

3rd OAI Data Users Workshop Advanced Topics

OARSI Annual Meeting
Montreal, Sept 10, 2009



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)
 - Study protocol and measurements

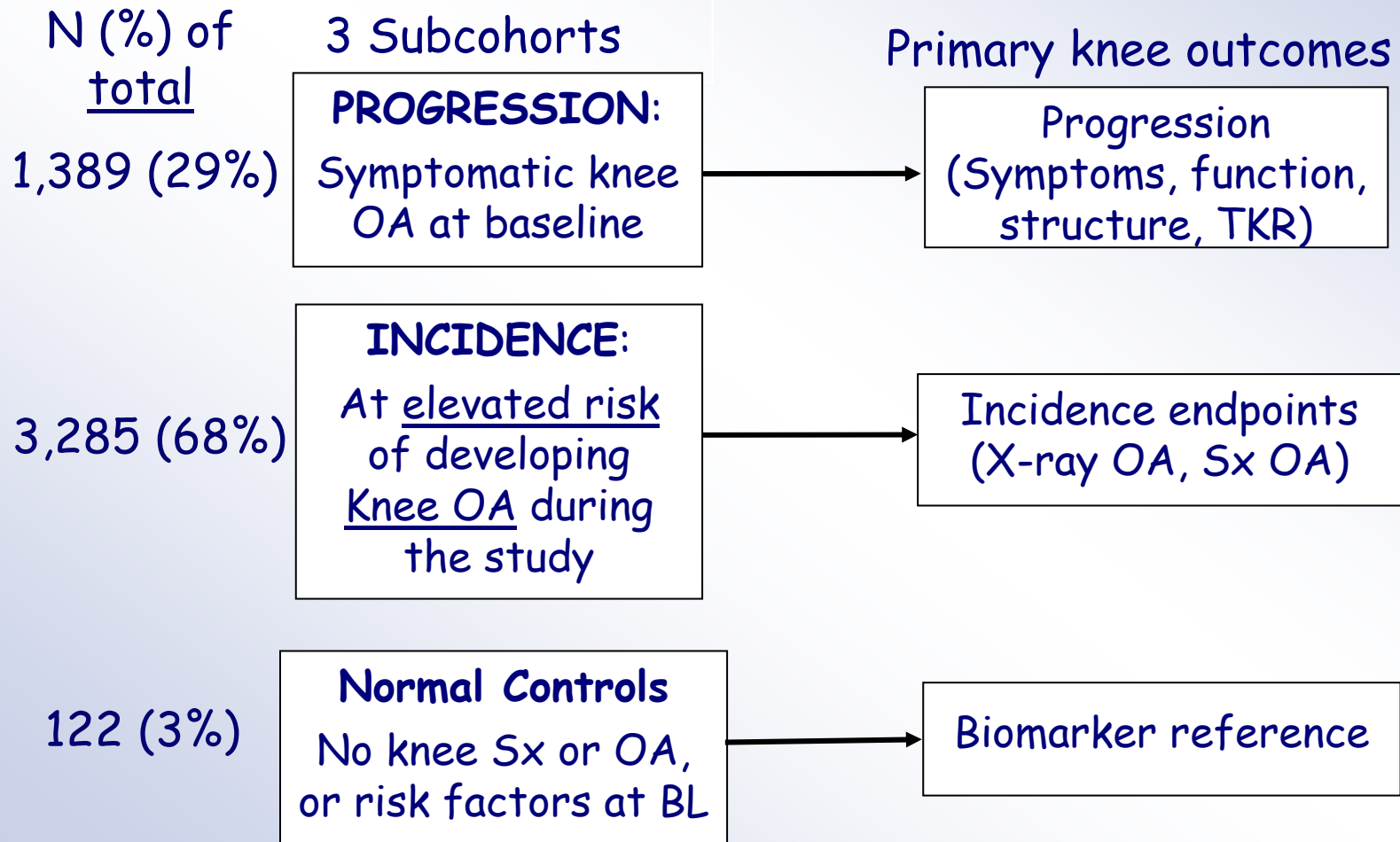
www.oai.ucsf.edu/datarelease/docs/about

www.oai.ucsf.edu/datarelease/docs/StudyDesignProtocol.pdf

www.oai.ucsf.edu/datarelease/operationsmanuals.asp



