:

- Total of 26 clinical trials found
- Only 7 trials (26.9%) were published
- Non of other completed trials on ClinicalTrials.gov reported any results.

Funding Sources:

- 50% funded by universities
- 38.5% sponsored by industry
- 11.5% funded by private institutions

Experimental Treatments:

- Primarily cell-based or cell-derived products with variable sources and concentrations
- Products with carriers (e.g., hyaluronic acid, fibrin) were more frequently funded by industry/private organizations ($p = 0.0112$)

Outcome Association:

- No significant differences in publication status based on funding or other extracted variables

Ambrosio L, Petrucci G, Russo F, Cicione C, Papalia R, Vadalà G, Denaro V. Why clinical trials in disc regeneration strive to achieve completion: Insights from publication status and funding sources. JOR Spine. 2024 May 24;7(2):e1329. doi: 10.1002/jsp2.1329. PMID: 38800643; PMCID: PMC11126785.

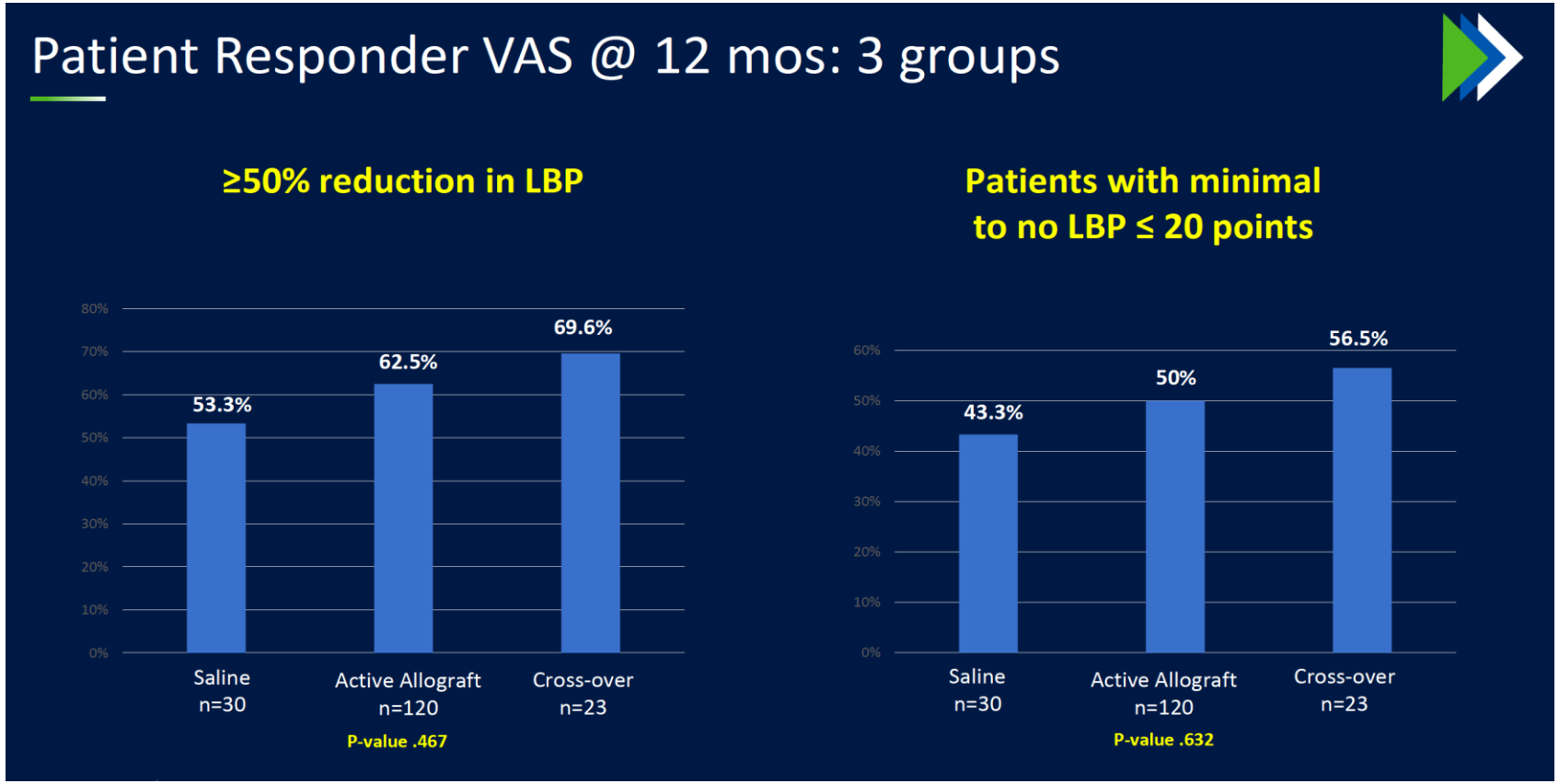
- **Limitations/Shortfalls:**
  - Majority of trials remain incomplete or unpublished
  - Overall, only a small fraction have reported preliminary data
  - Existing studies show only minor improvements, highlighting challenges in trial design and funding
- **Conclusion:**
  - Most clinical trials exploring cell-based disc regenerative therapies for chronic LBP have not reached completion
  - There is a critical need for more robust, well-designed studies to establish efficacy and overcome current obstacles

