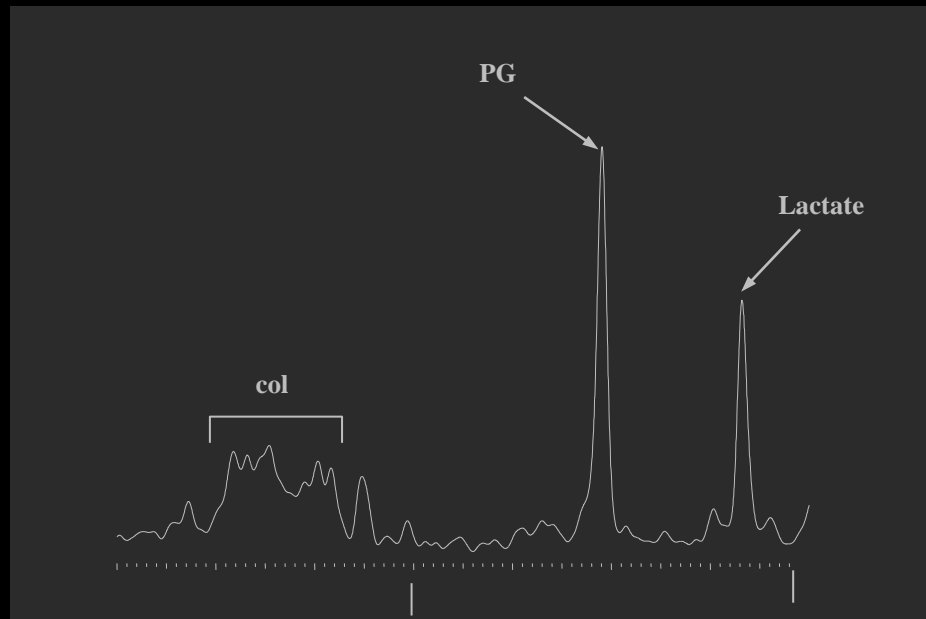


Single Voxel MR Spectroscopy in Non-Herniated Painful, Herniated Painful, and Non-Painful Lumbar Discs



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Disclosures

- Tanenbaum, L: Nocimed, LLC - advisory board
- Bradford, D; Lotz, J: Nocimed, LLC - management, shareholder, royalty
- Kane, P; Claude, J: Nocimed, LLC - shareholder, consulting
- Peacock, J: Nocimed, LLC - management, shareholder
- Schranck, F; Gornet, M: The Orthopedic Center of St. Louis - Nocimed sponsored research grant, Nocimed, LLC - shareholder

Purpose

- Evaluate non-invasive *in vivo* single voxel MR spectroscopy (SVS) in lumbar discs on two commercial 3T scanners - GE Signa & Siemens Verio for
 - a) discogenic low back pain (LBP) pain patients receiving provocative discography (PD), and
 - b) asymptomatic control volunteers (ASY)
- Correlate results to clinical phenotypes
 - non-herniated painful (NHP)
 - herniated painful (HP)
 - non-painful (NP) discs

Background

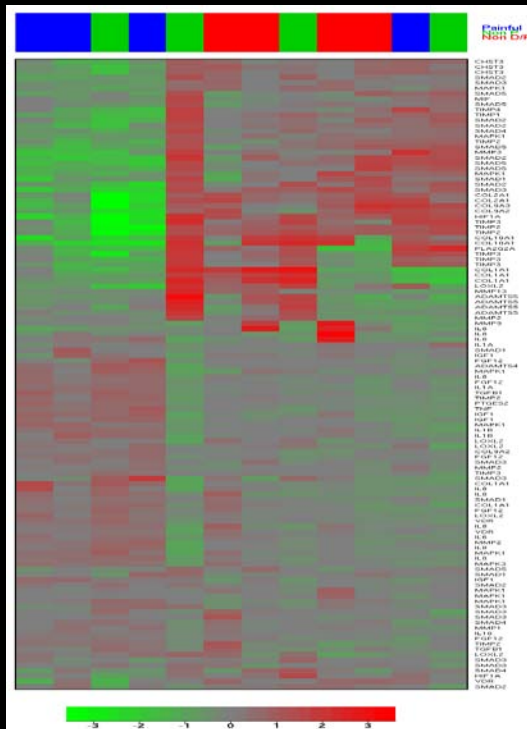
Disc degeneration

- altered disc structure and biochemical composition that may or may not cause pain
 - decreased proteoglycan synthesis
 - increase matrix catabolism
- features that differentiate painful from non painful degenerative discs not well understood.

Background

Disc degeneration

- consistent changes in markers of hypoxia, innervation and inflammation showed strong correlation with discs associated with pain



Nucleus samples



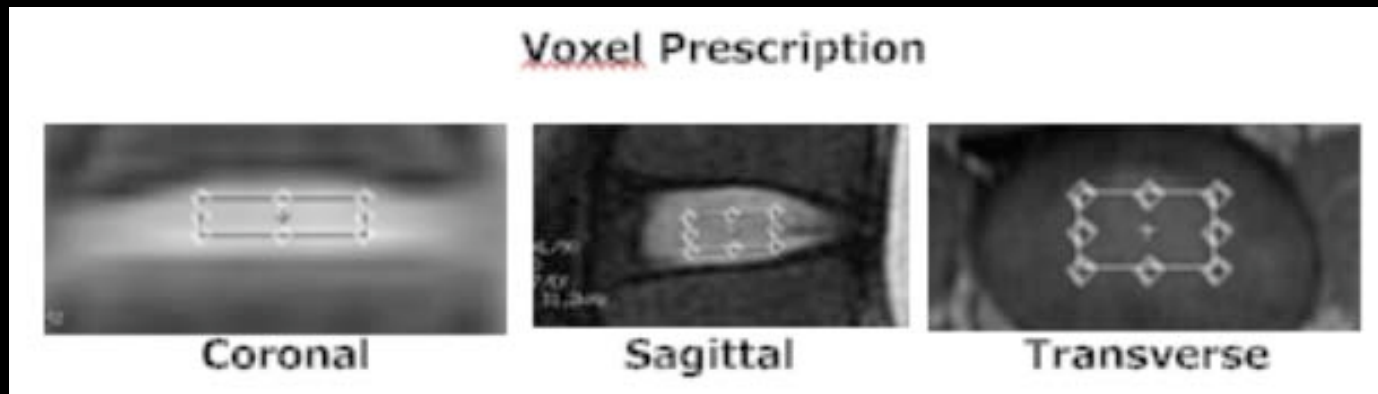
Gene expression with highest correlation between painful vs. non-painful discs relate to ($R^2=.67$):

1. hypoxia - lactate dehydrogenase;
2. innervation - nerve growth factor.