OAI longitudinal cohort study



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

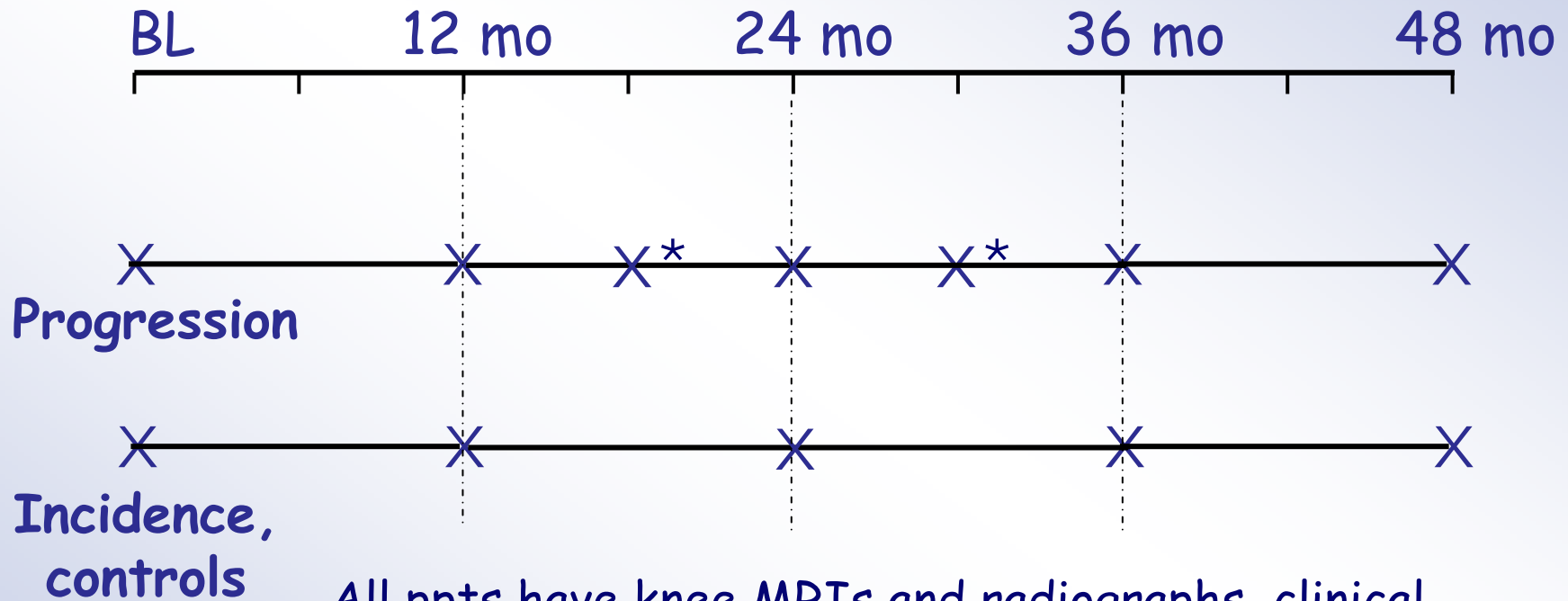
	<u>Progression</u>	<u>Incidence</u>
• Women	57%	59%
• Age 60-79	55%	54%
• Nonwhite	30%	18%
• BMI > 30	50%	33%
• Hx knee injury/surgery*	51%	39%
• Frequent knee Sx*	100%	30%
• X-ray knee OA*, **	100%	39%