Ambrosio L, Petrucci G, Russo F, Cicione C, Papalia R, Vadalà G, Denaro V. Why clinical trials in disc regeneration strive to achieve completion: Insights from publication status and funding sources. JOR Spine. 2024 May 24;7(2):e1329. doi: 10.1002/jsp2.1329. PMID: 38800643; PMCID: PMC11126785.

	Inclusion Criteria	Imaging Criteria	Discography	Outcom	# Patients	Total	Follow-Up	Responder Rate
	Platelet Rich Plasma (PRP)							
	Observational Studies							
Navani 2015	discogenic LBP ≥6 mos; failed conservative tx	disc height of ≥50%; degenerative discs, annular tears, or contained disc protrusion on CT	concordant pain on discography	Verbal Pain Scale	6	6	q2-4 weeks for 6 months	6 months: 6/6 100%
Levi 2016	back pain greater than leg pain with an intensity of 40mm on a 100mm VAS; facet pain excluded by blocks	feature suggestive of discogenic pain (e.g. HIZ, disc protrusion, decreased signal intensity on T2 imaging or Modic changes)	not required, but some had prior discogram	VAS	22	22	1,2,6 months	1 month: 7/22 [32% (12-51%)] 2 months: 9/22 [41% (20-61%)] 6 months: 9/22 [41% (20-61%)]
Akeda 2017	discogenic LBP ≥3 mos	disc degeneration, grade 3 on MRI; disc height ≥50%	concordant pain on discography or disc block	VAS	14	14	4,8,16,24, 32,40,48 weeks	4 weeks: 10/14 [71% (48-95%)] 24 weeks: 7/14 [50% (24-76%)] 48 weeks: 6/14 [43% (17-69%)]
	Bone Marrow Aspirate Concentrate - Autologous							
	Observational Studies							
Pettine 2015	centralized LBP≥6 mos; failed conservative tx≥3 mos; ODI of at least 30/100; VAS of at least 40/100	MRI modified Pfirmann score of 4-7; Modic I or II; disc height loss of <30%	not required, but 7 had discogram to confirm affected levels	VAS	26	26	3,6,12 months	6 months: 19/26 [73% (56-90%)] 12 months: 16/26 [62% (43-80%)]
Wolff 2020			positive discogram	NRS	33	33	2,6,12,24, 52 weeks	As reported: 2 weeks 4/29 (13.8%, 95% CI: 1.2-26.3%) 6 weeks 11/24 (45.8%, 95% CI: 25.6-65.8%) 12 weeks 7/17 (41.1%, 95% CI:17.8-64.6%) 24 weeks 4/17 (23.5%, 95% CI: 3.3-43.7%) 52 weeks 7/18 (38.9%, 95% CI: 16.4-61.4%) Worst Case analysis: 2 weeks 4/33 (12.1%, 95% CI: 1.0-23.3%) 6 weeks 11/33 (33.3%, 95% CI: 17.2-49.4%) 12 weeks 7/33 (21.2%, 95% CI: 7.3-35.2%) 24 weeks 4/33 (12.1%, 95% CI: 1.0-23.3%) 52 weeks 7/33 (21.2%, 95% CI: 7.3-35.2%)
	Mesenchymal Stem Cells - Autologous							17.8-64.6%) 24 weeks 4/17 (23.5%, 95% CI: 3.3-43.7%) 52 weeks 7/18 (38.9%, 95% CI: 16.4-61.4%) Worst Case analysis: 2 weeks
	Observational Studies							4/33 (12.1%, 95% CI: 1.0-23.3%) 6 weeks 11/33 (33.3%, 95% CI: 17.2-49.4%) 12 weeks 7/33 (21.2%, 95% CI: 7.3-35.2%) 24 weeks
Kumar 2017	discogenic LBP ≥3 mos; failed conservative tx; ≥4/10 VAS; ≥30% disability ODI	MRI (Pfirmann stages 3 or 4); decrease in disc height of >20%	degenerative symptomatic discs on discography	VAS	10	10	1 week, 1,3,6,9,12 months	4/33 (12.1%, 95% CI: 1.0-23.3%) 52 weeks 7/33 (21.2%, 95% CI: 7.3-35.2%)

Manchikanti L, Knezevic E, Knezevic NN, Kaye AD, Atluri S, Sanapati MR, Pampati V, Hirsch JA. Effectiveness of Intradiscal Regenerative Medicine Therapies for Long-Term Relief of Chronic Low Back Pain: A Systematic Review and Meta-Analysis. Pain Physician. 2024 Dec;27(10):E995-E1032. PMID: 39688822.

