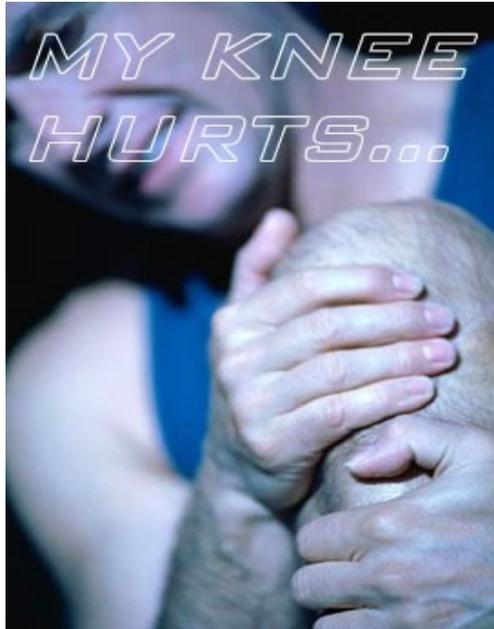


FNIH Osteoarthritis Biomarkers Consortium Project



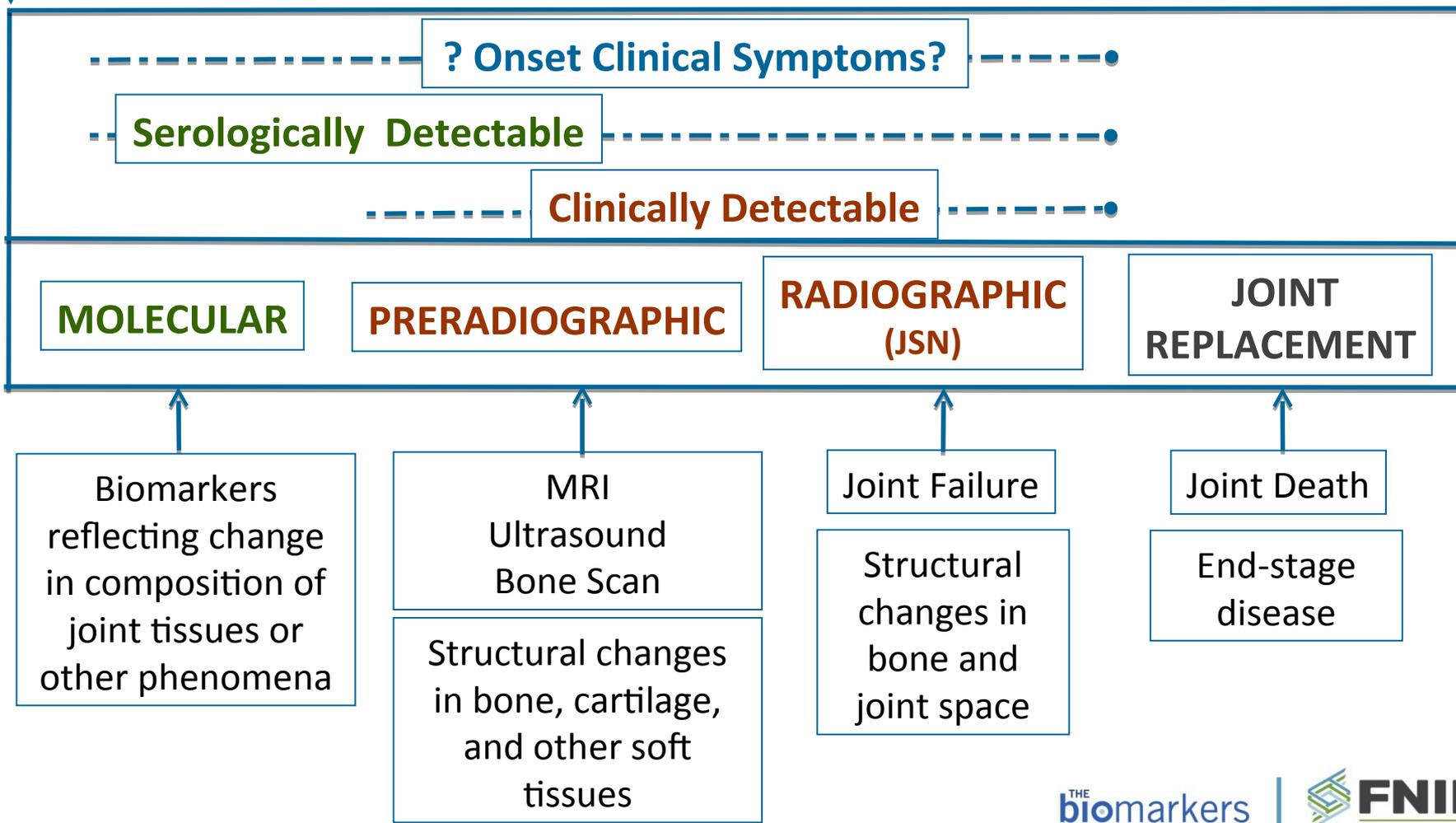
Osteoarthritis (OA): Increasingly Prevalent Disabling Disease



