OAI Data Users
ACR Study Group

ACR Annual Meeting
Oct 27, 2008
Outline of session

- **Objectives:** introduce prospective and new users to the OAI, describe how to access the public data, images and biospecimens, suggest analytical strategies for OAI data

- Overview of study design and data  *M Nevitt*

- ‘OAI On-line’, access to data, images and biospecimens  *S. Rubin*

- Using OAI images  *J. Lynch*

- Analysis methods and issues  *C. McCulloch*

- Open discussion
OAI design, subject characteristics, data and images

Michael C. Nevitt, PhD
Epidemiology & Biostatistics, UCSF
OAI Coordinating Center
Primary objectives of OAI

- A shared clinical research resource to
  - Describe the structural and biochemical changes of early and progressive knee OA
    - Understand natural history
  - Identify factors that influence knee OA onset and progression
  - Characterize imaging, biochemical and genetic biomarkers that predict and track the course and outcome of disease
    - Biomarker qualification
Achieving the OAI objectives:
1. Longitudinal cohort study of knee OA

- Well-defined and characterized community sample assessed longitudinally
  - Imaging, molecular, genetic and risk markers
  - Symptoms, function, disability, surgery

- Multiple stages in the spectrum of knee OA
  - At risk → Early/preclinical → Established → Endstage

- Evaluate biomarker level (and Δ) as predictors and correlates of disease and patient outcomes
Achieving the OAI objectives

2. Public data resources

- Open access to the data, images and biospecimens to speed the generation of new knowledge about OA, enlist the community of OA investigators worldwide in understanding natural history and biomarkers
  - Downloadable clinical data archive on the web
  - Archived images on demand
  - Archived biospecimens by application
OAI study design resources

- **OAI Online**  [www.oai.ucsf.edu/datarelease/docs/about](http://www.oai.ucsf.edu/datarelease/docs/about)
  - Study protocol and measurements
    [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 Design: Subcohorts**

**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 outcomes**

Progression (Symptoms, function, structure, TKR)

Incidence endpoints (Sx OA, X-ray OA)

Biomarker reference
Osteoarthritis Initiative

Schedule of clinic visits

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

**Progression**

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

**Incidence, controls**

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

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

Other joint imaging
- BL and FU hip/pelvis, hand x-rays
- Full limb for knee alignment
- MRI of the thigh

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

- Knee symptoms and function
- 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/datarelease/docs/ExamMeasures.pdf
www.oai.ucsf.edu/datarelease/docs/Questionnaires.pdf
Characteristics of OAI participants
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
Recruitment: March 04 - May 06

- 17,457 phone screen → 4,796 (27%) enrolled
  - Targeted mailing lists
- Main reasons not eligible
  - Gender age/cell full (n=2,954)
  - MRI contraindication (n=2,295)
  - Bilateral end-stage knee OA (n=514)
  - Not interested/dropped out (n=4,381)
Recruitment: March 04 - May 06

**Telephone Screen**
N = 17,457

3-6 wks  Drop out: 3,321 (19%)

**Screening Visit**
(Screening knee x-ray)
N = 7,686

3-6 wks  Drop out: 1,060 (6%)

**Enrollment Visit**
(Imaging, biospecimens, baseline assessments)
4,796 enrolled*

*27% of those screened

Not eligible: 6,450 (37%)
MRI exclusion: 1,595
Gender/age cell full: 2,954
Other exclusion: 1,901

Not eligible: 1,810 (10%)
MRI exclusion: 700
Bilat endstage knee OA: 596
Other: 514

*27% of those screened
Progression subcohort eligibility
Baseline Symptomatic T-F Knee OA (Sx OA)

- Co-occurrence of knee Sx and structural pathology in one or in both knees
  - cause of disability, public health impact

"Pain, aching or stiffness on most days of a month in past year"

Definite T-F osteophyte (OARSI atlas gr 1-3) from baseline clinic reading

- Population studies
  - ~ 50% overlap between knee Sx and x-ray OA
## Progression subcohort at baseline

<table>
<thead>
<tr>
<th>Subcohort PROGRESSION</th>
<th>Female</th>
<th>57%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age 60-79</td>
<td>55%</td>
</tr>
<tr>
<td></td>
<td>Nonwhite</td>
<td>30%</td>
</tr>
</tbody>
</table>