VIA –Disc Allograft: “VAST Clinical Trial”



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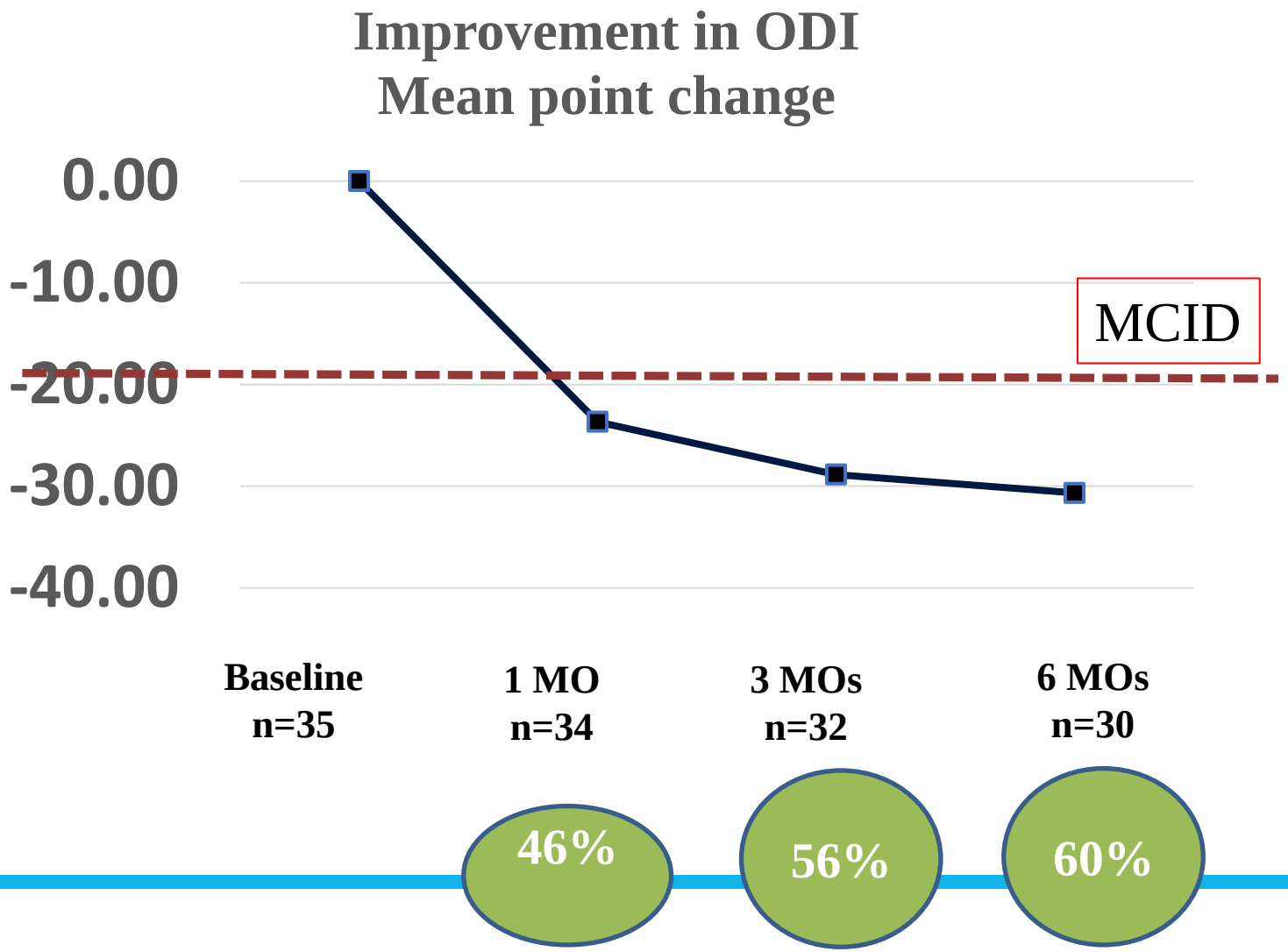
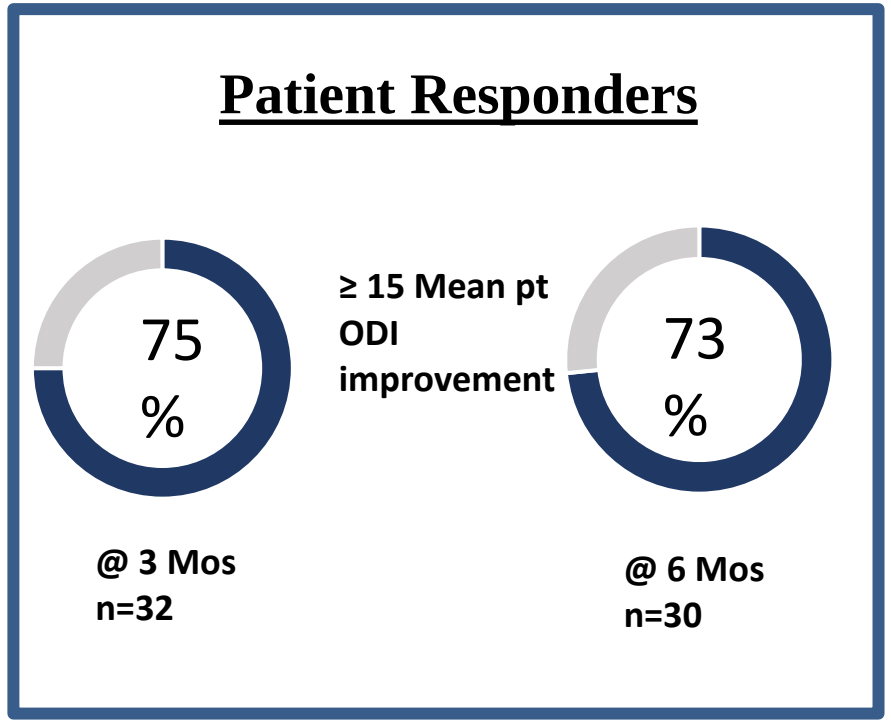
Nucleus Polyposis Allograft for Discogenic Pain





