Workshop topics

1. M. Nevitt “Overview of OAI data; Access to data and images; Research questions: possibilities and limitations”

2. J. Lynch “Working with images and image-derived biomarkers”

3. C. McCulloch “Longitudinal and hierarchical analytical strategies for biomarker analyses”

~25 minute presentations, each followed by 10 minute QandA
Overview of OAI data
Research questions: opportunities and limitations

- Study design, subcohorts, main measurements
- Public data releases
- Completeness of follow-up
- Central image assessments and primary endpoints
- Opportunities for analyses using baseline - 48mos follow-up data
- Access to Biospecimens
- Publications
Goals of OAI

A longitudinal cohort study resource to

- Investigate the natural history of knee OA across the spectrum of disease
  - At risk → Early/preclinical → Established → Endstage
  - Evolution of early OA to clinically significant disease

- At each stage of disease: relationship of imaging, biochemical, genetic and risk markers to clinical course of OA
  - Association of biomarkers (baseline and Δ) and risk factors with structural and clinical outcomes
Realization of OAI goals

- Open access to the data, images and biospecimens
- Enlist the community of OA investigators worldwide to understand natural history, evaluate biomarkers and speed the generation of new knowledge
  - Downloadable clinical data archive on the web
  - Archived images on demand
  - Archived biospecimens by application

www.oai.ucsf.edu
OAI study design resources

- **OAI Online** ([www.oai.ucsf.edu](http://www.oai.ucsf.edu))
  - Study protocol and measurements
    - [www.oai.ucsf.edu/datarelease/docs/about](http://www.oai.ucsf.edu/datarelease/docs/about)
    - [www.oai.ucsf.edu/datarelease/docs/StudyDesignProtocol.pdf](http://www.oai.ucsf.edu/datarelease/docs/StudyDesignProtocol.pdf)
    - [www.oai.ucsf.edu/datarelease/operationsmanuals.asp](http://www.oai.ucsf.edu/datarelease/operationsmanuals.asp)
OAI longitudinal cohort study

N (% of total)
1,389 (29%)

3,285 (68%)

122 (3%)

3 Subcohorts

PROGRESSION:
Symptomatic knee OA at baseline

INCIDENCE:
At elevated risk of developing Knee OA during the study

Normal Controls
No knee Sx or OA, or risk factors at BL

Primary knee outcomes

Progression (Symptoms, function, structure, TKR)

Incidence endpoints (X-ray OA, Sx OA)

Biomarker reference

Osteoarthritis Initiative
Overall inclusion and exclusion criteria

Inclusion
- Men and women ages 45 - 79
- With, or at risk for, symptomatic T-F knee OA
- All ethnic minorities (focus on African-Americans)

Major exclusions
- Inflammatory arthritis (RA)
- 3-T MRI contraindication
- Bilateral end-stage knee OA
Subcohort eligibility

- **Progression:** Symptomatic T-F Knee OA
  - Combination, in ≥ 1 knee, of
    - Definite T-F osteophyte (OARSI atlas gr 1-3) from baseline clinic screening reading
    - Frequent Sx: Pain, aching or stiffness on most days of a month in past year

- **Incidence:** No Sx T-F OA in either knee
  - Increased risk for Sx OA in ≥ 1 knee
    - Frequent knee Sx without x-ray OA*
    - Two or more other eligibility risk factors

* may have osteophytes in one or both knees, but not OST and freq Sx in the same knee
# Baseline subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Progression</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>57%</td>
<td>59%</td>
</tr>
<tr>
<td>Age 60-79</td>
<td>55%</td>
<td>54%</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>30%</td>
<td>18%</td>
</tr>
<tr>
<td>BMI&gt; 30</td>
<td>50%</td>
<td>33%</td>
</tr>
<tr>
<td>Hx knee injury/surgery*</td>
<td>51%</td>
<td>39%</td>
</tr>
<tr>
<td>Frequent knee Sx*</td>
<td>100%</td>
<td>30%</td>
</tr>
<tr>
<td>X-ray knee OA*, **</td>
<td>100%</td>
<td>39%</td>
</tr>
</tbody>
</table>

