Biochemical Markers in OA

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PRIMARY NEED for DRUG DEVELOPMENT in OA: PROGNOSTIC BIOCHEMICAL MARKERS LINKED TO CLINICALLY RELEVANT OUTCOMES
‘selection biomarkers’ for enrolling patients into clinical studies increase the likelihood of drug approval (from 8% to 26%)

CURRENT EVIDENCE
Single baseline measures in LONGITUDINAL TRIALS
urinary CTXII
serum/plasma CRTAC1

QUALIFICATION EFFORTS
urinary CTXII

DISCLOSURE: Patent pending related to proteomic panel for OA

‘Suspension Bridging’ Concept

**urinary** C-terminal telopeptide of type II collagen  
**Serum/plasma** Cartilage acidic protein 1 precursor

- uCTXII  
- s/pCRTAC1 (CRAC1)

**Clinically Relevant Progression** (worsening Pain AND Radiograph)  
Total Joint Replacement

**BIOCHEMICAL MARKERS**  

**‘MAIN CABLE’ DIRECT ASSOCIATION**  

**CLINICALLY RELEVANT OUTCOMES**
Predicts Clinically Relevant Knee OA Progression - uCTXII

- uCTXII predicted clinically relevant knee OA progression: odds ratio (OR) 1.29
- AUC 0.608

FNIH Biomarker Consortium for OA
Kraus et al. 2017 PMID 27296323
(AUC unpublished)
Predicts Total Joint (KNEE/HIP) Replacement – uCTXII

Calcitonin Trials; Bjerre-Bastos et al. 2019 OARSI S31:12

Calcitonin Trials; Garnero et al. 2020 PMID 31982562

Baseline 2 years (Calcitonin) 18 years (OFELY)

uCTXII  TJR

N=640 (Calcitonin) N=478 (OFELY)

Calcitonin

TJR

HR 8.94 Knee TJR
HR 3.08 Knee or Hip TJR
HR 3.0 Knee or Hip TJR

LOW
HIGH

CALCITONIN

% Free of TJR

Days

Calcitonin Trials; Bjerre-Bastos et al. 2019 OARSI S31:12

OFELY

% Free of TJR

Time (years)

OFELY (female) cohort; Garnero et al. 2020 PMID 31982562

LOW
HIGH

top 5th percentile)
Predicts Clinically Relevant Knee OA Progression – sCRTAC1

Pain & JSL Progression (13 peptides): **AUC=0.740**

<table>
<thead>
<tr>
<th>Peptide</th>
<th>P Value</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD44_3</td>
<td>0.201</td>
<td>0.83 (0.82, 1.11)</td>
</tr>
<tr>
<td>ZPI</td>
<td>0.057</td>
<td>1.36 (0.99, 1.87)</td>
</tr>
<tr>
<td>FAS_1</td>
<td>0.078</td>
<td>0.77 (0.57, 1.03)</td>
</tr>
<tr>
<td>HEP2_2</td>
<td>0.079</td>
<td>1.30 (0.97, 1.75)</td>
</tr>
<tr>
<td>HEMO_2</td>
<td>0.086</td>
<td>0.74 (0.53, 1.04)</td>
</tr>
<tr>
<td>FETAUA_2</td>
<td>0.078</td>
<td>0.78 (0.59, 1.03)</td>
</tr>
<tr>
<td>TSP1</td>
<td>0.006</td>
<td>1.44 (1.11, 1.87)</td>
</tr>
<tr>
<td>DOPO</td>
<td>0.085</td>
<td>0.82 (0.65, 1.03)</td>
</tr>
<tr>
<td>CRAC1_1</td>
<td>0.006</td>
<td>1.41 (1.10, 1.80)</td>
</tr>
<tr>
<td>PHLD</td>
<td>0.008</td>
<td>1.53 (1.12, 2.10)</td>
</tr>
<tr>
<td>KNG1_2</td>
<td>0.001</td>
<td>0.62 (0.47, 0.82)</td>
</tr>
<tr>
<td>CIR_1</td>
<td>0.001</td>
<td>0.54 (0.37, 0.78)</td>
</tr>
<tr>
<td>VTDB_5</td>
<td>0.000</td>
<td>2.10 (1.40, 3.17)</td>
</tr>
</tbody>
</table>