ODI mean point change versus baseline:
Baseline = 51.4 (ITT analysis)

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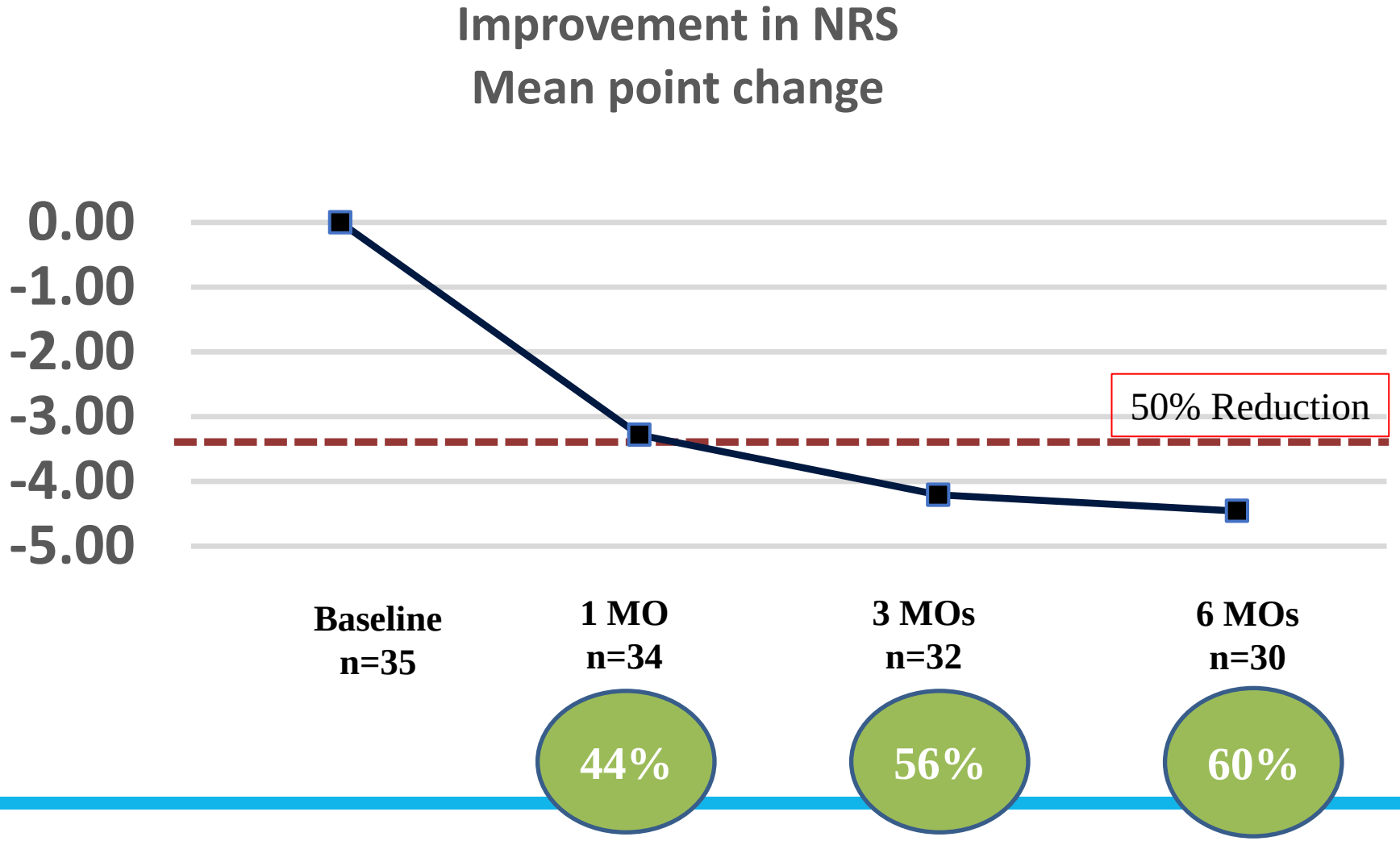
Nucleus Polyposis Allograft for Discogenic Pain