- Male N (%): 1,389 (29%)
- Female N (%): 725 (15%)

### BMI ≥ 30.0
- Total: 44% (1,389/3,170), Men: 44% (628/1,435), Women: 53% (761/1,435)

### Hx knee injury/surgery
- Total: 35% (1,389/3,170), Men: 35% (628/1,435), Women: 18% (761/4,150)

### Hand OA-DIP nodes
- Total: 38% (1,389/3,170), Men: 38% (628/1,435), Women: 48% (761/1,580)
Proportion subcohort
Baseline knee OA status

- All Progression pts have Sx OA (frequent knee Sx and definite osteophyte) in at least one knee
Progression subcohort
Baseline WOMAC Knee Pain scores

Mean WOMAC knee pain score

<table>
<thead>
<tr>
<th>WOMAC Likert Scale Score Range 0-20</th>
<th>OAI</th>
<th>DOXY</th>
<th>KOSTAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All knees</td>
<td>3.7</td>
<td>4.7</td>
<td>5.8</td>
</tr>
<tr>
<td>X-ray OA, No Freq Sx</td>
<td>1.3</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Sx OA</td>
<td>4.7</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>DOXY KOSTAR Knee OA Tx studies</td>
<td></td>
<td></td>
<td>8.0</td>
</tr>
</tbody>
</table>
Incidence subcohort eligibility

Inclusion criteria

- Does not have Sx T-F knee OA either knee
- Has an increased risk for knee OA in > 1 knee
  - Frequent knee Sx without x-ray T-F OA*
  - Two or more eligibility risk factors

* A ppt may have x-ray T-F OA (osteophytes) in one or both knees, but did not have freq Sx in the same knee
## Incidence subcohort at baseline

### Incidence Subcohort at Baseline

- **N (%) of total**
  - 3,285 (68%)

### Subcohort

**INCIDENCE**
- At elevated risk of developing Knee OA during the study

### Male: Female

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI ≥ 30.0</td>
<td>34%</td>
<td>33%</td>
</tr>
<tr>
<td>Hx knee injury/surgery</td>
<td>20%</td>
<td>9%</td>
</tr>
<tr>
<td>Family Hx of TKR</td>
<td>14%</td>
<td>16%</td>
</tr>
<tr>
<td>Hand OA/DIP nodes</td>
<td>37%</td>
<td>53%</td>
</tr>
</tbody>
</table>

- **Female**
  - 59%
- **Age 60-79**
  - 54%
- **Nonwhite**
  - 18%
Incidence subcohort
Baseline knee OA status

- No pts have Freq Sx and X-ray OA in the same knee

% of pts, at least one knee has:

<table>
<thead>
<tr>
<th>Condition</th>
<th>% of Men</th>
<th>% of Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freq Sx</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>Osteophytes</td>
<td>38</td>
<td>40</td>
</tr>
</tbody>
</table>
Things to keep in mind about the subcohorts

- Definition of Sx OA based on measures that change
  - Frequent knee Sxs come and go
  - X-ray OA defined by definite Osteophyte from clinic reading
    - Osteophyte ≠ K-L grade 2
    - Readers often disagree

- Incidence cohort includes some knees with symptoms, some with radiographic findings
  
  At risk → Early/preclinical → Established → Endstage

- Many analyses will use knees from both subcohorts
Why are there ppts in the “incidence” subcohort who already have Sx or x-ray OA?

- Key endpoint: incident Sx OA (freq Sx and x-ray OA in same knee)
Follow-up and retention of the cohort
Clinic visit timeline

- Baseline visit
- 12 month visit
- 18 month visit
- 24 month visit
- 30 month visit
- 36 month visit
- 48 month visit

Oct 08
## Follow-up status (10/08)