- 27 million Americans with OA
- Symptomatic knee OA occurs in 13% of persons \geq 60 yrs
- The risk of mobility disability attributable to knee OA greater than due to any other medical condition in people \geq 65 yrs
- By 2020 number of people with OA will double due to aging population and obesity
- Many promising OA drug and biomarker candidates; OA Biomarker Project critical next step

Changing The Paradigm of OA Drug Development: Identifying Patients With Earlier Stage Disease for Early Treatment Intervention

OA process begins 20 years before joint space (JSN) narrowing detects disease



Critical Need for OA Therapeutics

- No treatment exists that can preserve joint structure or modify progression
- Current therapeutics provide relief of symptoms but, largely palliative
- Therapeutics for knee OA limited to use of OTC* pain relievers (aspirin, acetaminophen), NSAIDs** (which have GI/CV ‡ risks) and cautious waiting for eventual referral for total joint replacement
- Biomarkers may provide a rapid indication of response to a particular intervention and streamline the discovery of new therapeutic agents
- However, currently, there is no consensus for a process of OA biomarker validation and qualification (e.g., biochemical markers, imaging markers).

*Over the Counter

**Nonsteroidal anti-inflammatory drugs

‡Gastrointestinal/cardiovascular

Osteoarthritis Biomarkers Project

■ **Project Goals:**

- Identification of one or more qMRI measures that surpasses sensitivity of joint space narrowing (JSN), an outmoded biomarker of disease progression and clinical outcome, the current regulatory endpoint
- Assess 12 biochemical markers (serum and urine) and correlate with clinical outcome
 - Biochemical markers can elucidate physiological joint changes more directly than imaging
 - Provide direct measure of drug effect, as pharmacodynamic markers, for confirmation of drug mechanism of action

■ **Sample Cohort:**

- Utilizes NIH OA Initiative (OAI) data set
- Large longitudinal study of 5,000 OA patients
 - use of 200 cases & 400 controls
- Clinical, structural and biochemical patient characteristics for study and preliminary qualification to determine which markers are most helpful to drug development

OA Biomarkers Project: Leveraging Previous Research Efforts

- NIH Osteoarthritis Initiative (OAI) : a multicenter, longitudinal, prospective, observational study of knee OA, with the aim of developing a public domain research resource to facilitate the scientific evaluation of biomarkers for OA, as potential surrogate endpoints for disease onset and progression
 - The OA Biomarkers Project is among the first to utilize the imaging and biospecimen resources of the OAI in a study of long-term structural and clinical outcomes



- The biomarkers being analyzed in the FNIH OA Biomarkers project were selected after a series of meetings by the Osteoarthritis Research Society International (OARSI), the leading professional society in OA, the FDA and key opinion leaders from the private and public sectors
 - OARSI-FDA OA Initiative: critical appraisal on the issues related to clinical development programs for the treatment and prevention of OA; recommendations to the FDA for updating the 1999 OA guidance for drug development

The Osteoarthritis Initiative

University of California, San Francisco (data coordinating center)
Memorial Hospital of Rhode Island, Pawtucket
The Ohio State University, Columbus
University of Maryland School of Medicine, Baltimore
University of Pittsburgh

Private sector sponsors

- GlaxoSmithKline
- Merck Research Laboratories
- Novartis Pharmaceuticals Corporation
- Pfizer, Inc.



