

# **The National Institute of Arthritis and Musculoskeletal and Skin Diseases**

**Reducing Chronic, Common, and Costly Conditions  
through Research**

**Stephen I. Katz, M.D., Ph.D.**

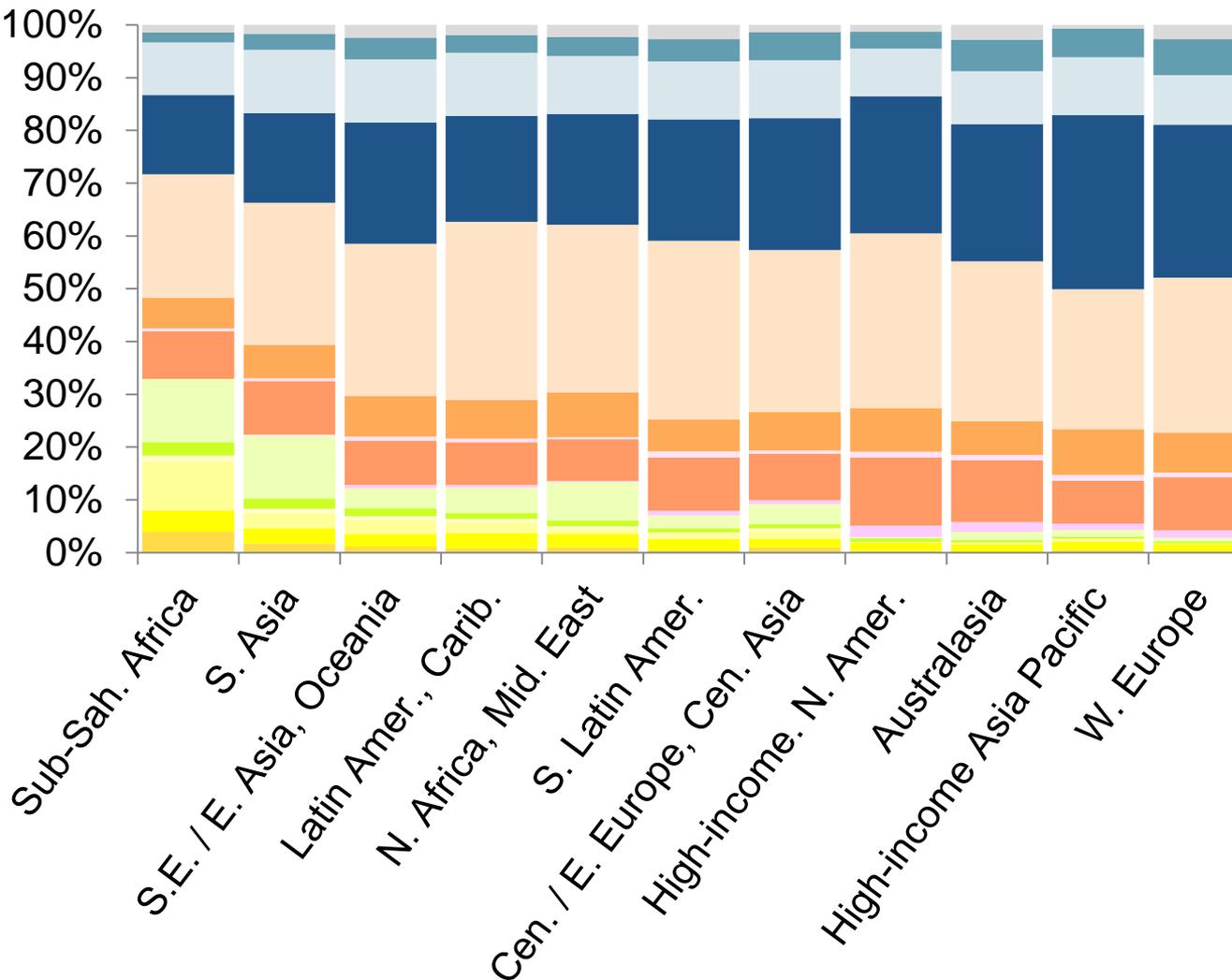
**Director, National Institute of Arthritis and  
Musculoskeletal and Skin Diseases**