Background

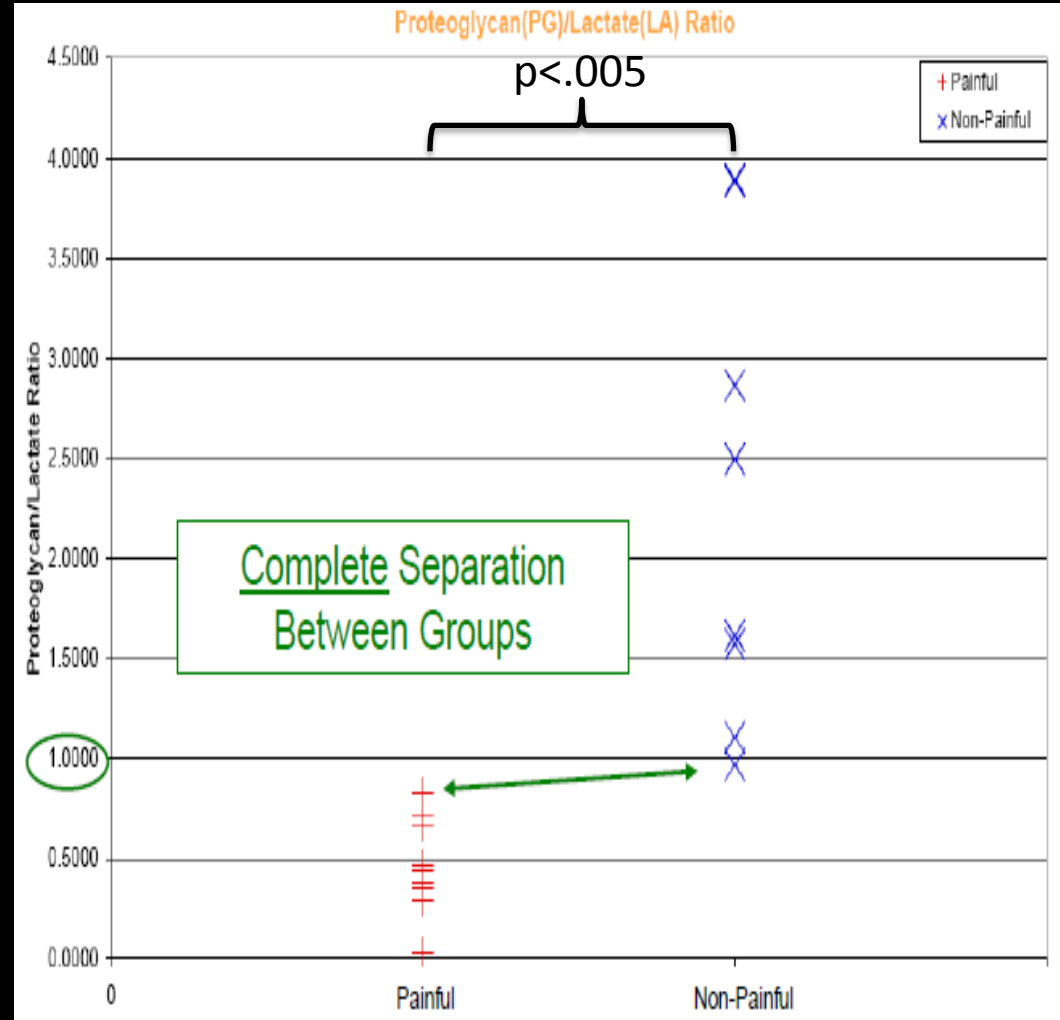
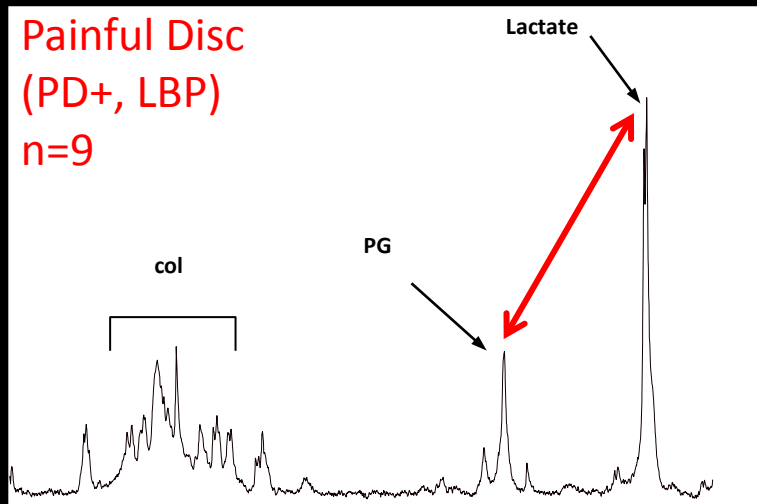
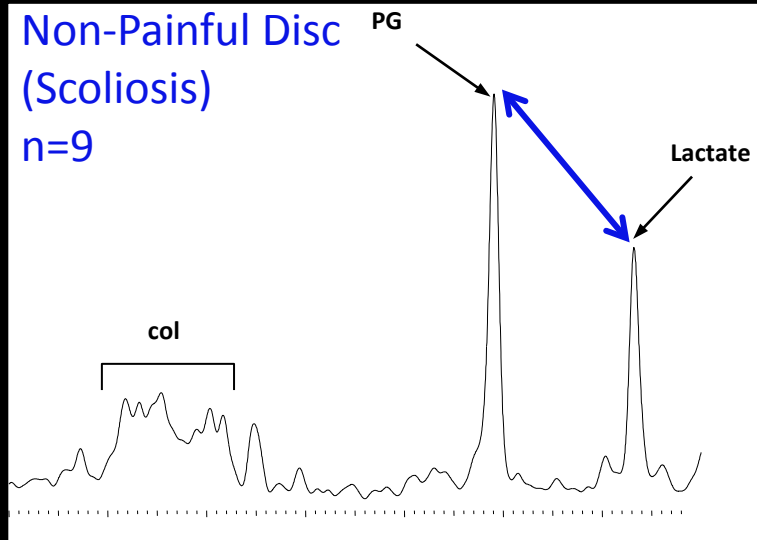
Identifying the painful disc

- Painful discs are distinguished by hypoxia, inflammation, neovascularization & neoinnervation*
- Consistent changes in biomarkers/chemical mediators detectable and quantifiable with MR spectroscopy