NRS mean point change versus baseline: Baseline = 7.5 (ITT analysis)

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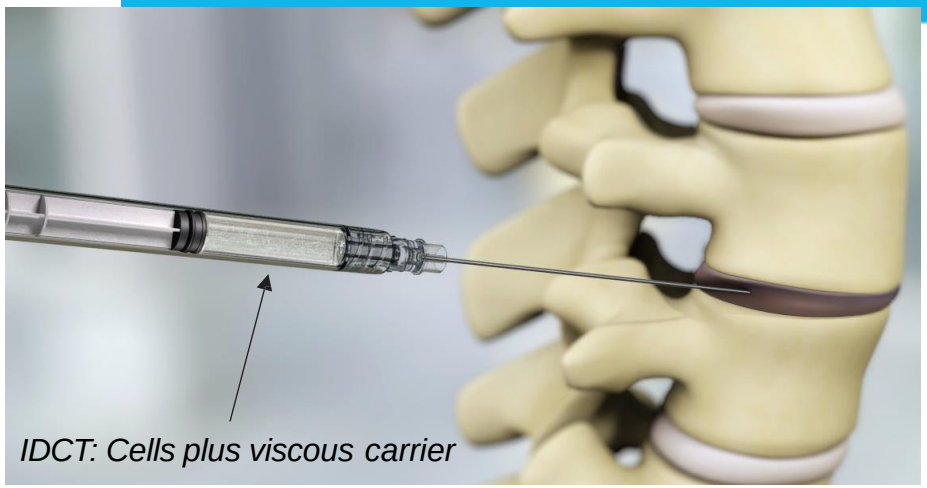
IDCT: A CELL-BASED BIOLOGIC DRUG THERAPY FOR DDD

- A single-injection cell-based biologic drug designed to halt the progression of DDD and **regenerate the disc from the inside-out**
- Active ingredient is a live **discogenic progenitor cell population** derived from donated adult human intervertebral disc tissue
  - Culture conditions optimized to maximize potency
  - Frozen to ensure viability with proven, validated cold chain logistics to 14 sites in US and 7 sites in Japan
- Injected into the degenerated disc in an out-patient procedure requiring no donor matching or immunosuppressants

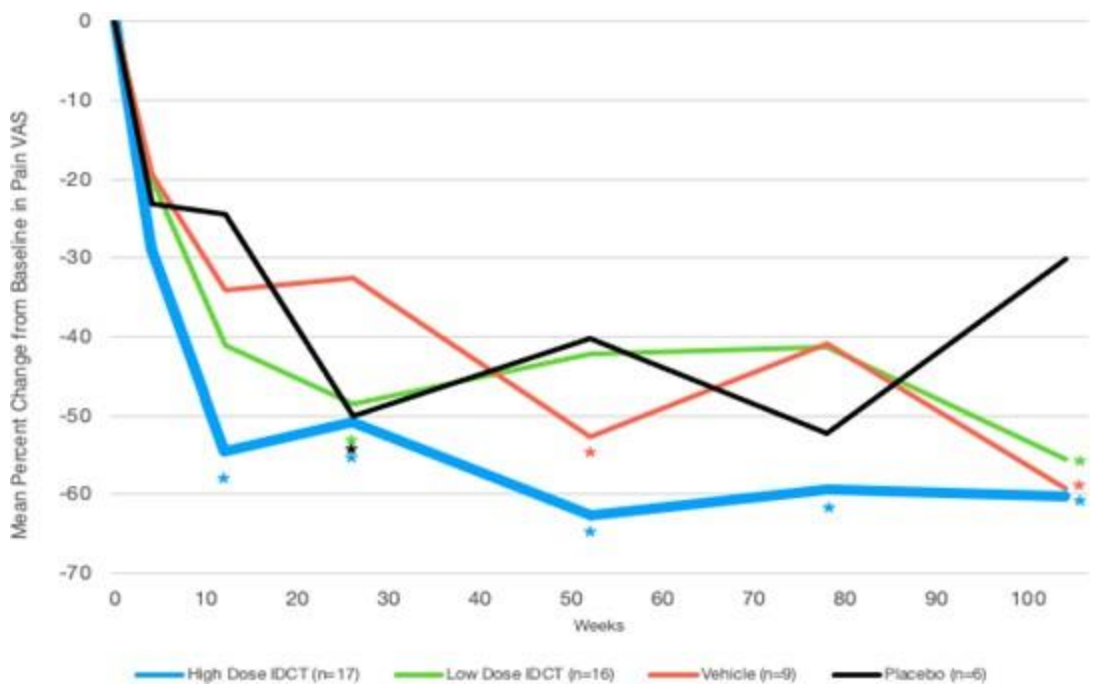
Injection of IDCT (rebonuputemcel) into Painful, Degenerated Lumbar Discs