* in ≥ 1 knee

** clinic screening reading



Schedule of clinic visits, measurements



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

*Interim 6-mo visit in a subset of Progression pts 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/datarelease/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/datarelease/docs/ExamMeasures.pdf

www.oai.ucsf.edu/datarelease/docs/Questionnaires.pdf



Things to keep in mind about Progression and Incidence subcohorts

- Purpose: balance of ppts 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 ppts had unilateral Sx OA at BL
 - 1/3 of ppts 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

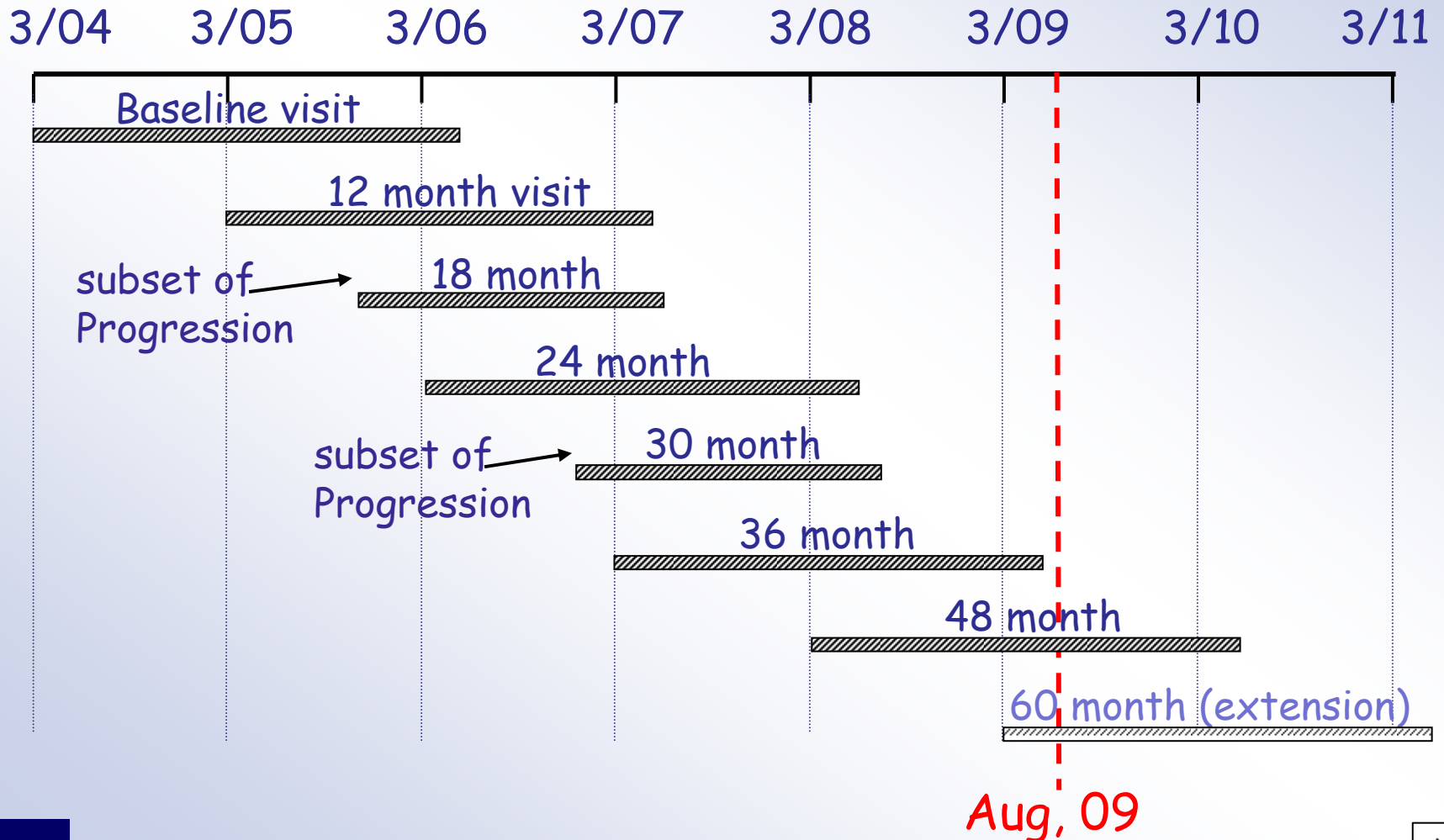
- Incidence cohort enriched for those at high risk
 - May not represent general population
 - E.g. Hx knee injury/surgery: 39%
- Ppts in Incidence cohort may have BL OA
 - 39% have X-ray OA (but not Sx OA) in ≥ 1 knee
- Measurements the same in both cohorts
- Analyses can combine ppts/knees from both cohorts
 - E.g. men with unilateral X-ray OA
 - Progression: n=213
 - Incidence: n=255