Background-Ex vivo Disc SVS, 11T HR MAS

Surgical Samples – PG/LA



Keshari, Spine 2008. 33(3): p. 312-317

Materials & Methods

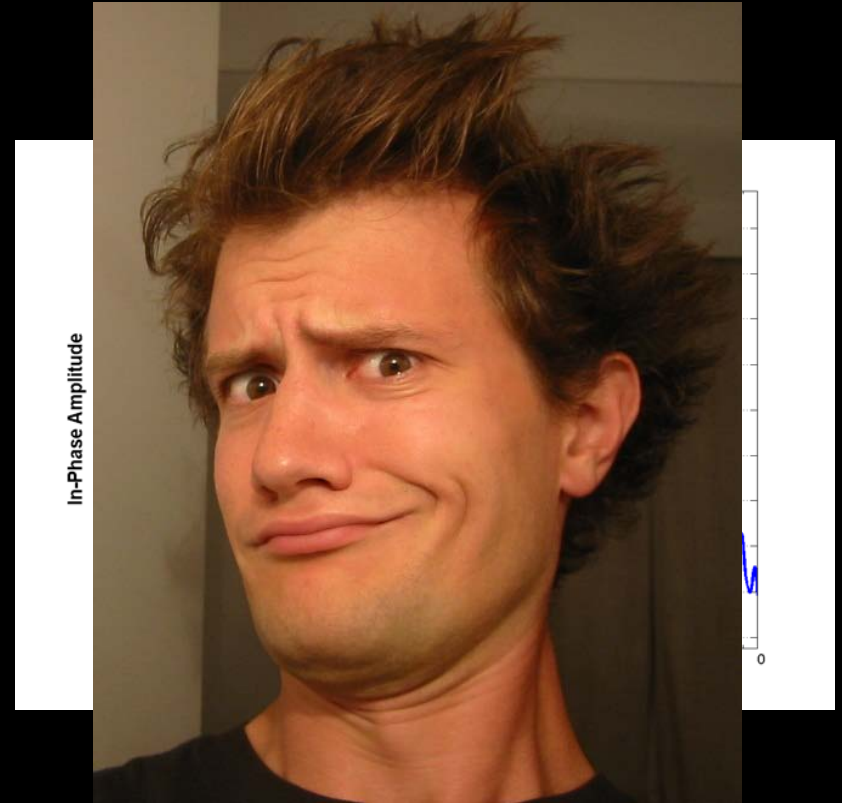
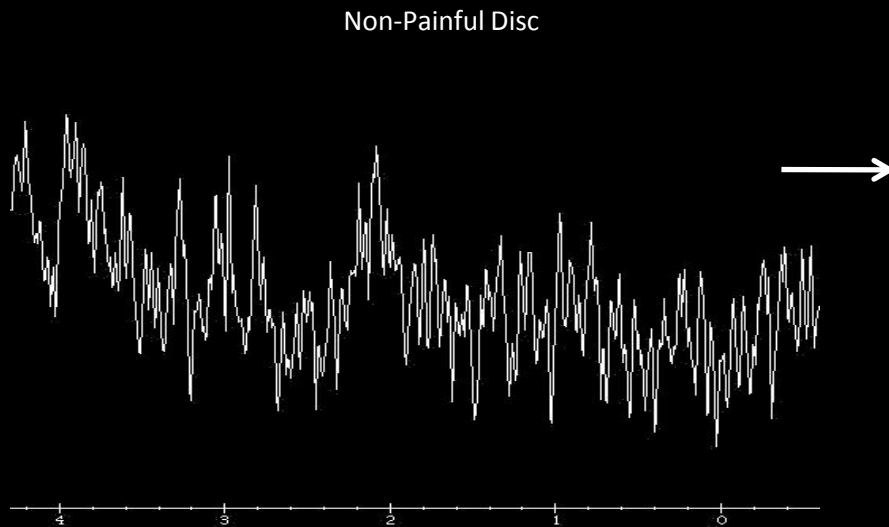
- Iterative technical development protocol
 - Conducted in series: GE (2008-10), Siemens (2011-13)
 - T1/T2 weighted imaging sequences
 - SVS acquisition, each lumbar disc sequentially
 - Inter-platform differences:
 - *OVS bands: GE only (not used for Siemens)*
 - *Autoshim → Auto + Manual shim: Siemens protocol refinement*
 - Manual voxel localization in disc to remove end-plates

Materials & Methods

- Acquisition Systems
 - GE Signa HDxt 3.0T, v14x
 - HDCTL 456 spine coil
 - Pulse Sequence: custom Chess/Press
 - “modified” PROSE™ for disc SVS: TR=1500, TE=28ms
 - Siemens 3T Verio, Model 10276755 Numaris/4
 - Spine Coil Model 8622743
 - Pulse Sequence: SVS Syngo VB17 Version 1.0
 - investigational “patch” for 3-5mm voxel height
- Both single center, Nocimed sponsored, IRB approved
 - GE 3T: University of California at San Francisco
 - Siemens 3T: The Orthopedic Center of St. Louis

Materials & Methods

signal post-processing



Automated Channel Select → Frame Edit → Phase/Freq → Apodize → Aggregate → Baseline

Materials & Methods

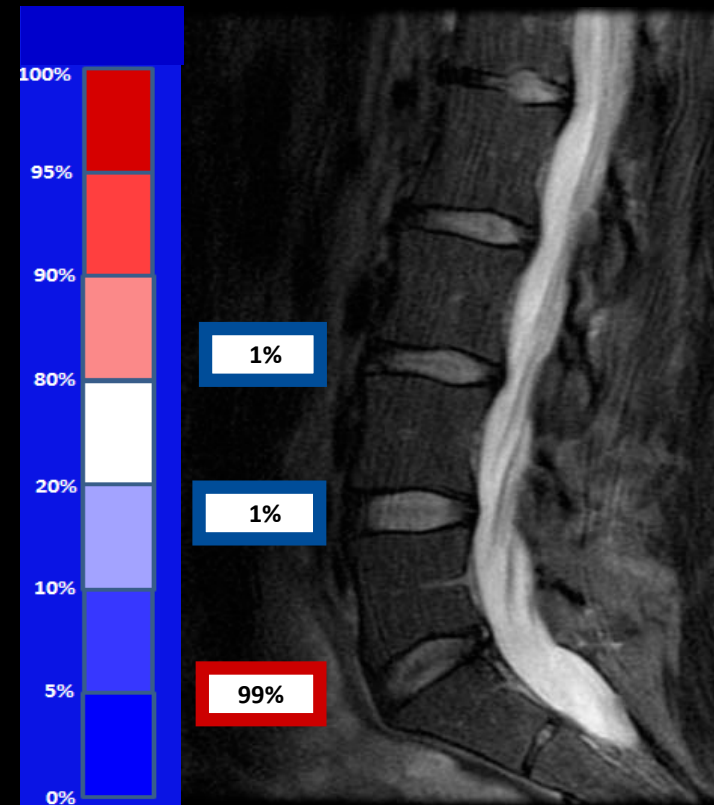
technical “success” & signal quality assessment

- **GE data:** initial *in vivo* development cycle of entire approach
 - Reported data not include technical failures for poor signal quality
 - Technical “failures” = only “indeterminate” results of Dx correlation algorithm
- **SIEMENS data:** x-platform application/refinement of prior learning
 - Less technical development required
 - Reported data includes all completed acquisitions - signal quality successes & failures
 - Primary Signal (satisfactory) Quality Assessment Criteria:
 - SNR > 3 for PG or LA peak regions
 - Water FWHM < 35 Hz
 - Presence (fail) or Absence (accept) of lipid motion artifact

Materials & Methods

diagnostic interpretation/correlation to disc type

- Different approach per platform, serial development phases
 - Earlier GE platform data:
 - Multi-variate (PG & LA) automated statistical algorithm development via “JMP” logistic regression software
 - Predictive value of SVS biomarker measures for painful vs. non-painful
 - Later Siemens platform data:
 - Simple PG/LA ratio
 - Predictive value/statistical modeling planned (> more pain patients)



Materials & Methods

study design – inclusion criteria

- Male and non-pregnant females, 18-70 yrs old
- Pain group:
 - Oswestry Disability Index $\geq 40\%$, or Visual Analog Scale ≥ 4
 - Indicated for Lumbar Spine Provocation Discography (PD)
 - Practice Guidelines for Spinal Diagnostic and Treatment Procedures (ISIS, 2004)
 - PD performed 6wk-6mo before, or 1mo after, Disc SVS exam
 - *Up to 12 mo before in earlier GE study*
- Asymptomatic control volunteers:
 - Absent chronic severe LBP
 - VAS ≤ 1 , ODI ≤ 10 .