<table>
<thead>
<tr>
<th>Status</th>
<th>Follow-up Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12-mo (4,796)</td>
</tr>
<tr>
<td></td>
<td>24-mo (4,755)</td>
</tr>
<tr>
<td>Clinic visit</td>
<td>4,294 (90%)</td>
</tr>
<tr>
<td></td>
<td>3,888 (85%)</td>
</tr>
<tr>
<td>Telephone contact only</td>
<td>198 (4%)</td>
</tr>
<tr>
<td></td>
<td>258 (5%)</td>
</tr>
<tr>
<td>Deceased, withdrew, LFU</td>
<td>304 (6%)</td>
</tr>
<tr>
<td></td>
<td>472 (10%)</td>
</tr>
</tbody>
</table>
Completion rates for biomarker measures in subjects with a follow-up clinic visit (10/08)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>% with a clinic visit who had the measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12-mo</td>
</tr>
<tr>
<td>Knee x-ray</td>
<td>98%</td>
</tr>
<tr>
<td>Knee MRI</td>
<td>97%</td>
</tr>
<tr>
<td>Blood and urine</td>
<td>&gt;99%</td>
</tr>
</tbody>
</table>
## Completeness of longitudinal knee imaging (10/08)

Percent of all subjects with: **both baseline and 24-mo images**

<table>
<thead>
<tr>
<th></th>
<th>Knee MRI</th>
<th>Knee X-ray</th>
<th>MRI and X-ray</th>
</tr>
</thead>
<tbody>
<tr>
<td>Images available at both timepoints</td>
<td>82%</td>
<td>85%</td>
<td>81%</td>
</tr>
</tbody>
</table>

## Completeness of longitudinal knee imaging (10/08)

Percent of all subjects with: **both baseline and 36-mo images**

<table>
<thead>
<tr>
<th></th>
<th>Knee MRI</th>
<th>Knee X-ray</th>
<th>MRI and X-ray</th>
</tr>
</thead>
<tbody>
<tr>
<td>Images available at both timepoints</td>
<td>77%</td>
<td>80%</td>
<td>76%</td>
</tr>
</tbody>
</table>
Central image assessment

- What is it?
  - Standardized measurement/interpretation of selected samples of images using validated methods
  - Sponsored by OAI (for public release) and/or by users (eventual public release)

- Structural progression and incidence endpoints for public users

- Ongoing
Central image assessments
Progression subcohort

Progression subcohort (n=1,389)

160 Subset (BL-12mo)

BL-12mo X-rays (completed)
- K-L grade, osteophytes, JSN
- Joint space width (JSW)*

BL-12mo MRIs (completed)
- quantitative cartilage*
* funded by OAI Pharma partners

N ~ 600 (BL-24mo)

BL-12-24mo X-rays (ongoing)
- BL K-L grade, Ost, JSN
- Longitudinal K-L, JSN, JSW

BL-12-24mo MRIs (ongoing)
- BL Whole organ score
- Long. quantitative cartilage
- Long. semiquantitative cartilage
Central image assessments
Incidence subcohort

- Primary goal: Identify incident knee OA for nested case-control studies of biomarkers

Follow-up
ppts eligible for
incidence endpoint

Incident
cases

Controls

Earlier
timepoints

X

Biochemical and
Imaging markers

X
Acknowledgements

- NIAMS and participating NIH institutes
- OAI Pharmaceutical company partners (Merck Research Laboratories; Novartis Pharmaceuticals Corporation, GlaxoSmithKline; and Pfizer, Inc.)
- Academic investigators and subcontractors
  - Ohio State University
  - University of Maryland
  - John’s Hopkins University
  - Brown University
  - University of Pittsburgh
  - University of California, San Francisco
  - Synarc, Inc
  - Boston University
OAI Coordinating Center - UCSF

Susan Rubin          Emily Kenyon
Alisa Boyd           Emily Scott
John Lynch           Susan Averbach
Todd Parsnick       Laura Bettencourt
Robin Hermias       Maurice Dockrell
Sue Bolton           Jean Hietpas
Peter Armour         Eve Benton
Coral Etkin          Jason Maeda
Charles McCulloch    Michael Nevitt

And the great team at Synarc!
OAI Collaborators (partial list)

Gayle Lester
Charles Peterfy
Joan Bathon
Erika Schneider
Marie-Pierre Gastineau
Thasia Woodworth
Kent Kwoh
Marc Hochberg
Monica Luchi

Rebecca Jackson
David Felson
Charles Eaton
Tim McAlindon
Jerry Mysiw
Michael LaValley
Charles McCulloch
Stefan Lohmander
Chan Beals