NIH Sponsors

- NIAMS
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- NIA
- NCCAM
- ORWH
- NIDCR

OAI Steering Committee

- OAI institutions
- Private sector sponsors
- NIH sponsors
- Liaison from the Food and Drug Administration
- Liaisons from other interested entities

NIH Management

- Project Officer
- Contracting Officer
- Institute Directors
 - NIAMS
 - NIA

Observational Safety and Monitoring Board



OA Biomarkers Project Overview

- A 2.5-year study assessing the change of plain radiographic measures, magnetic resonance imaging (MRI) measures and biochemical markers over 1 and 2 years as predictors of disease progression and clinical outcomes during a 4 year follow-up
 - Launch - February 2012
 - Targeted Completion and Public Data Release – August 2014
- **Principal Investigators:**
 - David J. Hunter, MD, PhD, University of Sydney, Royal North Shore Hospital
 - Virginia Byers Kraus, MD, PhD, Duke University Medical Center
- **Specific Aims:**
 - To examine the relationship between biochemical and imaging biomarkers and their progression and clinical outcomes over 4-years
 - To identify the most responsive marker(s) of OA progression
 - To develop a risk score based on baseline values of several biomarkers that would determine those who progress rapidly to case status

Benefits of OA Project

- Data will be produced qualifying the best candidate imaging/biochemical biomarkers, for immediate use in clinical trials (retrospective analysis or prospective trials).
- Clinical validation and qualification of high potential OA biomarkers is most effective means to drive development of new disease modifying drugs.

Assuming Success:

- Stratify patients who will be progressors (*enrich trials with targeted populations*)
- Facilitates smaller, shorter trials more closely linked to clinical outcome endpoints (*reduced cost, quicker results*)
- Validated biomarkers can be used to assess subjects at earlier stages of disease when therapeutics are presumed to be more effective (*improved treatments*)
- Provide a rich context of structural and biochemical measurements for evaluating other biomarkers in the same sample of OAI subjects (*advance knowledge base*)

OA Biomarkers Project Team

- **Neil Bodick, M.D.**
Flexion Therapeutics
- **Virginia Byers Kraus, M.D., Ph.D. (co-chair)**
Duke University
- **Sahar Dawisha, M.D.**
FDA, Center for Devices and Radiologic Health
- **Klaus Flechsenhar, M.D.**
Sanofi
- **Ali Guermazi, M.D.**
Boston University Medical Center
- **John Hardin, M.D.**
Arthritis Foundation
- **Yves Henrotin, Ph.D.**
University of Liege
- **David Hunter, M.D., Ph.D. (co-chair)**
University of Sydney
- **Joanne Jordan, MD**
UNC
- **Jeff Katz, M.D.**
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- **Kent Kwoh, M.D.**
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- **Christoph Ladel, Ph.D.**
Merck Serono
- **Gayle Lester, Ph.D.**
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- **Linda Sandell, Ph.D.**
Washington University
- **Bill Parrish, Ph.D.**
DePuy Mitek
- **Valorie Thompson, Ph.D.**
OARSI Consultant
- **Wayne Tsuji, Ph.D.**
Amgen
- **Josep Vergés , M.D., Ph.D.**
Bioiberica S.A.
- **Susanne Wang, M.D., Ph.D.**
AbbVie