Materials & Methods

study design – exclusion criteria

- Complicating extradiscal pain sources
 - fracture, spondylolisthesis, spondylolysis
- Prior lumbar surgery or intradiscal treatments
 - except diagnostic provocative or anesthetic discography
- Chronic disease or pain, or psychological dysfunction, relevant to study objectives

GE study

n = 42 Subjects, 79 Discs¹

Pain Pts (PD)

n=14

Volunteers

n=28

Painful Discs
(PD+)

Non-Painful Discs
(PD-)

Non-Painful Discs
(assumed)

n = 15

n = 49

n = 15

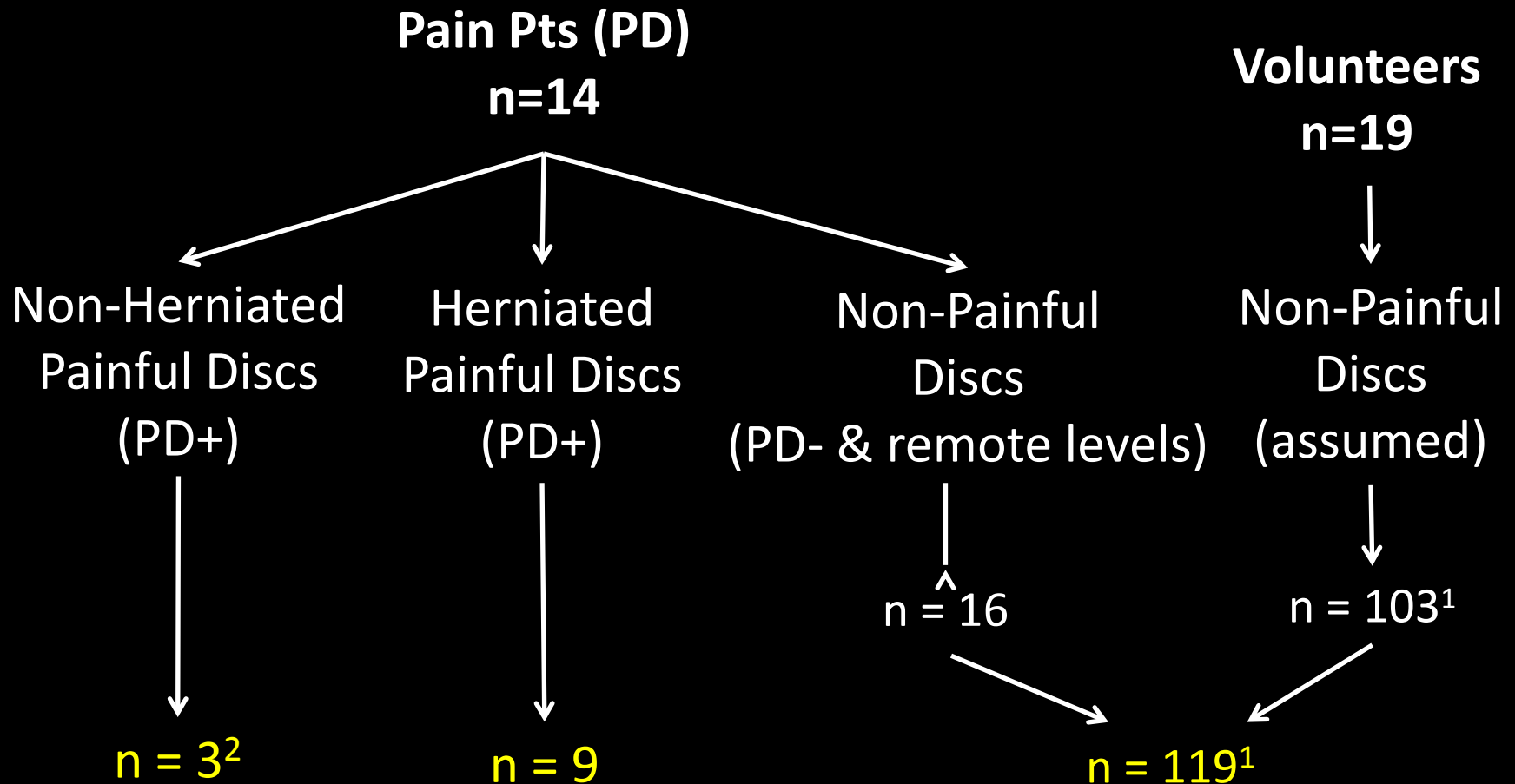
n = 64

+ Control, Painful

- Control, Non-Painful

Siemens study

n=33 Subjects, 130 Discs¹



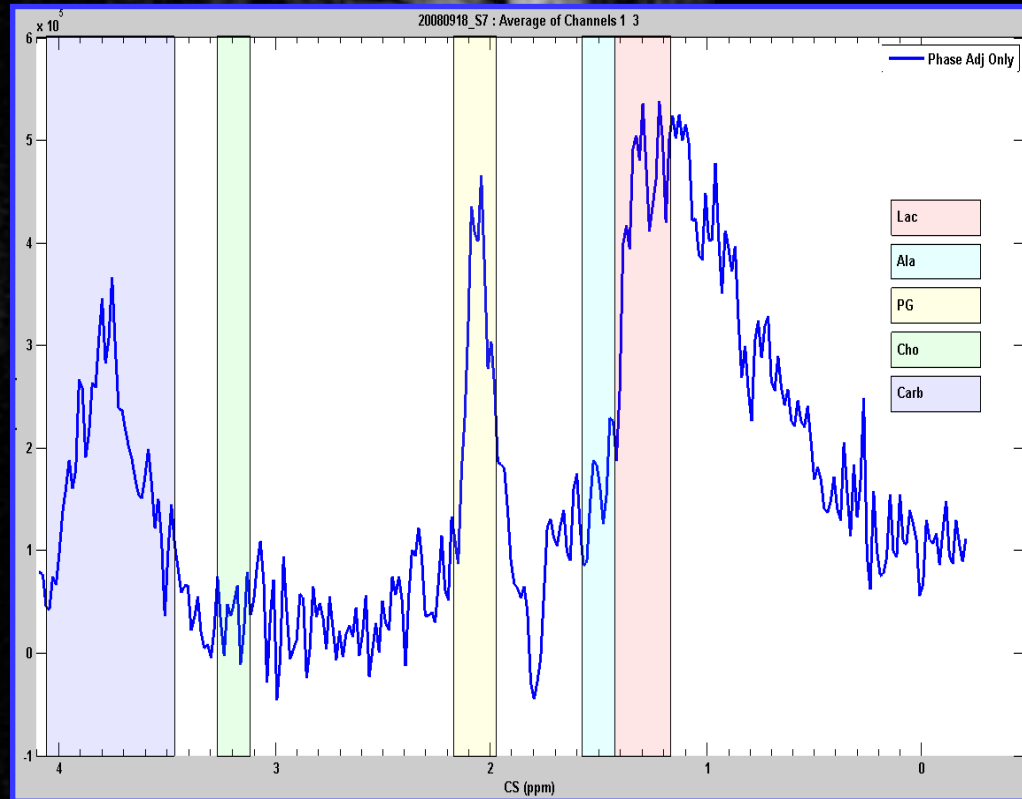
¹ Includes n=1 disc excluded from analysis as non-lumbar (S1-S2)

² Includes n=1 disc analyzed separately due to "extra" discal co-morbidities (spondylosis + facet arthropathy)

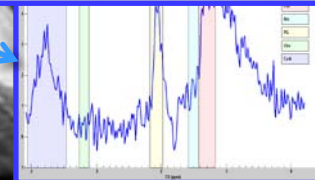
Results- 3T GE Signa

Case 1, Pain Pt (PD+ L5S1, PD- L4L5)