* in >1 knee
** clinic screening reading
Schedule of clinic visits, measurements

All ppts have knee MRIs and radiographs, clinical assessments and biospecimen collection at all visits

*Interim 6-mo visit in a subset of Progression ppts for knee MRI, biospecimens and clinical outcomes
Imaging

Baseline and annual knee imaging
- Bilateral x-ray, PA fixed-flexion
- Bilateral knee MRI, 3T Siemens Trio

Other joint imaging
- Hip/pelvis, hand x-rays (BL, 48 mos)
- MRI of the thigh for muscle (BL, 24, 48 mos)
- Full limb for knee alignment (various)

Imaging schedule and protocols
www.oai.ucsf.edu/datarerelease/docs/DataImaging.asp
Clinical data and biospecimens

- Knee symptoms and function (WOMAC, KOOS)
- Hip and other joint symptoms
- General function, QOL
- Physical performance
- Knee examination
- Risk factors, health behaviors, psychosocial measures
- Medications, supplements
- Blood, urine, DNA, lymphocytes (archived)

Measurement schedule
- [www.oai.ucsf.edu/datarerelease/docs/ExamMeasures.pdf](http://www.oai.ucsf.edu/datarerelease/docs/ExamMeasures.pdf)
- [www.oai.ucsf.edu/datarerelease/docs/Questionnaires.pdf](http://www.oai.ucsf.edu/datarerelease/docs/Questionnaires.pdf)
Things to keep in mind about Progression and Incidence subcohorts

- **Purpose:** balance of pts with Sx knee OA vs ‘at risk’
- **Assignment to Progression cohort based on having Sx OA in at least one knee at baseline**
  - 2/3 of pts had unilateral Sx OA at BL
  - 1/3 of pts had unilateral X-ray OA at BL
- **Freq Sx (and Sx OA) come and go over time**
  - 1/3 of knees change Freq Sx status, BL to 24mo
- **BL OA status from clinic screening reading (used in cohort assignment) may differ from central reading**
  - OARSI poster #430
Things to keep in mind about Progression and Incidence subcohorts

- Incidence cohort enriched for those at high risk
  - May not represent general population
  - E.g. Hx knee injury/surgery: 39%

- Ppts in Incidence cohort may have BL OA
  - 39% have X-ray OA (but not Sx OA) in ≥1 knee

- Measurements the same in both cohorts

- Analyses can combine ppts/knees from both cohorts
  - E.g. men with unilateral X-ray OA
    - Progression: n=213
    - Incidence: n=255
Public data release
Clinic visit timeline

- Baseline visit
- 12 month visit
- Subset of Progression
- 18 month
- 24 month
- Subset of Progression
- 30 month
- 36 month
- 48 month
- 60 month (extension)
- Aug, 09

Osteoarthritis Initiative
Public data release schedule

- Data released in 2 groups
  - 1\textsuperscript{st} group = 1\textsuperscript{st} half (56\% enrolled, n=2,686)
  - 2\textsuperscript{nd} group = Entire cohort (n=4,796)

- Release schedule
  - Two releases per visit cycle
  - 9-12 mos after last visit in 1\textsuperscript{st} and 2\textsuperscript{nd} group

- Concurrent release of images and clinical data
Data currently available on OAI Online

- Questionnaires and exam data, images for entire cohort
  - Baseline
  - 12-mo visit
  - 24-mo visit
  - 18-mo and 30-mo visits (subset of Progression)
Upcoming data releases

- Fall 2009
  - 36-month questionnaire, exams, images
    (1st group, n=2,686)
  - Central image assessments

- Spring 2010
  - 48-month questionnaire, exams, images
    (1st group, n=2,686)
Follow-up and retention
## Completeness of Follow-up (8/09)