National Institute of  
Arthritis and Musculoskeletal  
and Skin Diseases

# Musculoskeletal and Skin Disorders— Leading Causes of Disability

% YLDs (Years Lived with Disability)



**National Institute  
of Arthritis and  
Musculoskeletal and  
Skin Diseases**

**National Institute of  
Diabetes and Digestive  
and Kidney Diseases**

**National  
Institute on Aging**

**National Heart, Lung,  
and Blood Institute**

**National Center  
for Advancing  
Translational  
Sciences**

**National Institute  
of Allergy and  
Infectious Diseases**

**National  
Cancer Institute**

**National  
Library  
of Medicine**

**John E.  
Fogarty  
International  
Center**

**National Institute  
of Child Health and  
Human Development**

**The 27  
Institutes  
and  
Centers  
of the  
NIH**

**National Institute of  
Biomedical Imaging  
and Bioengineering**

**National  
Human Genome  
Research Institute**

**National Center  
for Complementary  
and Alternative  
Medicine**

**National Institute of  
Neurological Disorders  
and Stroke**

**National Institute of  
Nursing Research**

**Center for  
Scientific  
Review**

**National Institute  
on Minority Health  
and Health  
Disparities**

**National  
Eye Institute**

**National Institute  
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**National Institute of  
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**Clinical  
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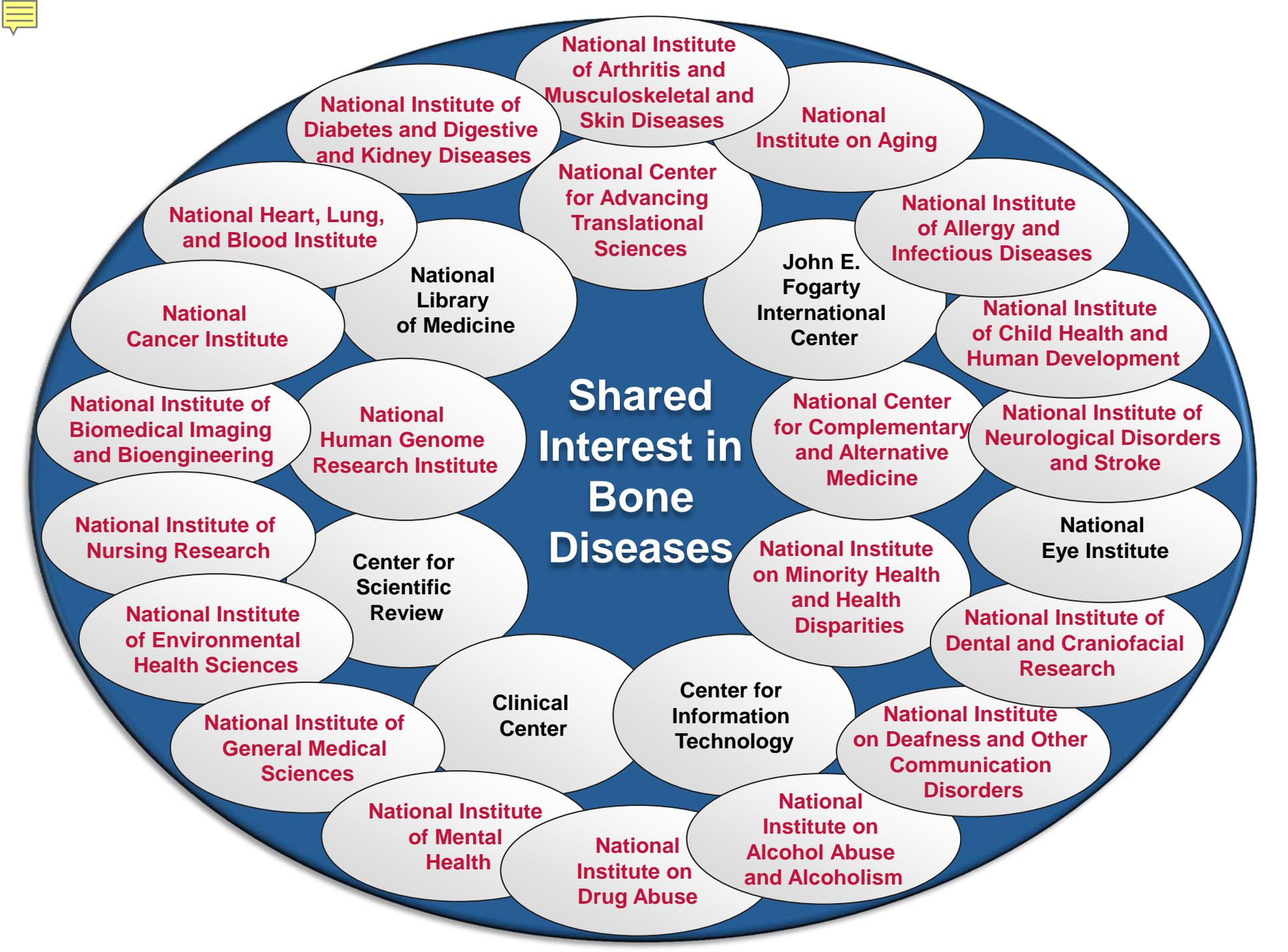
**Center for  
Information  
Technology**