Discogram: +/-



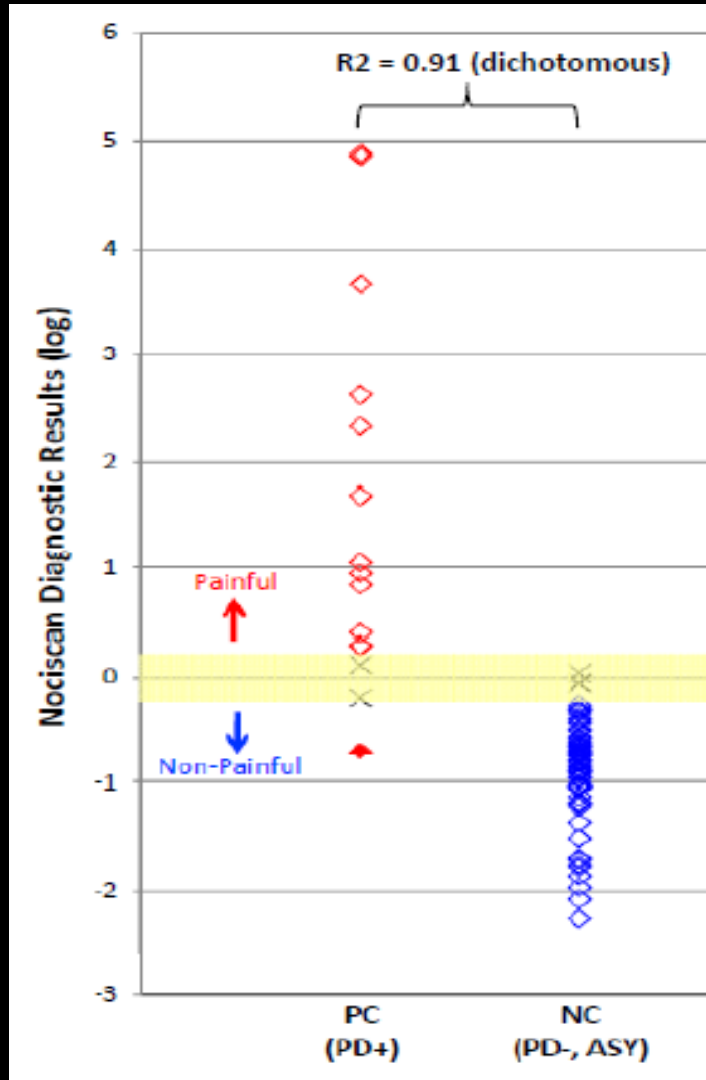
+



Results - GE 3T Signa

94% (74/79) Determinate, 99% (73/74) Accurate (PG,LA)

PG & LA-related Dx Algorithm "score"



SVS Positive
n=13 all true+

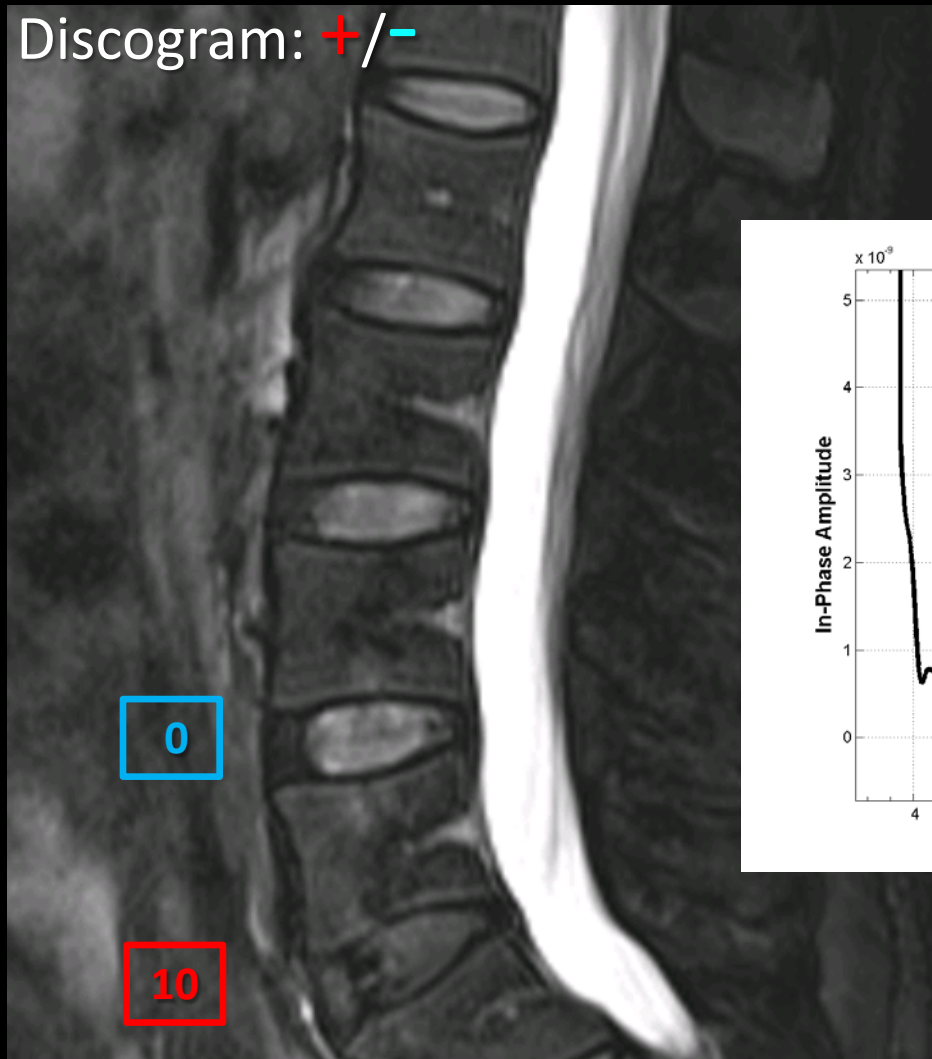
SVS Indeterminate
n=5

SVS Negative
n=60 true-, 1 false-

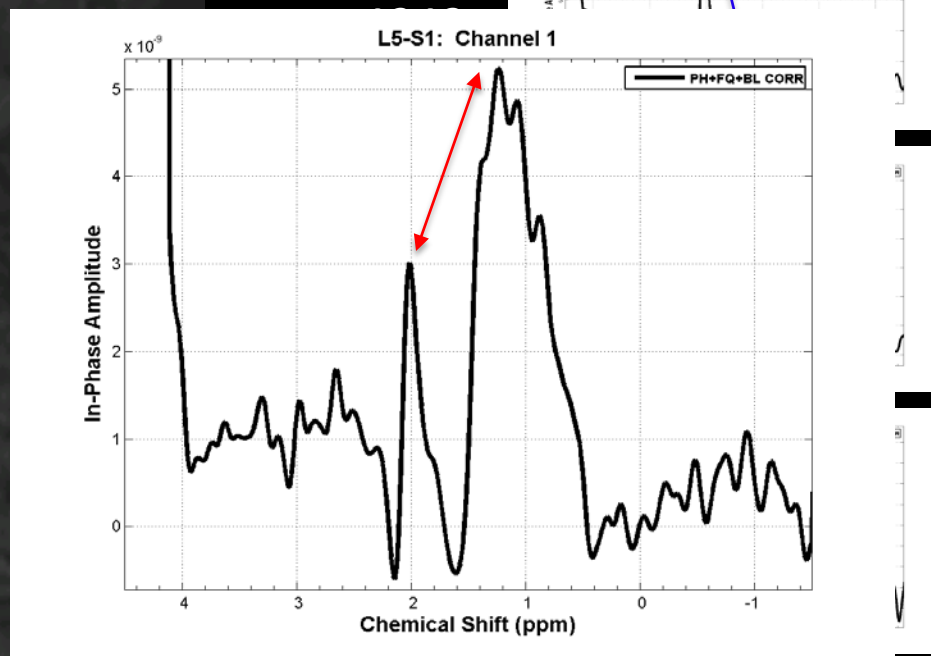
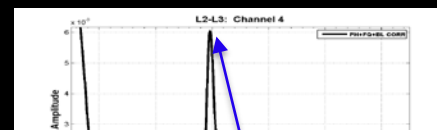
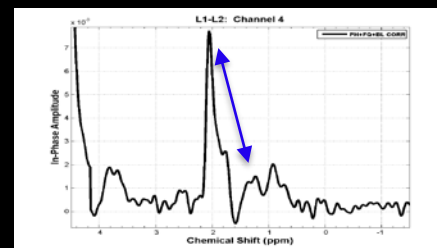
Case 2 – 3T Siemens Verio