OA Imaging Biomarkers

- OA Biomarker Project is assessing 15+ OA imaging markers and correlate with clinical outcomes
- Radiographic (x-ray) measures
 - Minimum JSW, JSW (X), FSA, OARSI JSN
- Quantitative MRI measures
 - Changes in cartilage (morphometry), sub-chondral bone, bone shape, bone marrow lesion volume, osteophyte volume
- Semi-quantitative MRI measures
 - Bone marrow lesion (BML) size, synovitis, effusion, meniscus morphology, cartilage morphology and attrition

Radiographic JSN: Current Regulatory Standard

- Radiographic (x-ray) JSN hinders drug development
- JSN is a poorly responsive endpoint requiring clinical trials of 2-4 years duration with 500 – 1,000 subjects to determine effect of therapy
- Poor correlation between radiographic JSN and severity of clinical symptoms
- Identifies patients with more advanced OA who may not be as responsive to pharmacologic intervention

Clinical Outcome Definition: Clinically Meaningful Change

- Case Group will be defined by the combination of x-ray **AND** symptom outcomes each achieved by 48 month follow-up period (not necessarily concurrently)
 - Definition of x-ray medial tibiofemoral (TF) JSW decrease from ~0.7-1 mm but dependent on smallest detectable difference in OAI
 - AND**
 - Pain and function WOMAC* minimum clinically important difference (MCID) definitions from the literature
- Inclusion criteria
 - KLG 1, 2 or 3 at baseline from central reading
 - Subject has knee radiographs at 24 months

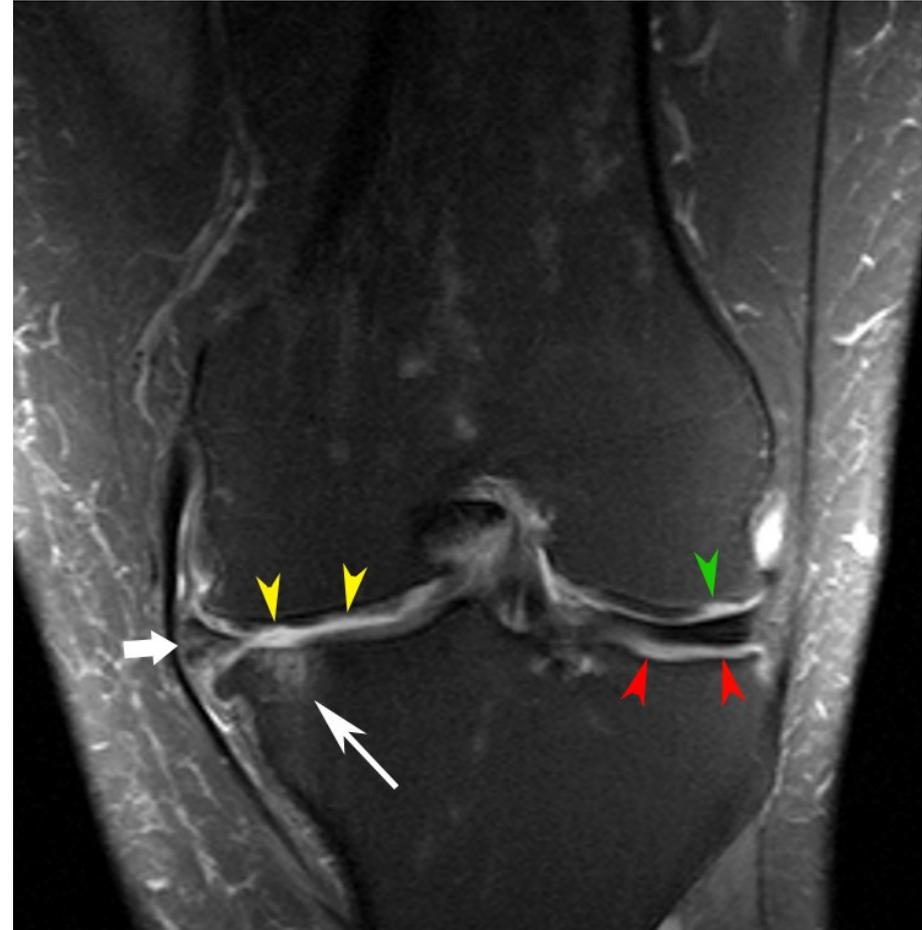
*Western Ontario and McMaster Universities Arthritis Index