**National Institute  
on Deafness and Other  
Communication  
Disorders**

**National Institute  
of Mental  
Health**

**National  
Institute on  
Drug Abuse**

**National  
Institute on  
Alcohol Abuse  
and Alcoholism**



**Shared  
Interest in  
Bone  
Diseases**

National Institute  
of Arthritis and  
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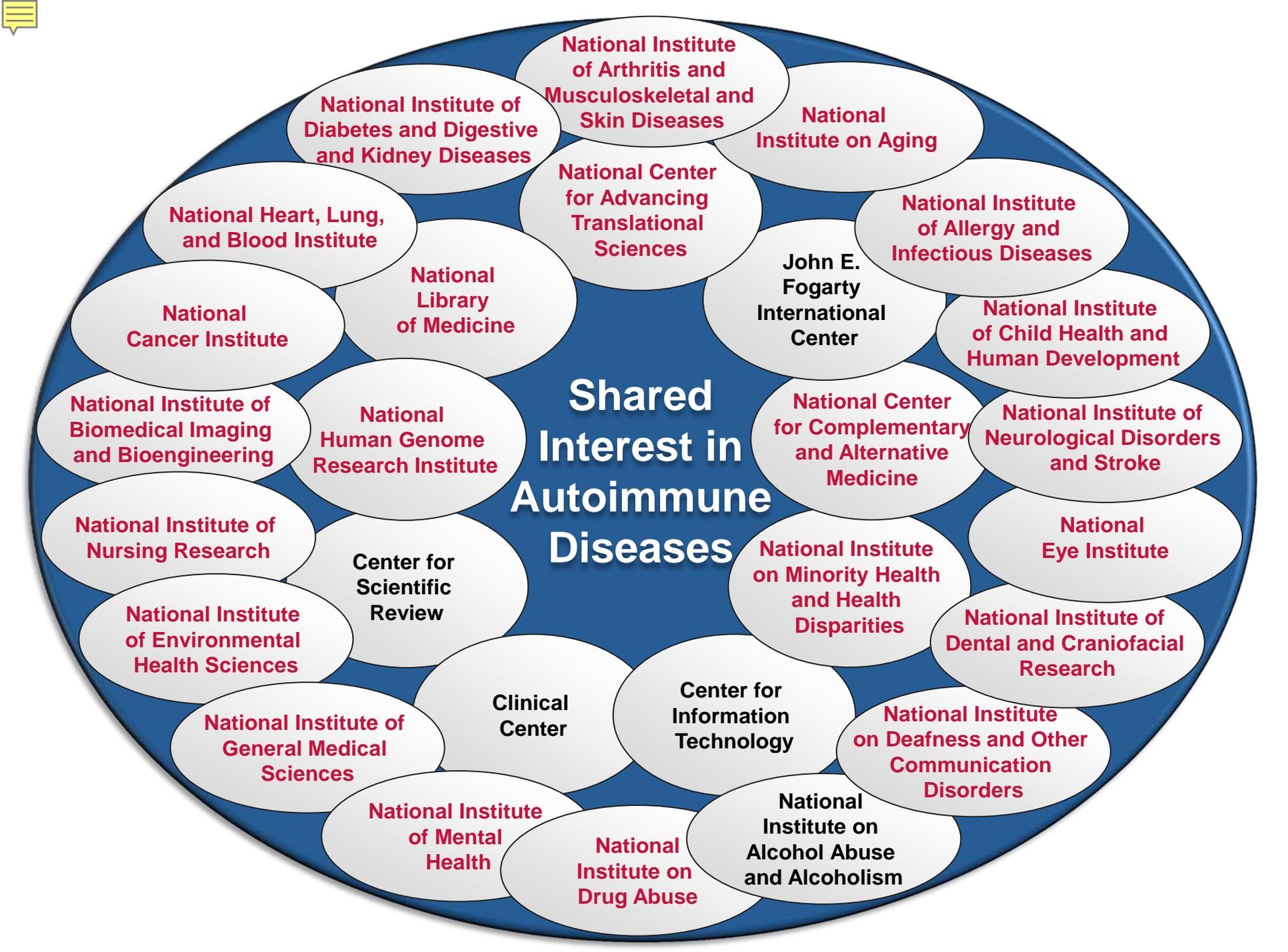
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and Alcoholism