IDCT: Cells plus viscous carrier

IND-ALLOWED PHASE I/II RESULTS: LOW BACK PAIN & FUNCTION

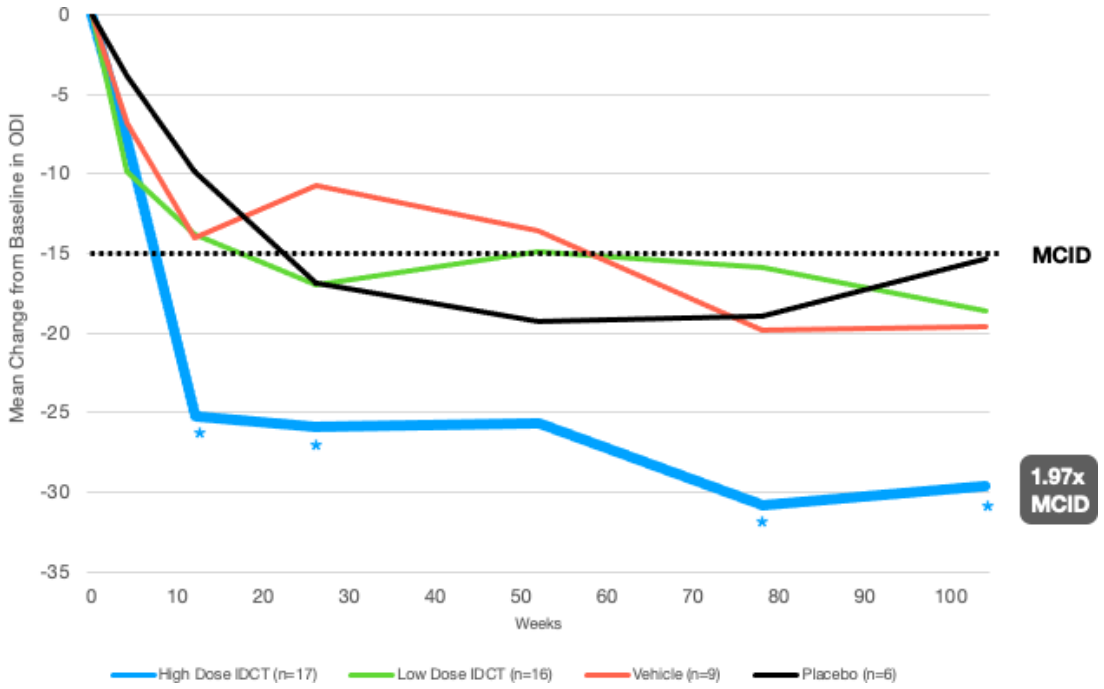
Mean % Change from Baseline in Low Back Pain 100-mm VAS (mITT Set)



*Asterisk indicates statistically significant for improvement >30%

Opioid use decreased among the high dose IDCT group and increased among the vehicle group compared to baseline.