Quantitative MRI Allows for Identification of Multiple Tissue Targets for Richer Information on Patient Characterization and Drug Effects

JSN X-ray



Quantitative MRI



Figures provided courtesy of ALi Guermazi, MD, PhD, Boston Imaging Corp Lab

How MRI Biomarkers Will Advance Disease Modifying OA Drug (DMOAD) Development

MRI protocols can detect subtle changes in cartilage, bone, synovium, menisci and other joint structures

- Stronger MRI magnets and more sensitive protocols for cartilage imaging, allows for detection of subtle structural changes
- The OA Biomarkers Project will start to answer whether the imaging progressions seen on MRI are clinically meaningful
 - Initial results presented at OARSI 2013
- Clinical trials using MRI for rheumatoid arthritis, multiple sclerosis, carotid artery disease and Alzheimer's have developed protocols to optimize the consistency of data in multi-center trials

OARSI 2013 Abstract

- **Title: Preliminary Assessment of Predictive Validity of periarticular bone area and shape markers in knee OA**
 - *Poster Presentation: OARSI 2013 (April 18-21, Philadelphia, PA)*
- Abstract focused on initial qMRI image assessments of periarticular bone area and 3D shape markers at 24 months to see if this will predict clinical OA progression in the knee over a 48 month follow-up
- Results: Greater changes in bone area and shape markers over 24 months in knees with mild to moderate radiographic OA predict greater likelihood of progression over 48 months. Analysis shows statistically significant differences in joint space loss (JSL) in cases vs. controls but not for pain cases.

OA Biochemical Markers

- The OA Biomarkers Project is assessing 12 different biochemical markers (and urine creatinine for normalization of urinary markers) and correlate with clinical outcome
 - Biochemical markers can elucidate physiological joint changes more directly than imaging
 - Provide direct measure of drug effect, as pharmacodynamic markers, for confirmation of drug mechanism of action
- Biomarker assays and validation are being performed by LabCorp Clinical Trials, a CLIA-certified laboratory with global expertise in laboratory testing

Panel of 12 OA-Related Biomarkers

Biomarker	Process (preliminary)	BIPEDS Classifications	Surrogacy Based on Human Clinical Trials (preliminary)	ELISA assay type
urinary CTX-II *	type II collagen degradation	Knee: BPED Hip: BPD	characterization: changed significantly in 3 pharmacologic trials that met primary clinical endpoints	competitive-inhibition
serum COMP *	cartilage degeneration	Knee: BPD Hip: BPD	exploration: not used to date in pharmacologic trial	competitive-inhibition and sandwich
serum HA	osteophyte burden, synovitis	Knee: BPED Hip: P	demonstration: changed significantly in one pharmacologic trial that met primary clinical endpoints	sandwich protein binding assay
serum and urine C1,2C *	Types I and II collagen degradation	Knee: D(u) Hip: none	exploration: nonsignificant change in one pharmacologic trial that met primary clinical endpoint	competitive-inhibition
serum and urine C2C *	type II collagen degradation	Knee: E(s), D(u) Hip: B(s)	demonstration: nonsignificant change in one pharmacologic trial that met primary clinical endpoint	competitive-inhibition
serum CPII *	type II collagen degradation	Knee: D(s) Hip: B(s)	exploration: nonsignificant change in one pharmacologic trial that met primary clinical endpoint	competitive-inhibition
Serum PIIANP	Type II collagen synthesis	Knee: BPD Hip: none	exploration: not used to date in pharmacologic trial	competitive-inhibition
urine/serum NTX-I *	bone resorption	Knee: P(u),E(u) Hip: P(s)	demonstration: changed significantly in one pharmacologic trial that met primary clinical (WOMAC) endpoint	competitive-inhibition
Urine and serum CTX-I *	bone resorption	Knee: B(u), D(s/u), P(u) Hip: none	exploration: not used to date in pharmacologic trial	competitive-inhibition
serum CS846 *	cartilage aggrecan synthesis/turnover	Knee: P Hip: none	exploration: nonsignificant change in one pharmacologic trial that met primary clinical endpoint but changed associated with concurrent JSN	competitive-inhibition
serum MMP-3	protease involved with joint tissue degradation	Knee: E Hip: none	characterization: changed significantly in two pharmacologic trials that met primary clinical endpoints	sandwich for total MMP-3 assay
Urine Col-2-1NO2 *	Type II collagen degradation	Knee: P Hip: B	demonstration: nonsignificant change in one pharmacologic trial that met primary clinical endpoint but short-term change predicted long-term progression in 3 trials	competitive-inhibition