NHP Pain Pt, 2-level PD+/-

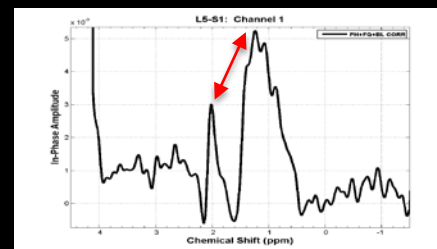
Discogram: +/-



L1-L2
4mm



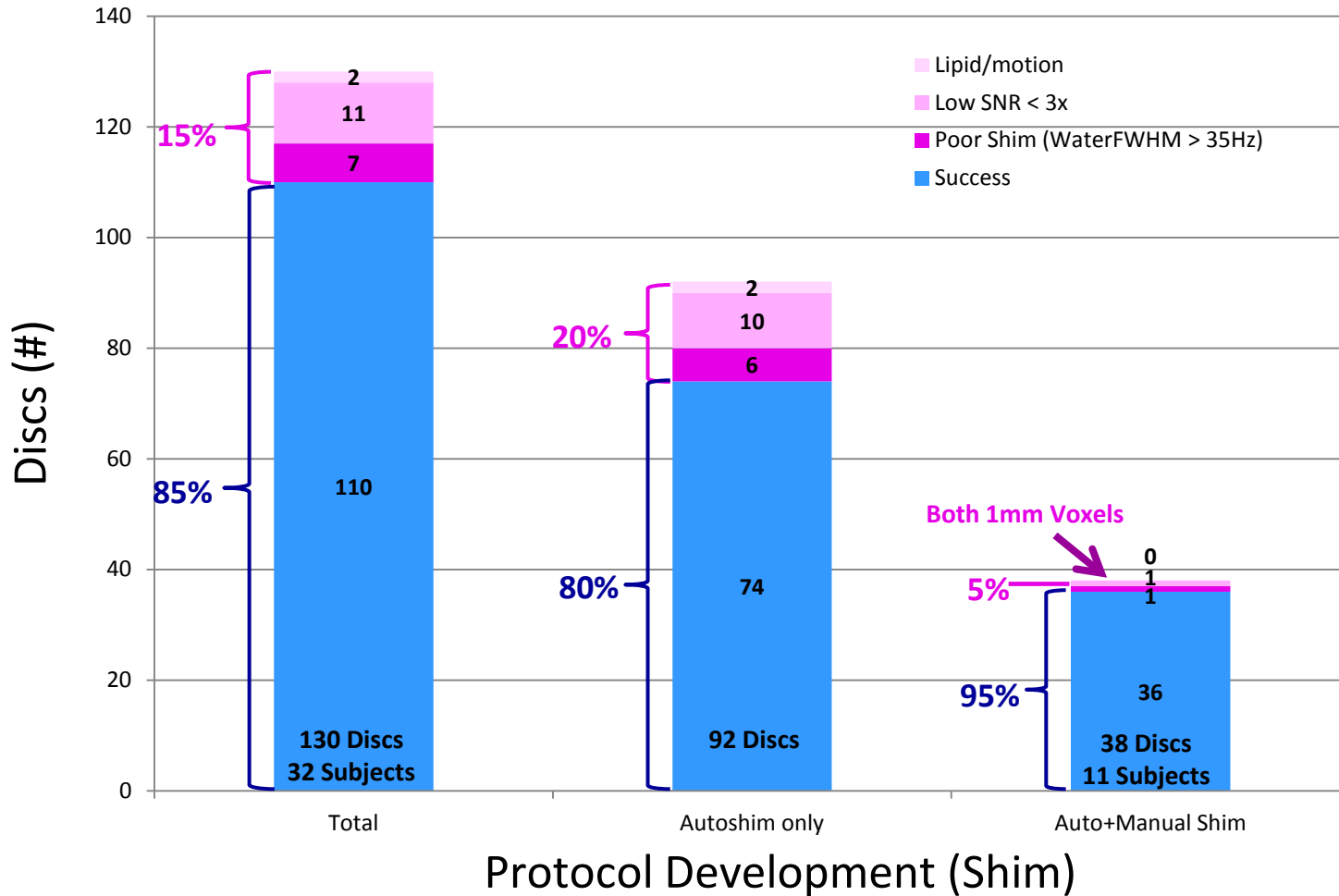
L5-S1
6mm



Results - Siemens 3T Verio

Signal Quality Success → 85% (100% Manual Shim, >1mm)

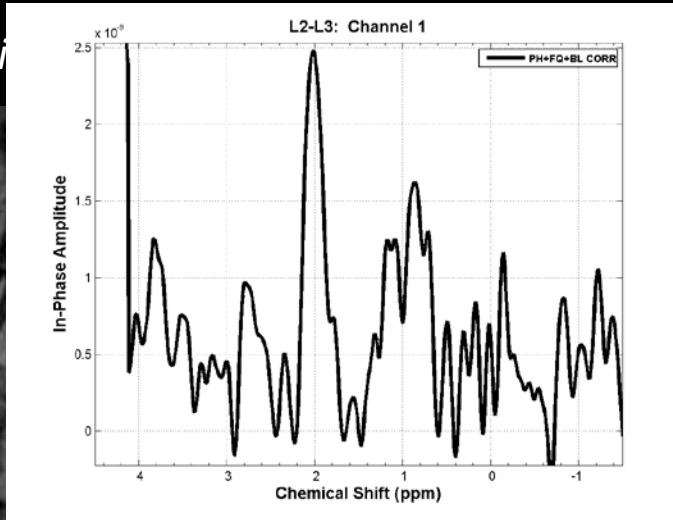
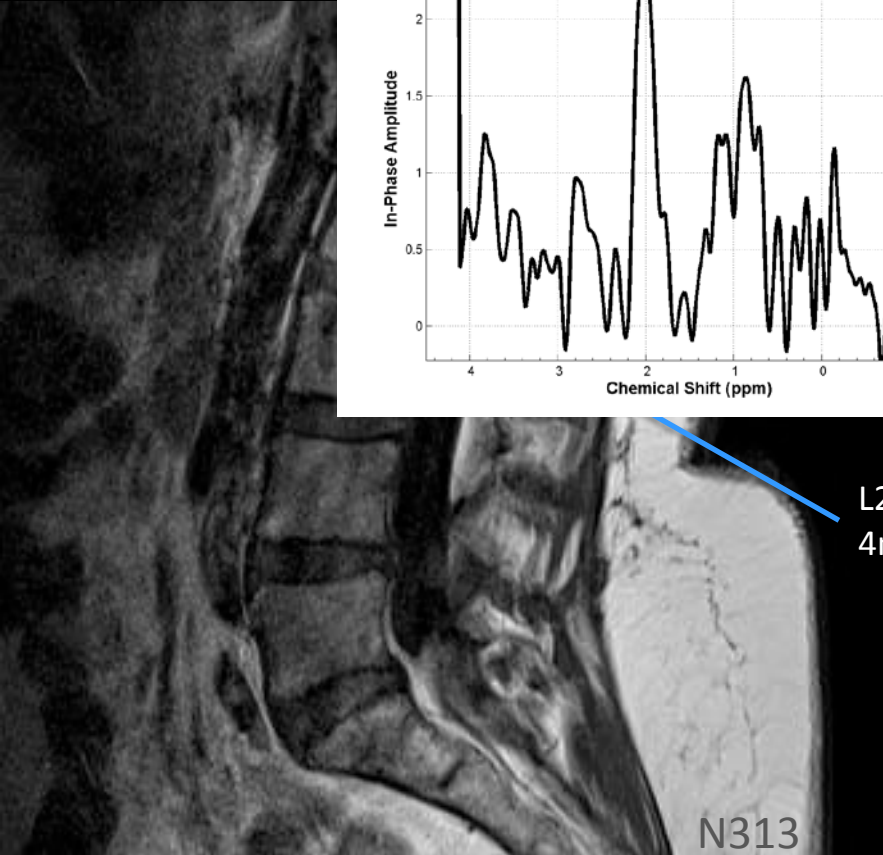
Technical Success, Signal Quality - Siemens 3T Verio