<table>
<thead>
<tr>
<th>Follow-Up Status</th>
<th>12-mo</th>
<th>24-mo</th>
<th>36-mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic visit</td>
<td>90%</td>
<td>85%</td>
<td>82%</td>
</tr>
<tr>
<td>Telephone contact only</td>
<td>4%</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>Deceased, withdrew, LFU</td>
<td>6%</td>
<td>10%</td>
<td>11%</td>
</tr>
</tbody>
</table>

- Ppts with follow-up visits (12-mo to 36-mo)
  - ≥ 1 visit: 95%
  - ≥ 2 visits: 88%
Completeness of longitudinal knee imaging (6/09)

Percent of subjects with knee images:

<table>
<thead>
<tr>
<th></th>
<th>BL and 24-mo images</th>
<th>BL and 36-mo images</th>
<th>BL, 12-mo, 24-mo and 36-mo images</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X-ray</td>
<td>MRI</td>
<td>MRI and Xray</td>
</tr>
<tr>
<td></td>
<td>85%</td>
<td>82%</td>
<td>81%</td>
</tr>
<tr>
<td></td>
<td>80%</td>
<td>77%</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>74%</td>
<td>71%</td>
<td>68%</td>
</tr>
</tbody>
</table>
Central image assessments and primary endpoints
Central image assessments

- Standardized measurement/interpretation of samples of images using validated methods
  - Sponsored by OAI for public use
  - Sponsored by users and available to public

- OAI-sponsored
  - Baseline X-ray knee OA status
    - Clinic screening reading (all)
    - Central reading (Progression cohort)
  - Knee outcomes/endpoints for natural history, biomarker and risk factor studies
    - Structural progression (X-ray, MRI)
    - Incident X-ray OA
Central image assessments: OAI sponsored - Progression subcohort

- **Image assessment Core Sample** (~1,050 ppts)
  - Have BL and 24-mo knee x-rays and MRIs
  - X-ray reading (K-L gr, IRFs, bilat)
  - JSW measurement (bilat)

- **Index knees** from Core Sample (~600; 1 knee/ppt)
  - frequent knee symptoms
  - K-L gr 2-3 (central reading)
  - minJSW ≥ 1.0mm

- **MRI assessments** in Index knees
  - Quantitative cartilage of T-F joint using sagDESS - ongoing, est. completion 2010
  - SQ whole organ score - maybe
Other central image assessments (available 2/09 data release)

Images B sample, BL and 12-mo (n=160)
- Knee X-ray (bilateral data)
  - K-L gr, IRFs, JSW
  - Knee alignment from full limb
- Knee MRI/Quant cartilage (selected knees)
  - VirtualScopics/Merck (sagDESS, n=150)
  - Chondrometrics/Pfizer (FL, n=158)

Other samples
- Knee MRI/Quant cartilage
  - Chondrometrics/OAI (corDESS, BL,12-mo, n=80)
  - Chondrometrics/OAI (FL, BL and 24-mo, n=146)
Central assessment of all knee X-rays at all time-points

- All knees and/or time-points not yet centrally read in all 3 subcohorts
  - Longitudinal reading K-L gr, IRFs, JSN progression
  - Identify incident knee OA cases
  - Knees with X-ray OA: JSW at all time-points

- Timeline
  - Rolling release as assessments are completed
Central image assessments: Incidence

- Identify incident X-ray knee OA for nested case-control studies of biomarkers

Follow-up of knees eligible for incidence endpoint

Earlier time-points

Incident cases

Biochemical and Imaging biomarkers

Controls
Estimated number of knees with incident X-ray OA

- New T-F OA: BL KLG<2 → KLG ≥2 follow-up
- Estimate based on risk in Multicenter Osteoarthritis Study

<table>
<thead>
<tr>
<th>Expected incident T-F X-ray OA*</th>
<th>Incidence and Progression cohorts combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st 4 years</td>
</tr>
<tr>
<td>Men</td>
<td>100</td>
</tr>
<tr>
<td>Women</td>
<td>167</td>
</tr>
<tr>
<td>All</td>
<td>267</td>
</tr>
</tbody>
</table>