Improving DMOAD Development

The OA Biomarker Project will directly provide DMOAD outcome imaging and biochemical biomarkers that are validated to:

- Be more sensitive and informative than JSN, to show that disease progression has been slowed by investigational therapies (e.g. reduced cartilage loss).
- Correlate slowing of disease progression with symptom improvements (patient pain and function/WOMAC).

Important that validated biomarkers can be used to assess subjects at earlier stages of disease when therapeutics are presumed to be more effective.

OA Biomarker Validation

- The conclusion of most experts in the OA drug development field is that the clinical validation and qualification of high potential OA biomarkers is the most effective means to driving breakthroughs that will lead to viable new chemical entities (NCE)

Potential Deliverables

- Qualification of most responsive biomarkers for immediate use in DMOAD clinical trials (either in retrospective analyses or prospective trials)
- Identification of one or more quantitative MRI measures that surpasses sensitivity of JSN measure, an outmoded biomarker of disease progression and clinical outcome, the current regulatory endpoint

Direct Benefits of OA Biomarkers Project

- Stratification of OA subjects who are progressors; will allow for enrichment of clinical trials with identified progressors
- Will facilitate smaller, shorter trials more closely linked to clinical outcome endpoints, thereby dramatically reducing OA clinical trial costs
- Will inform the biological and clinical context of marker performance

Project Timeline and Status (as of April 18, 2013)



Timeline of Study Activities	Year 1 2012				Year 2 2013				Year 3 2014			
Dates	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Launch 2/14/2012	█											
Database development and study protocol development	█	█										
Biochemical marker measurements		█	█	█	█	█	█					
Plain radiographic measures		█	█	█	█	█	█					
Semi-quantitative MRI scoring			█	█	█	█	█					
Quantitative MRI measures			█	█	█	█	█					
Data collection, QC/QA activities, data integration	█	█	█	█	█	█	█	█	█	█	█	
Data cleaning and statistical analyses, presentation of findings, manuscript preparation												

>50% imaging and 25% of serum/urine testing **completed**

Key Milestones:

- **Launch February 14, 2012**
- **6 months post-launch (August 2012)** – Complete recruitment of team, set up database infrastructure and mechanisms of data access established, study population defined. **COMPLETED**
- **8 months post-launch (Oct 2012)** – Biospecimens distributed to biochemical marker laboratory and imaging sent to respective selected imaging vendors. **COMPLETED**
- **18-24 months post-launch (August 2013)** – Completed analysis of imaging endpoints and biochemical marker assays. Raw data sent to UCSF/OAI coordinating center.
- **30 days upon Project Team approval of data analyses** - All data available to scientific researchers via OAI data website; publication of main aims submitted.
- **30 months post-launch (August 2014)** - Preparation and submission of manuscripts

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- The OAI is a public-private partnership comprised of five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the National Institutes of Health. Funding partners include Merck Research Laboratories; Novartis Pharmaceuticals Corporation, GlaxoSmithKline; and Pfizer, Inc.
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