# Shared Interest in Autoimmune Diseases

National Institute of Arthritis and Musculoskeletal and Skin Diseases

National Institute on Aging

National Institute of Diabetes and Digestive and Kidney Diseases

National Center for Advancing Translational Sciences

National Institute of Allergy and Infectious Diseases

National Heart, Lung, and Blood Institute

John E. Fogarty International Center

National Library of Medicine

National Institute of Child Health and Human Development

National Cancer Institute

National Center for Complementary and Alternative Medicine

National Human Genome Research Institute

National Institute of Neurological Disorders and Stroke

National Institute of Biomedical Imaging and Bioengineering

National Institute on Minority Health and Health Disparities

Center for Scientific Review

National Eye Institute

National Institute of Nursing Research

National Institute of Dental and Craniofacial Research

National Institute of Environmental Health Sciences

Center for Information Technology

Clinical Center

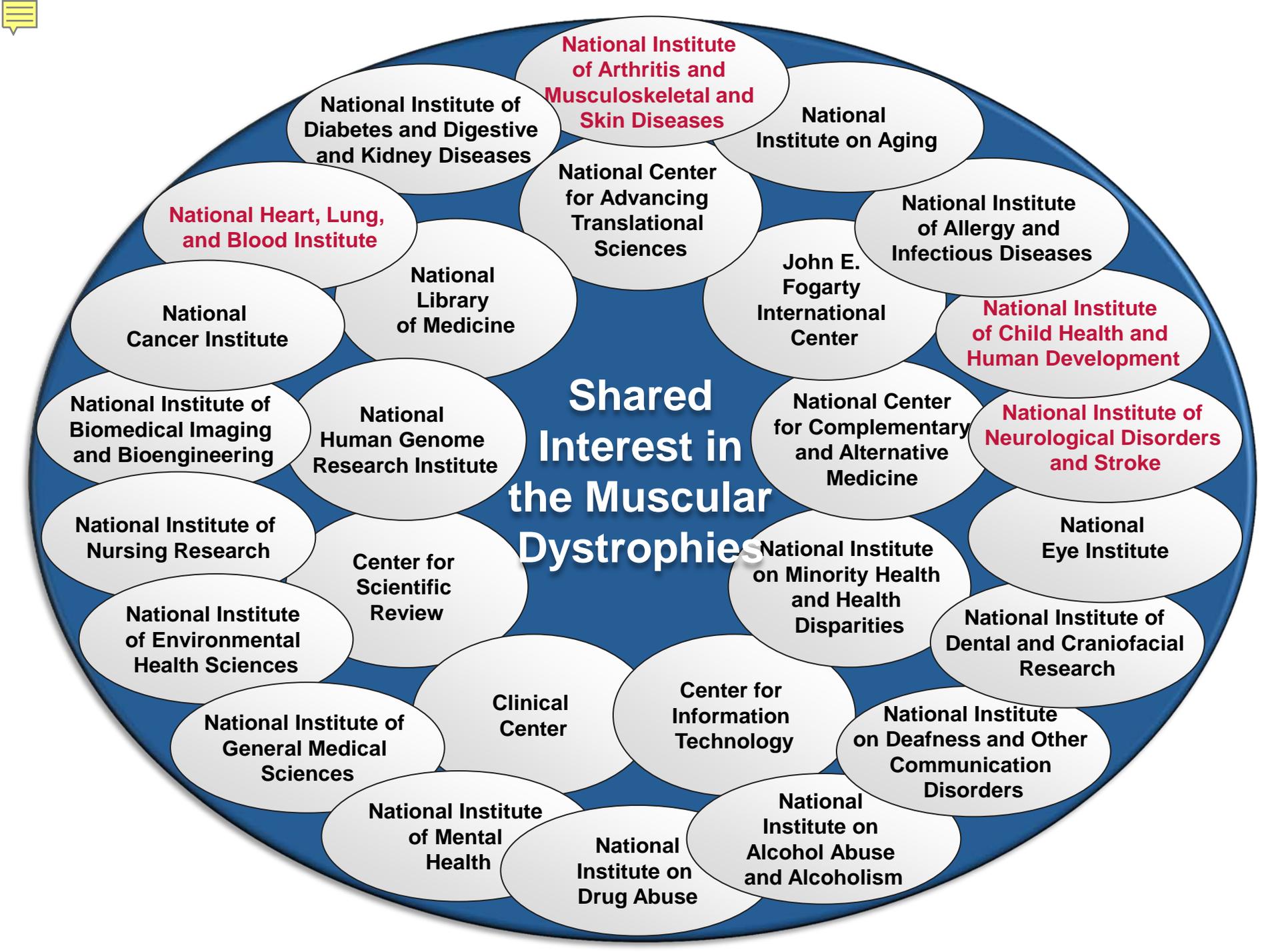
National Institute on Deafness and Other Communication Disorders

National Institute of General Medical Sciences

National Institute on Alcohol Abuse and Alcoholism

National Institute of Mental Health

National Institute on Drug Abuse



**Shared  
Interest in  
the Muscular  
Dystrophies**

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Musculoskeletal and  
Skin Diseases**