* Projections allow for aging of the cohort and dropouts.
Incident symptomatic knee OA

- Incident Sx OA = development of freq Sx and X-ray OA in same knee

Knees eligible at baseline

- Freq Sx only
- X-ray OA only
- Neither

Follow-up

- Incident SxOA
- X-ray OA and Freq Sx

Of 1,100 knees at BL, 22% had Freq Sx at 24-mo
Knee replacement in the OAI

- Confirm TKRs for OA by medical record
- Risk of TKR in knees with X-ray OA, first 24 mos
  - Men 1.4% /yr
  - Women 1.7% /yr

<table>
<thead>
<tr>
<th></th>
<th>4 years</th>
<th>8 years (ext)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>46</td>
<td>118</td>
</tr>
<tr>
<td>Women</td>
<td>80</td>
<td>206</td>
</tr>
<tr>
<td>All</td>
<td>126</td>
<td>324</td>
</tr>
</tbody>
</table>

* Projections allow for aging of the cohort, dropouts, and confirmation of TKRs from medical records
Knee replacement (cont.)

- Theoretical indication for joint replacement (OARSI/OMERACT initiative)*
  - Intermittent/persistent OA pain measure (ICOAP)
  - WOMAC function index
  - X-ray JSN

- Increased number of end-stage outcomes

- Reduce the effect of demographic disparities in utilization of joint replacement
  - E.g. African Americans under-utilize JR
    (Kane, ArthRheum, 2007)

*Gossec, OMERACT/OARSI initiative to define states of severity and indication for joint replacement. JRheum, 2007
Opportunities for analysis of existing data
Key research questions for existing longitudinal data and images

- Natural history of knee OA
  - What is the temporal sequence of structural and/or biochemical changes?
  - What occurs first and what does it lead to?
  - Defining early OA?
Natural history of knee OA

Evolution of pathology on MRI e.g.
meniscal damage → bone marrow lesions → cartilage loss/JSN

\[ \text{X = imaging, samples, clinical data} \]

<table>
<thead>
<tr>
<th></th>
<th>12mo</th>
<th>24mo</th>
<th>36mo</th>
<th>48mo</th>
<th>extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>12mo</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>24mo</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>36mo</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>48mo</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>extension</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

- Meniscal damage
  - \( \Delta \)
  - X
  - \( \Delta \)
  - \( \Delta \)
  - \( \Delta \)

- BMLs
  - \( \Delta \)
  - X
  - \( \Delta \)
  - \( \Delta \)

- Cartilage loss
  - \( \Delta \)
  - X
  - \( \Delta \)
  - X

- Select knees: no BL pathology
- Risk of new BMLs in knees by BL meniscal damage
- Risk of Cart loss by BL-12m BMLs

Knees with no BL pathology uncommon

Multiple MRI features will change concurrently
Natural history of knee OA

Evolution of pathology on MRI e.g.
meniscal damage → bone marrow lesions → cartilage loss/JSN

What is the relative frequency that change in one feature precedes vs follows change in the other features?

- Select knees with “early OA”
- BL pathology, ∆ during F-Up, in all MRI features will be common.
- Assess concurrent ∆s
Natural history: ‘Early’ knee OA

- Evaluation of ‘Early OA’ definitions
  - Based on symptoms, pathology or both?
  - Sensitive: account for a large % of clinical OA knees?
  - Specific: a large % develop clinical OA?

- Adequate study material in OAI?
  - >3,000 knees with Sx but no BL X-ray OA
  - >1,100 knees with osteophytes only and no or mild Sx

- 4 years of follow-up adequate?

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Onset/progression

Biomarker precursors

Structural pathology

Symptoms

Early OA?

At risk

Preclinical / Early

Clinical OA

Endstage

Adequate study material in OAI?

4 years of follow-up adequate?

Evaluation of ‘Early OA’ definitions

- Based on symptoms, pathology or both?
- Sensitive: account for a large % of clinical OA knees?
- Specific: a large % develop clinical OA?