Public data release



Clinic visit timeline



Public data release schedule

- Data released in 2 groups
 - 1st group = 1st half (56% enrolled, n=2,686)
 - 2nd group = Entire cohort (n=4,796)
- Release schedule
 - Two releases per visit cycle
 - 9-12 mos after last visit in 1st and 2nd 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)

Follow-Up Status	Follow-up Visit		
	12-mo	24-mo	36-mo
Clinic visit	90%	85%	82%
Telephone contact only	4%	5%	7%
Deceased, withdrew, LFU	6%	10%	11%

- 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:

BL and 24-mo images

X-ray	MRI	MRI <u>and</u> Xray
85%	82%	81%

BL and 36-mo images

X-ray	MRI	MRI <u>and</u> Xray
80%	77%	75%

BL, 12-mo, 24-mo and 36-mo images

X-ray	MRI	MRI <u>and</u> Xray
74%	71%	68%

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 ppt)**
 - 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 \geq 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)

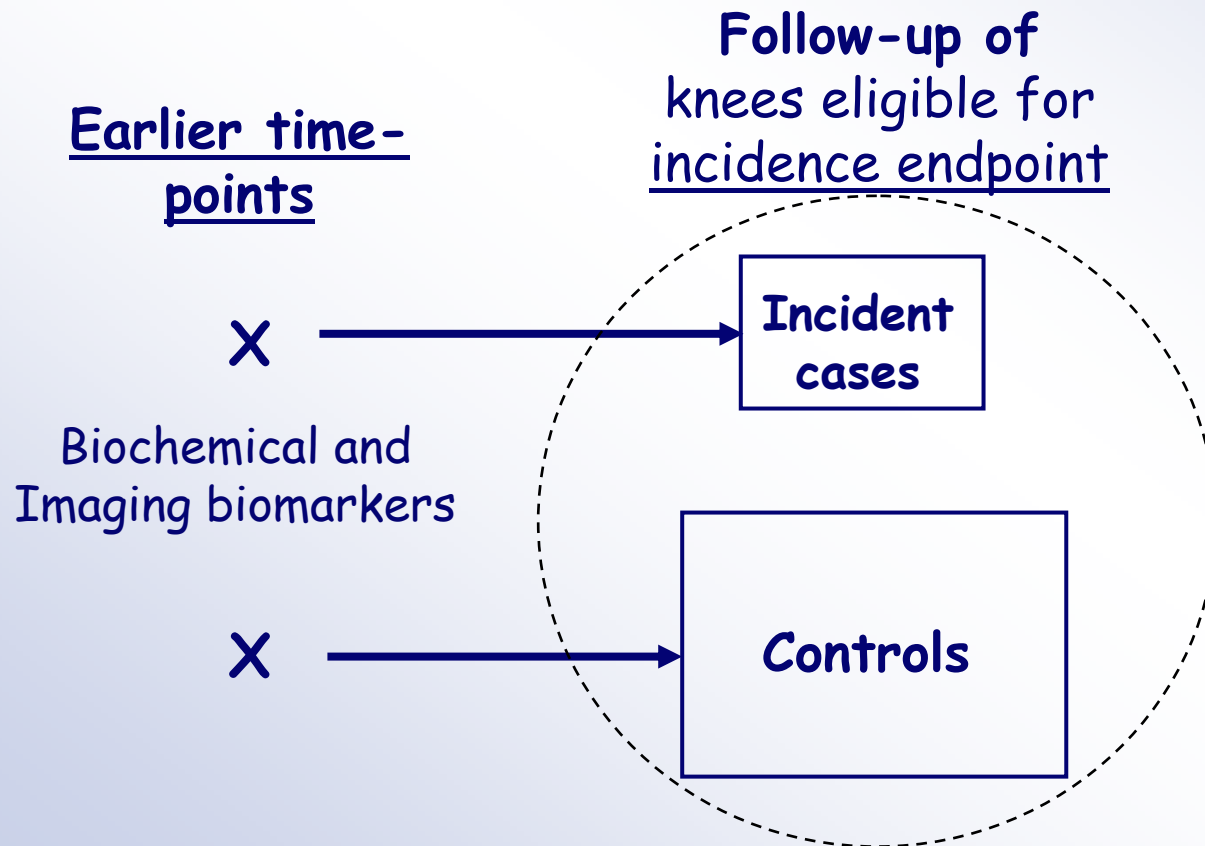
Central assessment of all knee X-rays at all time-points

