Biomarkers for Low Back Pain: 
The *Right* Treatment for the *Right* Patient 
at the *Right* Time

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Disclosures
Research Funding from NIH (NCMRR, NIA, NIAMS, NCCAM), PCORI, The Pittsburgh Foundation, The Beckwith Foundation
Biomarkers for Diagnosis?
The Most Common *Diagnosis* in Low Back Pain is Disc Degeneration

Molecular mechanisms of biological aging in intervertebral discs.
MRI as the Gold Standard?

MRI study of asymptomatic individuals with mean age 43, 52% had disc abnormality

Percent of individuals >=65 with DDD

Degenerative lumbar disc and facet disease in older adults: prevalence and clinical correlates. Hicks et al. Spine 2009
Magnetic Resonance imaging of the lumbar spine in people without back pain. Jensen et al. NEJM 1994
Imaging as a Biomarker

Lumbar Imaging in patients without indications of serious underlying conditions does not improve clinical outcomes

A Disc Specific Molecular Biomarker?

<table>
<thead>
<tr>
<th></th>
<th>Responders to Injection</th>
<th>Nonresponders to Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibronectin–aggrecan</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>complex present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibronectin–aggrecan</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>complex absent</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Risks of Improper Selection

- Delay in appropriate treatment and risk of transition to chronic
- Financial
- Patient satisfaction
- Risk of procedures, injections and injectates

- Low back pain is a multi-factorial syndrome
Existing Biomarkers Fall Short

• Imaging?
  – Not relevant to symptoms

• Pain Scores?
  – Subjective and variable relationship to function

• Assessment of Function?
  – Ceiling and floor effects make survey selection challenging

• The need: Biomarkers with increased sensitivity to change of disease activity in real time and specificity to patient phenotype and individual biology
Circulating Biomarkers May Have Greater Utility than Imaging

Identification of candidate serum biomarkers for intervertebral disk degeneration in an animal model.
Sowa et al. PM&R 2009
Protein Biomarkers are Associated with Pain and Pain Related Function

Associations between serum biomarkers and pain and pain related function in older adults with low back pain: a pilot study. Sowa et al. JAGS 2014
MRI does not correlate with pain or pain related function in older adults with LBP

Correlation between MRI Index and pain score

\[ R^2 = 0.0242 \]

Correlation between composite MRI score and pain score

\[ R^2 = 0.0005 \]
Biomarkers to Guide Treatment?
Biomarkers for Response to Exercise in LBP?

Tissue Biomarkers released in response to loading

Circulating changes in inflammatory markers in response to activity associated with function

Associations between serum biomarkers and pain and pain related function in older adults with low back pain: a pilot study. Sowa et al. JAGS 2014

Circulating Biomarkers to Predict Response to Epidural Steroid Injection

**Inclusion Criteria**
- Age > 18
- Low back pain > other pain
- Spinal injection performed as part of routine clinical care

**Exclusion Criteria**
- Leg/radicular pain
- Sacroiliac joint pain
- Medical illness
- Pregnancy
- Systemic inflammatory conditions or recent steroid use

Responder defined as >=50% improvement in NPRS
Responders (n=17) v. Non-Responders (n=31)

Protein Biomarkers in Plasma

Genetic Biomarkers in Patients Undergoing ESI

Big Data using Clinical Biomarkers to Predict Response

<table>
<thead>
<tr>
<th>PRE-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>alcohol</td>
</tr>
<tr>
<td>tobacco</td>
</tr>
<tr>
<td>ILL drug</td>
</tr>
<tr>
<td>MuscleRelaxant</td>
</tr>
<tr>
<td>Opioid drug use</td>
</tr>
<tr>
<td>non-Steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>Antidepressant use</td>
</tr>
<tr>
<td>Seizure</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Congestive heart failure (CHF)</td>
</tr>
<tr>
<td>Fibro Myalgia</td>
</tr>
<tr>
<td>Irritable bowel syndrome (IBS)</td>
</tr>
<tr>
<td>Rheumatoid Arthritis (RA)</td>
</tr>
<tr>
<td>CTD</td>
</tr>
<tr>
<td>Hypothyroidism (HypoTHIR)</td>
</tr>
<tr>
<td>Thyroid disorder (ThyroDisord)</td>
</tr>
<tr>
<td>Anxiety</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Sleep Apnea</td>
</tr>
<tr>
<td>Post-traumatic stress disorder (PTSD)</td>
</tr>
</tbody>
</table>

**Relative correctness (gray region=100.0%)** is **30.80%** expected.

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**For an individual patient (purple patterned circle)**
- The distance from the group center in the direction of green arrows indicates OR proportionally HIGHER than average for improvement.
- The distance from the group center in the direction of red arrows indicates OR proportionally LOWER than average for improvement.