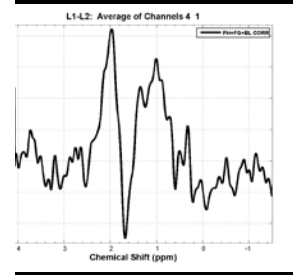
Results - Siemens 3T Verio

Autoshim only vs. Auto+Manual Shim – Example

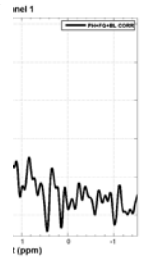
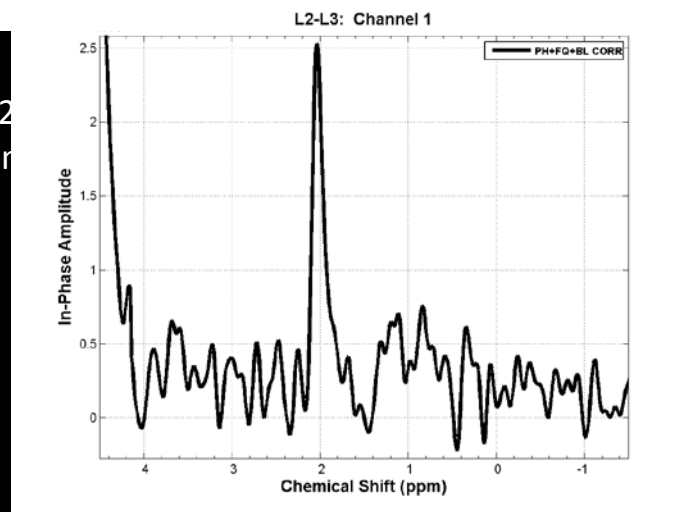
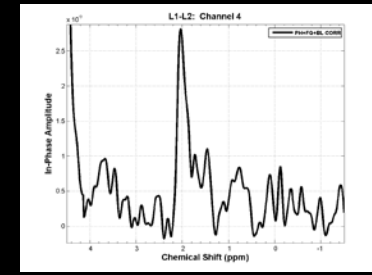
Asymptomatic



Autoshim Only
(Water FWHM)



Auto+Manual shim



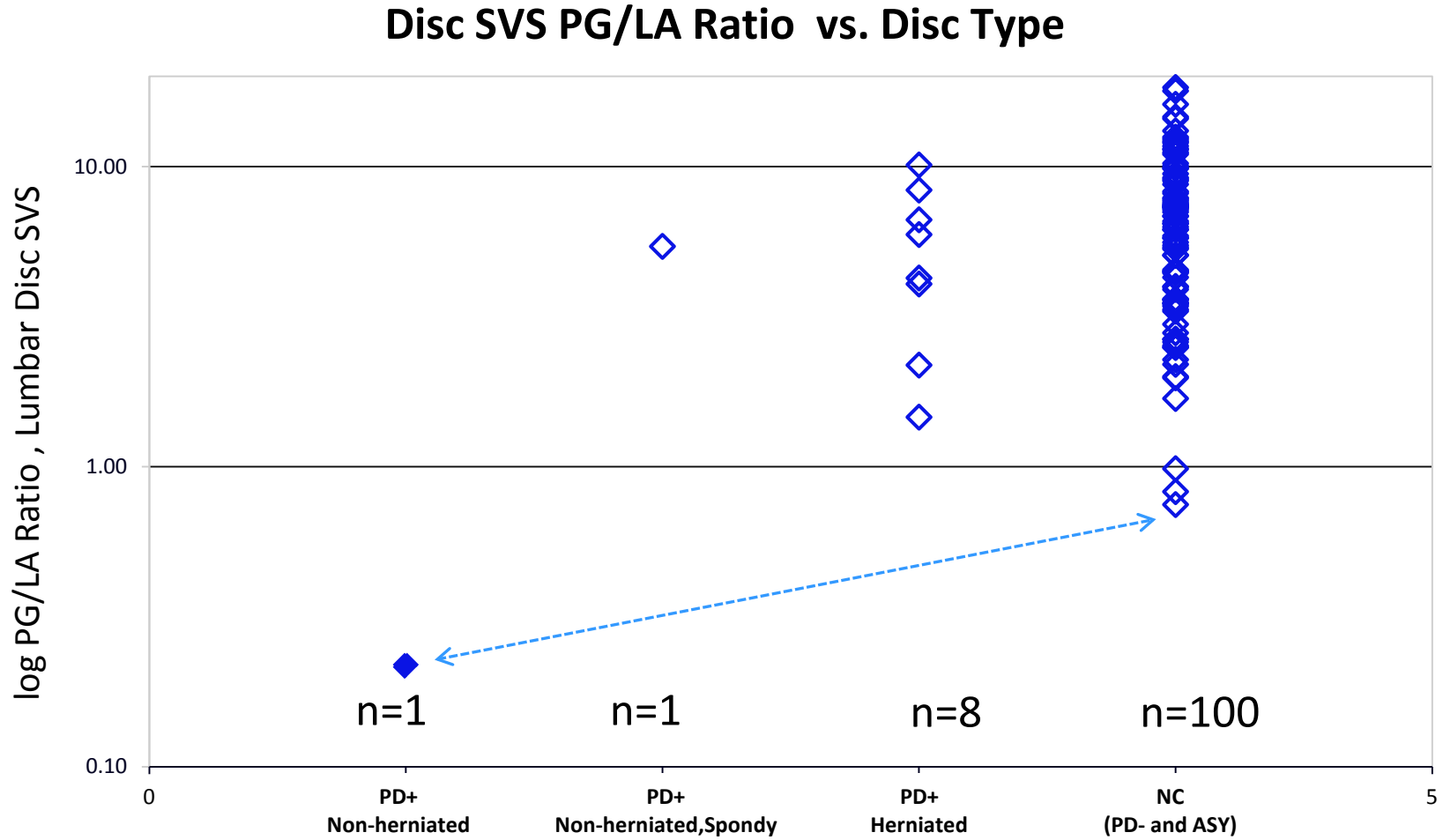
Conclusions

disc SVS signal quality - reliability

- 100% robust disc spectra per signal quality criteria @ $\geq 3\text{mm}$ disc height per later protocol refinements (autoshim + manual shim) of the Siemens 3T platform study
 - 80% reliability w/ autoshim only