- 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
 - 11/2009 - 9/2011
 - Rolling release as assessments are completed



Central image assessments: Incidence

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



Estimated number of knees with incident X-ray OA

- New T-F OA: BL $KLG < 2 \rightarrow KLG \geq 2$ follow-up
- Estimate based on risk in Multicenter Osteoarthritis Study

Expected incident T-F X-ray OA* Incidence and Progression cohorts combined			
	1 st 4 years	2 nd 4 years	8 years (extension)
Men	100	121	221
Women	167	200	367
All	267	321	588

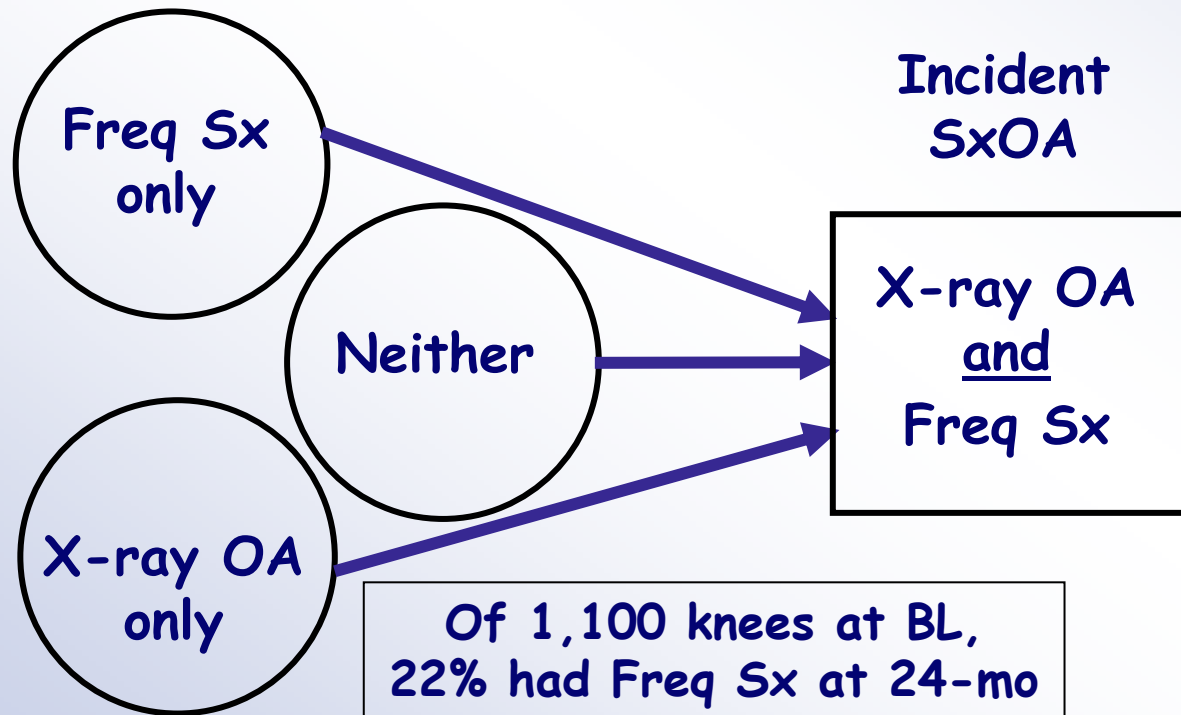
* Projections allow for aging of the cohort and dropouts.