Adequate study material in OAI?

- >3,000 knees with Sx but no BL X-ray OA
- >1,100 knees with osteophytes only and no or mild Sx

4 years of follow-up adequate?
Key research questions for existing longitudinal data and images (Cont.)

- Risk/prognostic biomarker for structural/clinical outcome
  - Baseline value of biomarker predicts outcome
  - $\Delta$ biomarker predicts subsequent outcome
Risk and prognostic biomarkers

Does abnormal T2 predict JSN / functional loss?

\( X = \text{imaging, samples, clinical data} \)

- Select knees like those targeted by test
- Clinically relevant time-points for predictor and outcome

\( \Delta \)
Key research questions for existing longitudinal data and images (Cont.)

- Risk/prognostic biomarker for structural/clinical outcome
  - Baseline value of biomarker predicts outcome
  - Δ biomarker predicts subsequent outcome

- Potential efficacy biomarker
  - Δ biomarker associated with structural/clinical outcome over the same interval and...
  - ...predicts subsequent long-term outcome
Potential efficacy biomarker

Does Δbiomarker track closely with structural/clinical outcome?

ΔCTXII correlates with ΔJSN, Δfunction?
ΔCTXII predicts long-term outcome?

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>12mo</th>
<th>24mo</th>
<th>36mo</th>
<th>48mo</th>
<th>extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTXII</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>JSN</td>
<td>x</td>
<td>Δ</td>
<td>x</td>
<td>Δ</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Function loss</td>
<td>Δ</td>
<td>x</td>
<td>Δ</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

• Select knees like those targeted for treatment
• Clinically relevant time-points for predictor and outcome

Strong association of Δbiomarker with concurrent and subsequent outcomes suggests potential as efficacy biomarker/surrogate endpoint.
Challenges and limitations

- Selecting ppts/knees for study requires careful thought
- Users need to generate biomarker data from images and specimens
- Structural outcomes and endpoints in public datasets at present limited to
  - mostly Progression subcohort
  - BL through 24 mos only
  - Some analyses require additional outcome data
- Users dependent on OAI for incidence endpoints - in process
- Extended follow-up needed to cover full spectrum of disease in same ppts/knees: At risk → endstage
Biospecimens and Publications
Applications for OAI biospecimens being accepted

- Biospecimens from baseline, 12-mo, and 24-month
  - Serum
  - Plasma (EDTA, citrated)
  - DNA
  - Urine

- Application deadlines
  - January 15
  - May 15
  - September 15
Application process for biospecimens

- Complete application form and proposal
  - Describe level of technical and method validation
  - Justify type/amount of specimen requested
  - Data sharing plan
    - Data from biospecimen to be made public via OAI Online
  - Submit to OAIbiospecimens@kai-research.com

- Review process
  - Biospecimen Review & Allocation Committee (BRAC)
  - Proposals reviewed for feasibility, scientific merit and consistency with OAI goals
  - Review process takes 6-10 weeks
  - Specimens released once funding confirmed
Publication guidelines for public data users (OAI Online)

- Encourage use of public datasets
- Ensure appropriate citation and acknowledgement of OAI
- Inform us about OAI publications
  - Publications listed on OAI Online
  - Electronic archive of PDFs (if available)
Additional publication options

- Participate in OAI publications process
  - E-mail: OAIPublications@psg.ucsf.edu

1. Complete analysis form to “register” topic
   - Avoid unintended duplication of effort and let others know your area of interest

2. Submit analysis proposal to OAI Publications Committee for feedback
   - Constructive critiques and analytic guidance
   - Foster collaboration among OAI investigators
   - ‘Good housekeeping seal of approval’

   “This manuscript has received the approval of OAI Publications Committee based on review of scientific content and data interpretation"
OAI publications options

- OARSI abstracts 2008, 2009
  - ~35 abstracts accepted for presentation
  - 15 “registered” analysis topics via OAI Online
Thank you for your attention.
Questions?

Contact info
mnevitt@psg.ucsf.edu