JSL Progression **AUC=0.698**  
Validation cohort **AUC=0.697**  
Pain Progression **AUC=0.673**

Zhou and Kraus et al. 2021 OARSI poster 748
Risk of Total Joint Replacement

- Screened 4,792 SomaScan plasma proteins
- 45 associated with OA--CRTAC1 most highly associated
- CRTAC1 associated with joint pain
- CRTAC1 dropped after surgery (Total Joint Replacement)

**CUMULATIVE RISK OF JOINT REPLACEMENT BASED ON CRTAC1 ALONE**

<table>
<thead>
<tr>
<th>Joint Replacement</th>
<th>N</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee Replacement</td>
<td>672</td>
<td>1.4</td>
</tr>
<tr>
<td>Hip Replacement</td>
<td>376</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Baseline

Risk of Total Joint Replacement

**N=10,701 OA**

**Styrkarsdottir et al. Arthritis Rheum 2021 PMID:33982893**
Predicts Incident Radiographic Knee OA – sCRTAC1

Baseline

6-11 SERUM PEPTIDES BY MASS SPECTROMETRY

4-8 years

INCIDENT RADIOGRAPHIC KNEE OA

N=200 (Chingford)

8 YEARS AHEAD   AUC 0.76

<table>
<thead>
<tr>
<th>Variable</th>
<th>P Value</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRAC1_1</td>
<td>0.16</td>
<td>1.62 (0.83, 2.29)</td>
</tr>
<tr>
<td>APOE</td>
<td>0.25</td>
<td>1.41 (0.79, 2.19)</td>
</tr>
<tr>
<td>PRG4_1</td>
<td>0.067</td>
<td>0.46 (0.2, 1.22)</td>
</tr>
<tr>
<td>HPT_1</td>
<td>0.12</td>
<td>1.75 (0.86, 3.57)</td>
</tr>
<tr>
<td>CO5_5</td>
<td>0.148</td>
<td>0.58 (0.28, 1.32)</td>
</tr>
<tr>
<td>LYAM1</td>
<td>0.038</td>
<td>0.48 (0.24, 1.27)</td>
</tr>
<tr>
<td>COMP_1</td>
<td>0.227</td>
<td>1.58 (0.75, 2.12)</td>
</tr>
<tr>
<td>HABP_2_2</td>
<td>0.003</td>
<td>4.09 (1.6, 9.97)</td>
</tr>
<tr>
<td>VTNC</td>
<td>0.028</td>
<td>0.35 (0.14, 1.15)</td>
</tr>
<tr>
<td>FBLN1</td>
<td>0.028</td>
<td>0.42 (0.19, 1.21)</td>
</tr>
<tr>
<td>HRG_4</td>
<td>0.038</td>
<td>2.49 (1.05, 5.87)</td>
</tr>
</tbody>
</table>

Model AUC (95% CI): 0.76 (0.70, 0.82)

4 YEARS AHEAD   AUC 0.77

<table>
<thead>
<tr>
<th>Variable</th>
<th>P Value</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMP_1</td>
<td>0.052</td>
<td>1.86 (0.99, 3.48)</td>
</tr>
<tr>
<td>FBLN3_2</td>
<td>0.036</td>
<td>0.53 (0.3, 0.95)</td>
</tr>
<tr>
<td>PLF4</td>
<td>0.056</td>
<td>0.39 (0.15, 1.03)</td>
</tr>
<tr>
<td>CRAC1_1</td>
<td>0.056</td>
<td>2.58 (0.97, 8.88)</td>
</tr>
<tr>
<td>RET4</td>
<td>0.057</td>
<td>0.5 (0.25, 1.02)</td>
</tr>
<tr>
<td>ZPI</td>
<td>0.03</td>
<td>2.52 (1.12, 5.68)</td>
</tr>
</tbody>
</table>

Model AUC (95% CI): 0.77 (0.67, 0.86)