Incident symptomatic knee OA

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

Knees eligible at baseline

Follow-up



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

Expected number of TKRs in OAI *		
	4 years	8 years (ext)
Men	46	118
Women	80	206
All	126	324

* 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



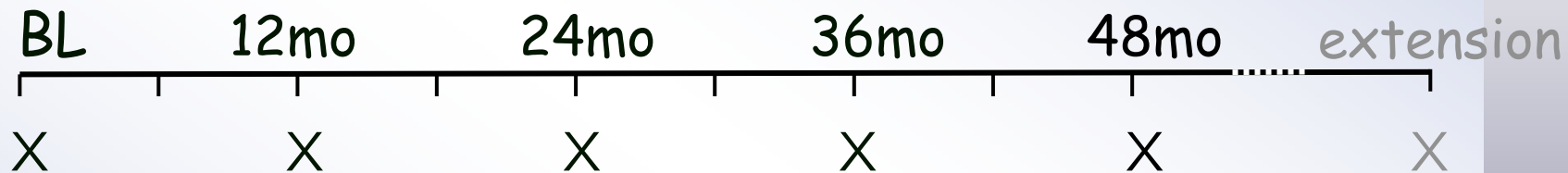
Key research questions for existing longitudinal data and images

- 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

X = imaging, samples, clinical data



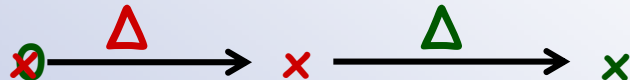
Meniscal damage



BMLs



Cart loss

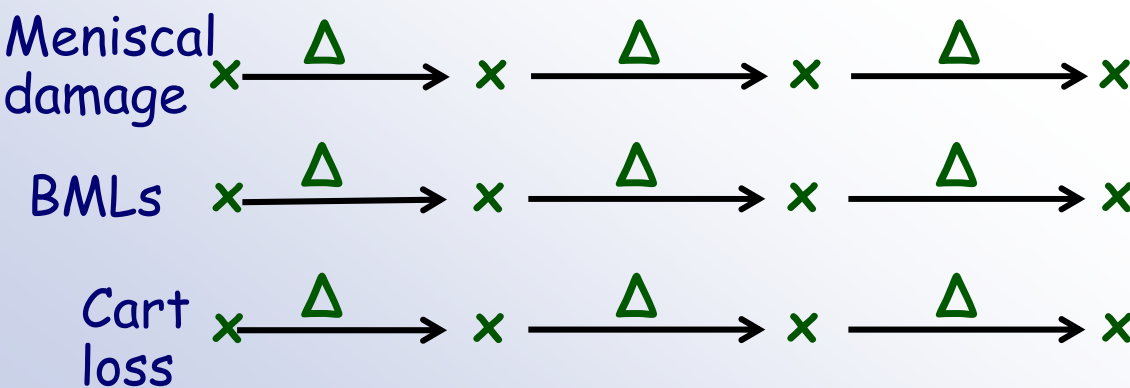
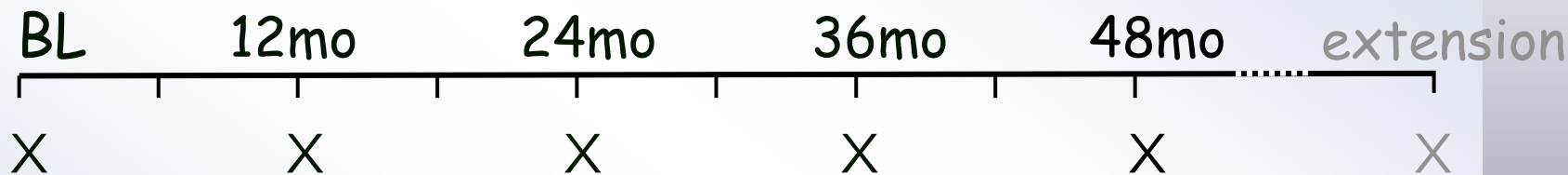