**National  
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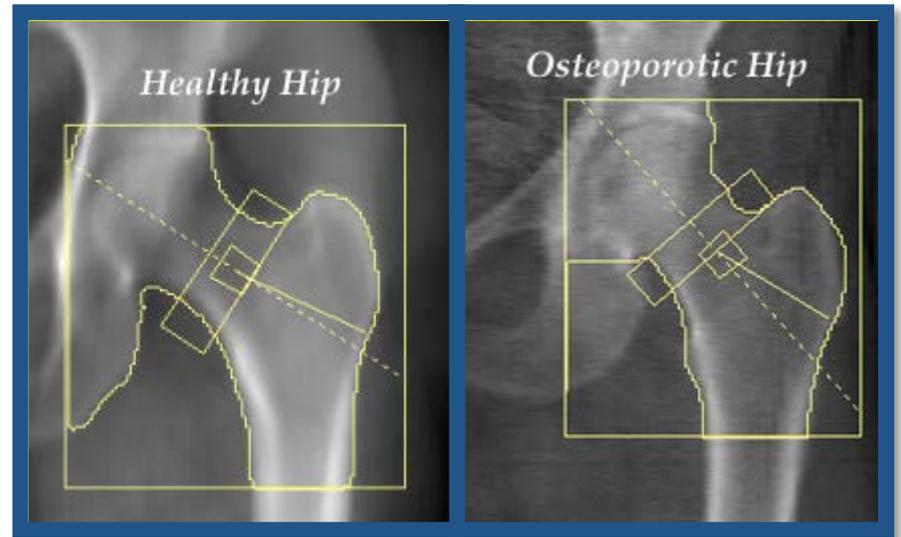
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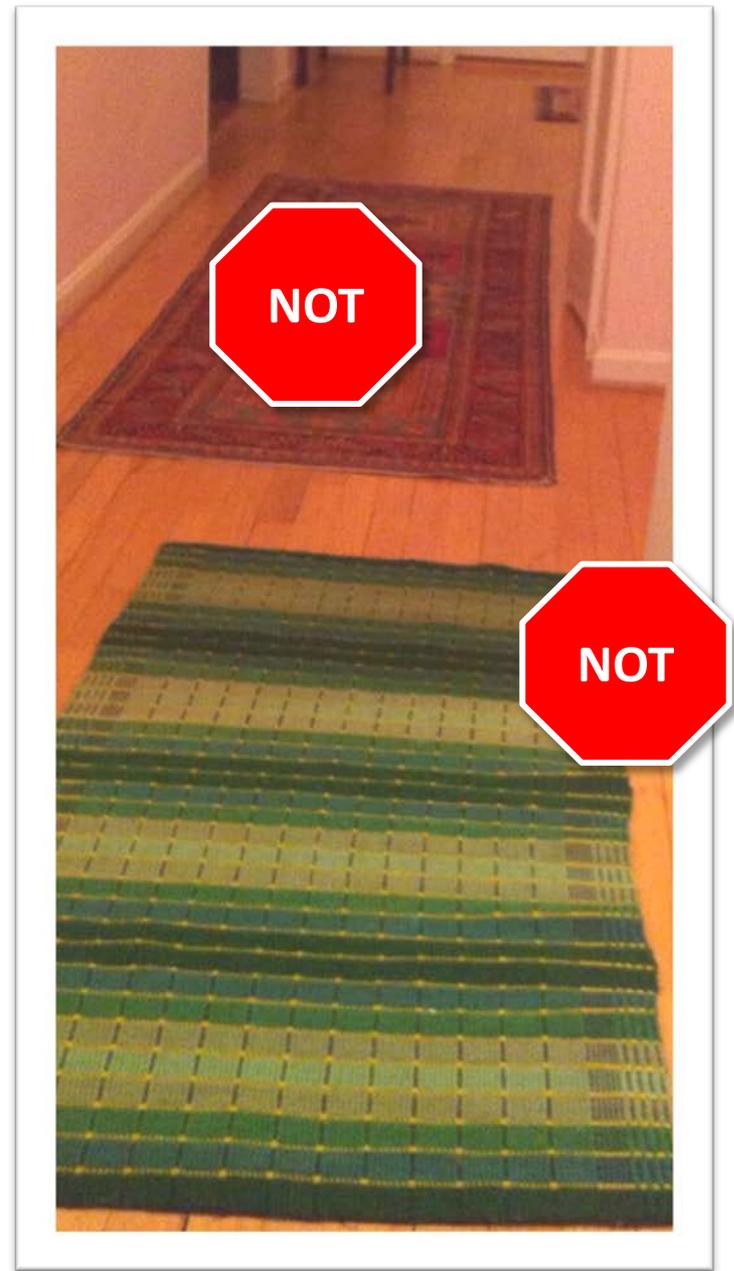
# Overview

- **Trans-NIH efforts**
- **Multi-center clinical studies**
- **Basic and translational research**