Sun and Kraus et al. 2021 OARSI poster 741
Clinical Evaluation and Qualification by FDA of Osteoarthritis Biomarkers
FNIH Biomarkers Consortium

https://fnih.org/our-programs/biomarkers-consortium/programs/progress-oa

Biochemical Biomarkers: measured at baseline in placebo arms of 2 clinical trials—(n=871)

MRI Biomarkers: measured at baseline in placebo arms of 5 clinical trials—(n=434)

Trabecular Bone Texture (radiographic) Biomarkers: measured at baseline in placebo arms of 6 clinical trials (n=1271)

Study visits

Baseline (BL) 12 mo 24 mo 36 mo

9 biochemical markers Including uCTXII

➢ Endpoint: 24M (12M when 24M unavailable; 36M ancillary when available)

➢ Primary Outcome: Radiographic progression (0.7 mm joint space narrowing)

➢ Secondary Outcomes: Radiographic (0.5 mm joint space narrowing); Pain; Radiographic+Pain Progression
Clinical Evaluation and Qualification of 9 Osteoarthritis Biochemical Biomarkers

Group Process

- **Group 1** Type II Collagen Degradation
  - uCTXII
  - uC2C-HUSA

- **Group 2** Type II Collagen Synthesis
  - sPIIBNP

- **Group 3** Type I Collagen Degradation
  - uNTXI
  - sNTXI
  - sCTXI
  - uCTXI-alpha
  - uCTXI-beta

- **Group 4** Inflammation
  - sHA

Selection Process

FINAL
4, 3, 2 OR 1

Notes: s=serum, u=urine, urine biomarkers are normalized to Creatinine
## FNIH PROGRESS OA Project – Regulatory Update

### FDA Biomarker Qualification Program

#### 21st Century Cures Act

<table>
<thead>
<tr>
<th>BMQ Step</th>
<th>MRI</th>
<th>Biochemical</th>
<th>TBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. LOI</td>
<td>Submitted to FDA 2015; received acceptance</td>
<td>Submitted to FDA 9/2019; <strong>Status:</strong> LOI accepted 2/2020</td>
<td>Submitted to FDA 9/2019; <strong>Status:</strong> LOI accepted 2/2020</td>
</tr>
<tr>
<td>2. LBQSU</td>
<td>Submitted 11/2018; FDA 507 acceptance letter to move forward 5/2019</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. QP</td>
<td>Submitted 1/2020; FDA review pending</td>
<td>Submission in preparation</td>
<td>Submission in preparation</td>
</tr>
<tr>
<td>4. FQP</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LOI = letter of intent  
LBQSU = legacy biomarker qualification status update  
QP = qualification plan  
FQP = full qualification package
Accelerated Approval – Within Reach for OA?

- Alzheimer’s Disease has multiple similarities with OA
- Serious disease of unmet need
- No treatments on the market “attack the cause of disease rather than just easing symptoms”
- High prevalence – patients matter
  - Alzheimer’s Disease 5.8 million in US
  - OA 32.5 million in US
- A history of multiple drug failures
- Biomarkers now exist in OA that are “reasonably likely to predict important benefits to patients”
- OARSI proposed study designs for accelerated approval trials in OA (Kraus et al. 2019 PMID:30465809)
- “History has shown us that approvals of the first drug in a new category invigorates the field” (Maria Carrillo, CSO Alzheimer’s Association)

Summary by Kelly Servick Jun. 7, 2021:
Conclusions

Biochemical markers have been linked to clinically relevant outcomes in OA but more work is needed to establish amount of biomarker change that equates to a clinically meaningful benefit.

Demonstration of biomarker relationship to a causal pathway in human OA awaits existence of a disease modifying drug (DMOAD).

Formal qualification of uCTXII as an OA drug development tool is ongoing.

CRTAC1 represents a second generation (emerging) biomarker for OA that may be a superior prognostic compared to existing biomarkers.

Incident and progressive knee OA share biomarkers and therefore molecular pathophysiology—suggesting the false dichotomy of the radiograph to define “OA” vs no “OA.”

Biomarkers that are “reasonably likely to predict important benefits to patients” can be used as endpoints for accelerated drug approval in serious diseases—such as osteoarthritis—with a post-marketing trial to show drug impact on patient relevant outcomes.