- Select knees: no BL pathology
- Risk of new BMLs in knees by BL meniscal damage
- Risk of Cart loss by BL-12m BMLs

- 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



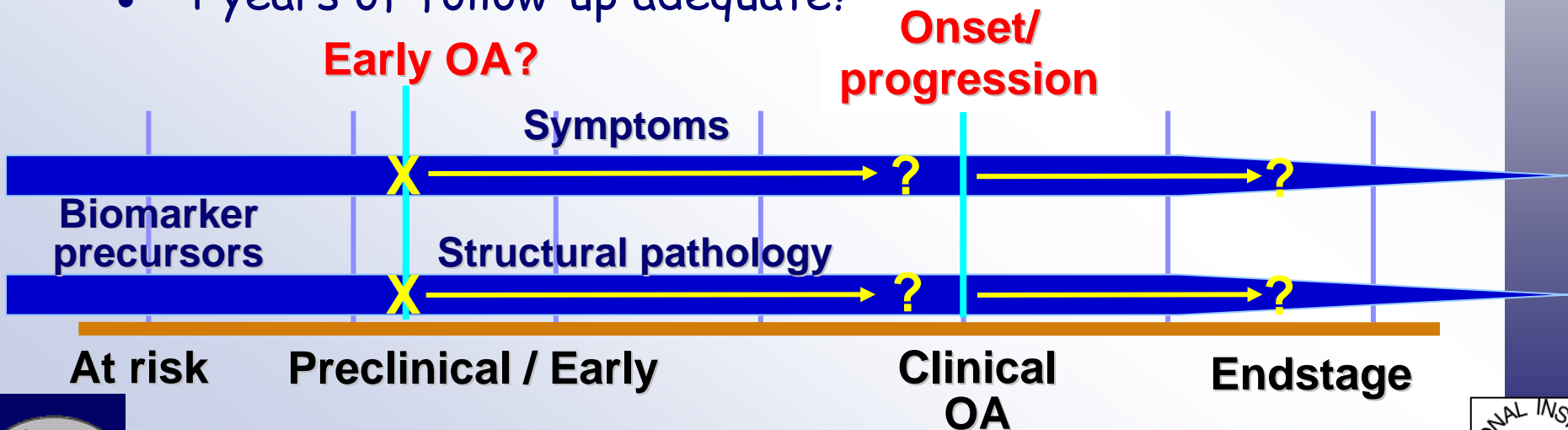
- Select knees with "early OA"
- BL pathology, Δ during F-Up, in all MRI features will be common.
- Assess concurrent Δs

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



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?