Results – Siemens 3T Verio

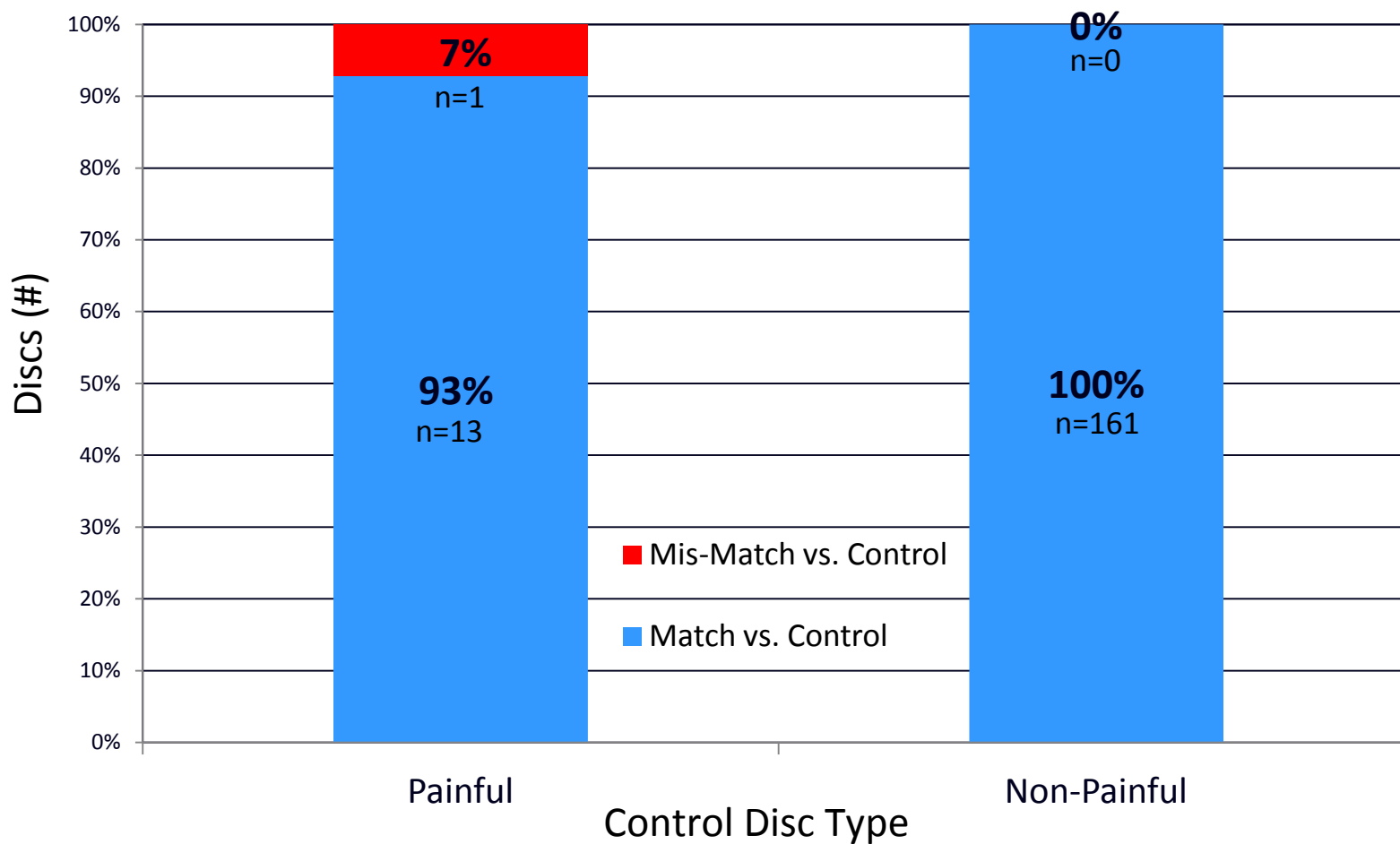
PG/LA Dx Correlation vs. Disc “Type” Controls (n=110)



Combined Siemens & GE 3T Results

PG & LA correlate 174/175 (>99%) discs, 72 subjects

Dx Correlation Results, GE & Siemens 3T Combined
(PG & LA-based Dx Algorithms separately developed, MR platform-specific)



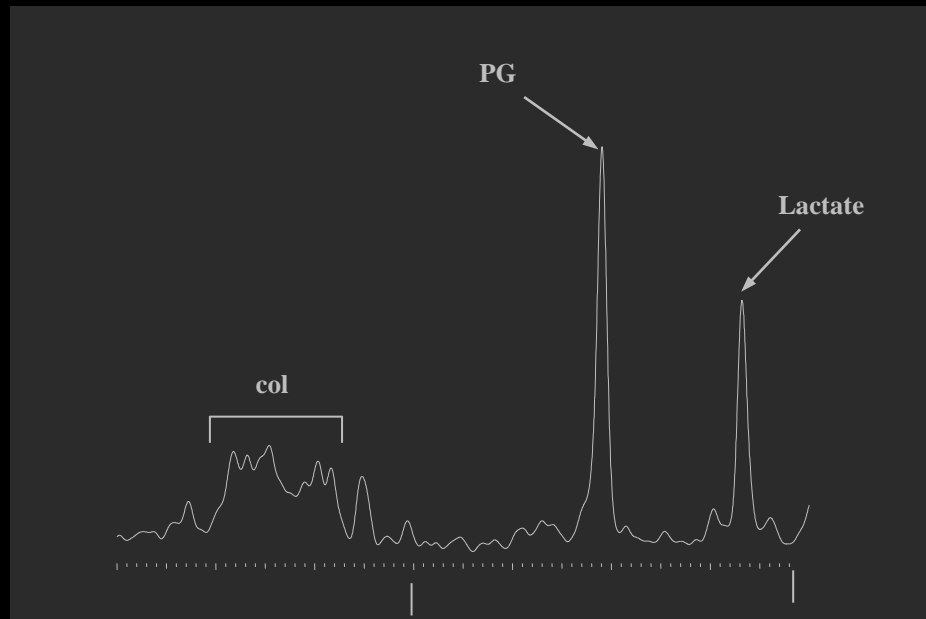
Conclusions

- Combined PG & LA-related results from the two serial GE & Siemens 3T platform disc SVS development studies reflects >99% correlation between classic “contained” discogenic pain and non-painful discs in 175 total discs in 72 subjects
 - *100% PPV for pain in 13 painful PD+ discs*
 - *0% False+ in 161 non-painful discs*

Conclusions

- Disc SVS may be most appropriate for classic contained axial discogenic low back pain w/o extradiscal pain generators, vs. pain caused by extradiscal morbidities (e.g. herniations, facet, vertebral abnormalities)
 - *may still enhance Dx regimen in multi-factorial cases involving both intra-discal and extra-discal pain sources*

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