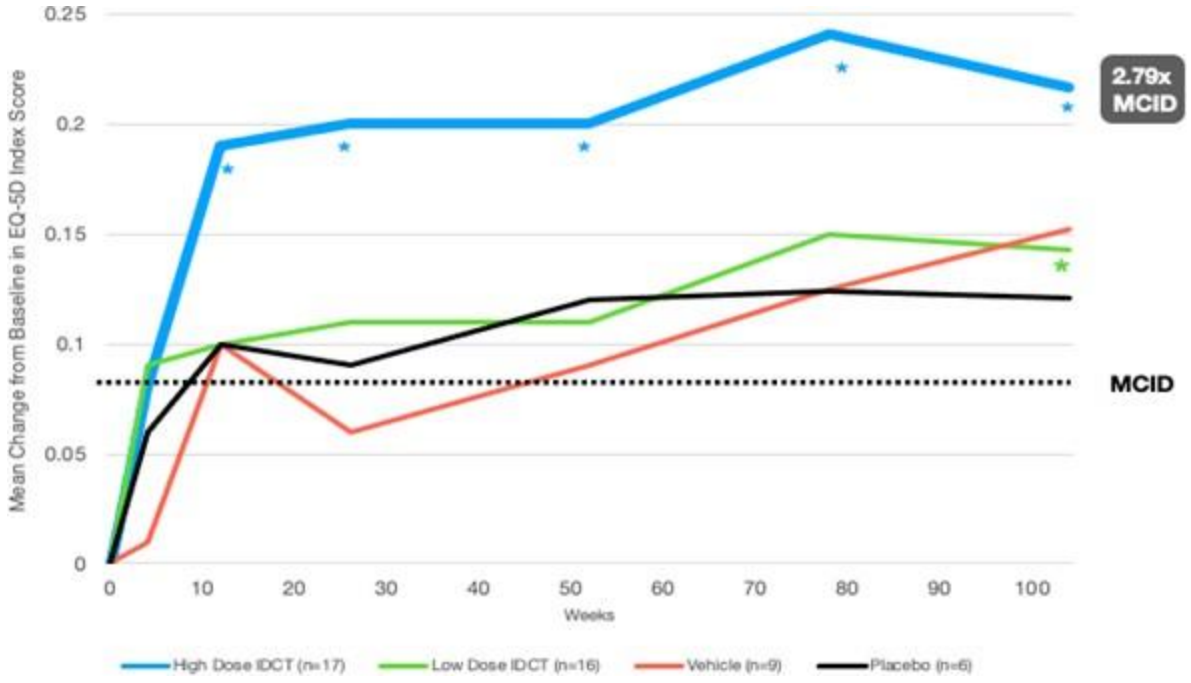
Mean Change from Baseline in ODI by Visit (mITT Set)



*Asterisk indicates statistically significant over MCID of -15

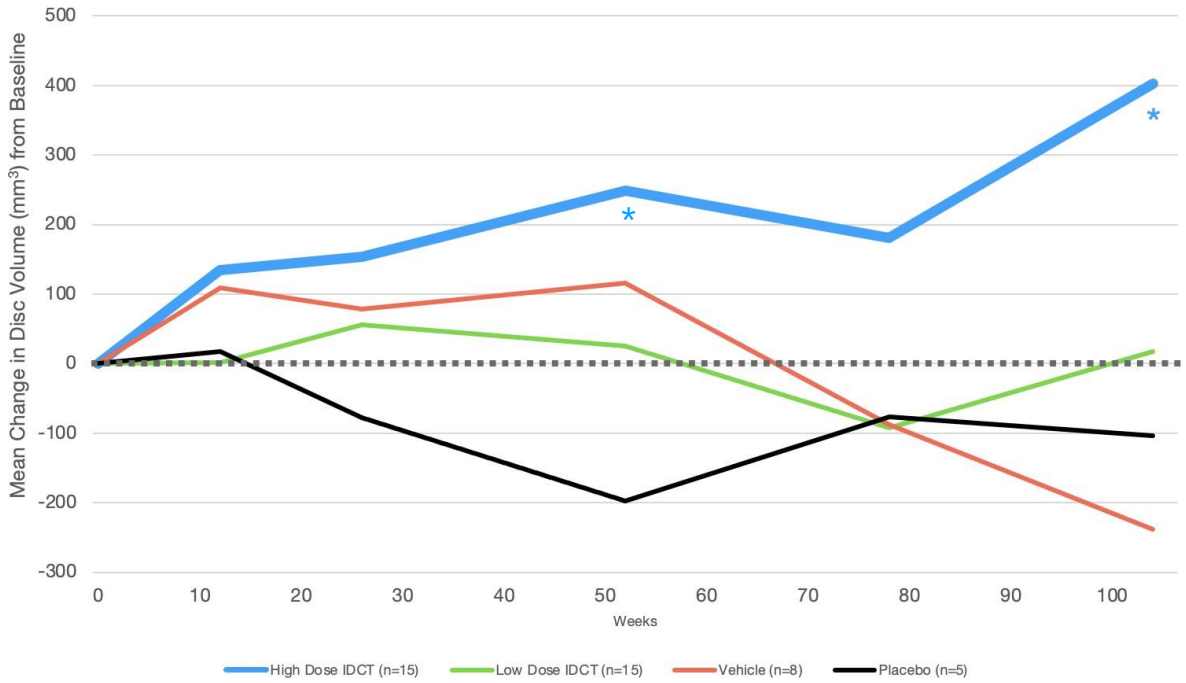
IND-ALLOWED PHASE I/II RESULTS: QUALITY OF LIFE & DISC VOLUME

Mean Change from Baseline in EQ-5D (mITT Set)