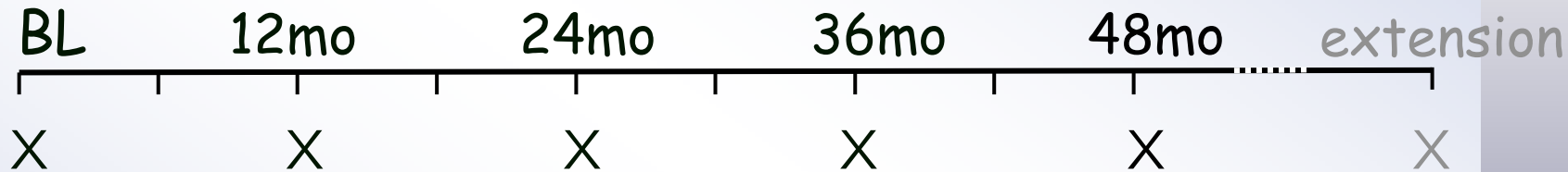
Key research questions for existing longitudinal data and images (Cont.)

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

Risk and prognostic biomarkers

Does abnormal T2 predict JSN / functional loss?

X = imaging, samples, clinical data



T2 x

JSN x ————— Δ —————> x

Function loss x ————— Δ —————> x

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

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

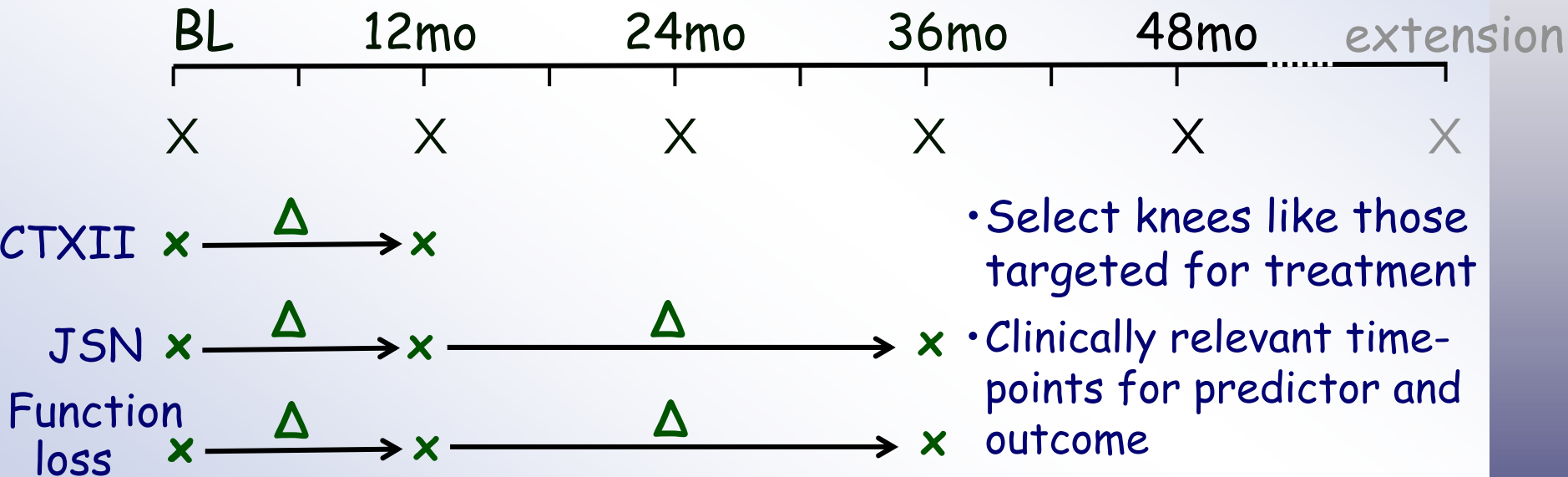
- Risk/prognostic biomarker for structural/clinical outcome
 - Baseline value of biomarker predicts outcome
 - Δ biomarker predicts subsequent outcome
- Potential efficacy biomarker
 - Δ biomarker associated with structural/clinical outcome over the same interval and...
 - ...**predicts** subsequent long-term outcome

Potential efficacy biomarker

Does Δ biomarker track closely with structural/clinical outcome?

Δ CTXII correlates with Δ JSN, Δ function?

Δ CTXII predicts long-term outcome?



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

Challenges and limitations

- Selecting pts/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 pts/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?

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