- **PRO improvement NPS predictor**
- **Improving** ($\Delta$Score $<$ 0) increases in x-direction.
- **Worsening** ($\Delta$Score $>$ 0) increases in y-direction.

- **Bars indicate the average OR's for a group, into which the patient belongs, based on PRE.**

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UPMC Clinical Analytics
Oscar Marroquin, Steven Koscumb, Petr Pancoska, Kevin Quinn, Susie Ho

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The million small victories Institute.

UPMC Rehabilitation Institute
<table>
<thead>
<tr>
<th>Condition</th>
<th>40-60</th>
<th>Tobacco</th>
<th>Ill Drug</th>
<th>Musculoskeletal</th>
<th>Non-Steroidal Anti-Inflammatory Drugs</th>
<th>Antidepressant Use</th>
<th>Seizure</th>
<th>Diabetes</th>
<th>Congestive Heart Failure (CHF)</th>
<th>Fibro Myalgia</th>
<th>Irritable Bowel Syndrome (IBS)</th>
<th>Rheumatoid Arthritis (RA)</th>
<th>CTD</th>
<th>Hypothyroidism (HypoTH)</th>
<th>Thyroid disorder (ThyDisord)</th>
<th>Anxiety</th>
<th>Depression</th>
<th>Sleep Apnea</th>
<th>Post-traumatic Stress Disorder (PTSD)</th>
<th>Range</th>
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<tbody>
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<td>40-60</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<td>No</td>
<td>No</td>
<td>No</td>
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</tbody>
</table>

**Relative correctness (gray region=100.0) is 61.59%**

**Set all to No**

**For an individual patient (pers. pattern=red circle)**
- The distance from the group center in the direction of green arrows indicates OR proportionally **higher** than average for improvement
- The distance from the group center in the direction of red arrows indicates OR proportionally **lower** than average for improvement

**Bars indicate the average OR’s for a group, into which the patient belongs, based on PRP.**

**In this group, 88 patients out of 100 WORSENED**

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**The million small victories Institute.**

**UPMC Rehabilitation Institute**
Improved Phenotyping with Biomarkers from Multiple Domains

A) Clinical Data Only

B) SNP Data Only

C) Clinical & SNP Data

Increasing trend for ODI improvement

Increasing trend for ODI worsening

Increasing trend for ODI worsening
Biomarkers to Phenotype LBP Types
**Differences in Relationships with Pain and Inflammatory Biomarkers**

<table>
<thead>
<tr>
<th></th>
<th>McGill Affective</th>
<th>Pain Scale</th>
<th>Depression</th>
<th>Gait speed</th>
<th>SPPB</th>
<th>FABQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPY</td>
<td>0.23*</td>
<td>0.04</td>
<td>0.20*</td>
<td>0.00</td>
<td>0.01</td>
<td>0.22*</td>
</tr>
<tr>
<td>RANTES</td>
<td>0.03</td>
<td>0.15*</td>
<td>0.04</td>
<td>0.19*</td>
<td>0.15*</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Combinations of Biomarkers demonstrated larger significant associations*
Network Phenotyping Strategy

Increasing odds of discontinuing opioid use

Increasing odds of continued opioid use

Funded by the Beckwith Foundation
Oscar Marroquin, Petr Pancoska, Ajay Wasan, Howard Gutstein
NIH/NIAMS U19AR076725

CLBP pain human subjects

Saliva
DNA
PCR

Serum
Protein
ELISA, Western

Spinal tissues
RNA
qRT-PCR

Transcriptomics
RNAseq

Genomics
(whole genome sequencing)

Omnics:

Proteomics
(mass spectrometry)

Biplane Radiography

Wearable Motion Sensors
Wearable IMUs

Biomechanical data

Performance-Based Measures of Function

Translational Potential

Sensitivity

NIH HEAL INITIATIVE

BACPAC

Mechanistic Research Center

Behavior

Biology

Biomechanics

The Person with Pain:
Social, Behavioral, and Psychological Context

Social Context:
stress, trauma, medico-legal, social activity participation

Behaviors and Lifestyle:
physical activity, sleep, smoking, alcohol, substances

Psychological:
general and pain-specific emotions, beliefs, cognitions

Pain Characteristics

NIH TOOLBOX
Motor
Emotion
Sensation
Cognition
The right *treatment*, for the right *patient*, at the right *time*

Development of phenotyping capabilities that includes clinical history, exam, radiographic findings and personal biology