*Asterisk indicates statistically significant over MCID of 0.08

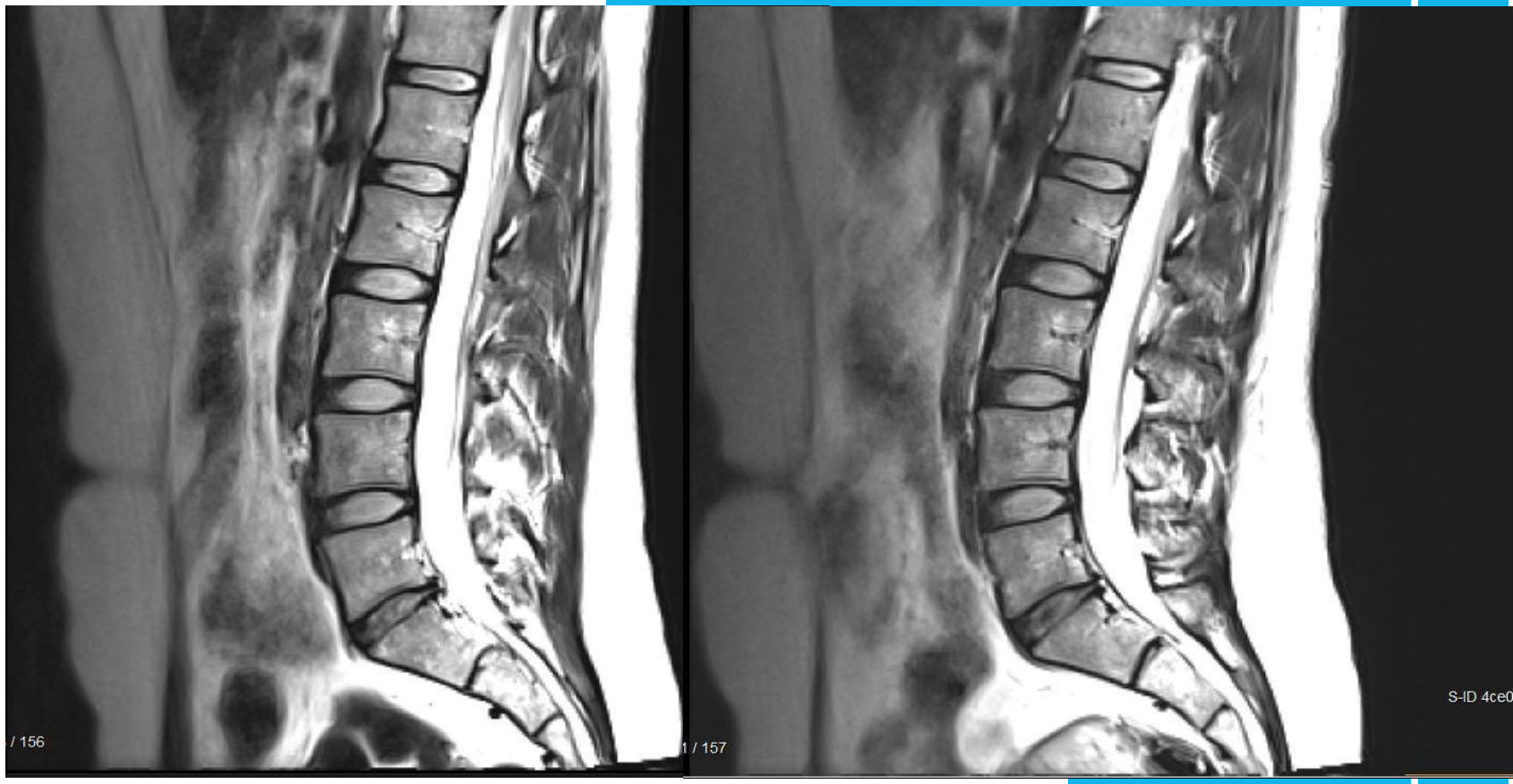
Mean Change from Baseline in MRI Measurement** of Disc Volume (mITT Set)



*Asterisk indicates statistically significant over baseline
** Based on validated, semi-automated analysis methodology

CASE STUDY SCREENING MRI

- Single-level disc pathology L5-S1
- Posterior annular tear
- Loss of disc height



Thank you