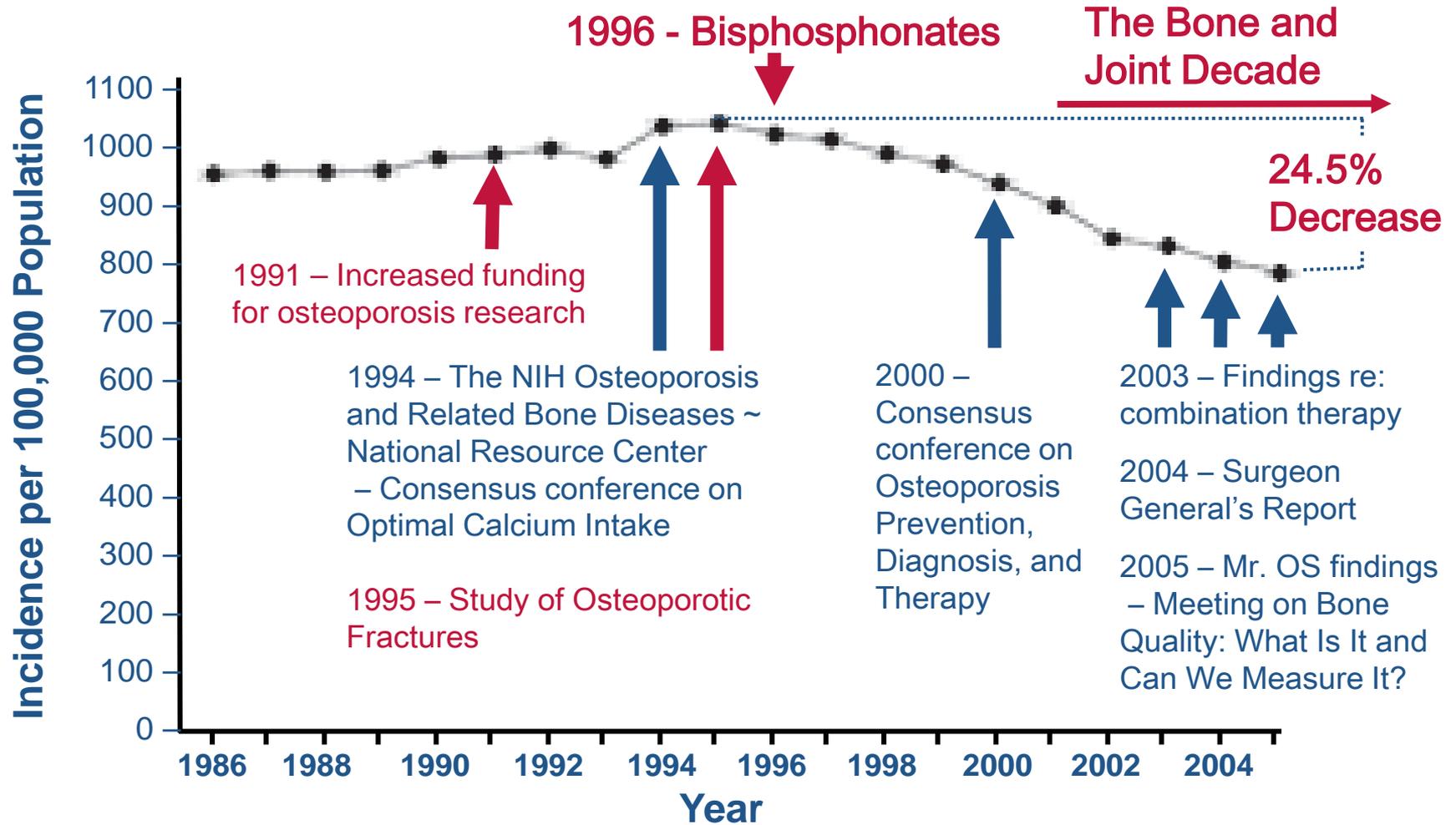
# Study of Osteoporosis (SOF) and Mr. OS

- **Bone mineral density of the hip**
  - One of the best predictors of fracture
- **Factors influencing bone mineral density**
  - Diet
  - Body weight
  - Family history
  - Physical activity
  - Smoking
  - Medications
- **Other factors influencing fracture development**
  - Visual acuity
  - Medications
  - Clutter





# Hip Fractures Among Women Aged $\geq 65$ Years, United States





# Foundation for NIH (FNIH) Biomarkers Consortium Bone Quality Project

- **Advance the qualification of biomarkers for drug development and patient management**
  - **Qualify imaging and biochemical markers from clinical trials**
- **Goal**
  - **Improve ability to predict fracture**
- **Project team**
  - **NIH**
  - **U.S. Food and Drug Administration**
  - **Academic researchers**
  - **Pharmaceutical industry (Amgen, Eli Lilly, Merck)**
  - **American Society for Bone and Mineral Research**
  - **The Dairy Research Institute<sup>®</sup>**

# Osteoarthritis (OA)

- Degenerative joint disease resulting in breakdown of cartilage and loss of joint function
- Often develops in weight-bearing joints
  - Injury can trigger OA development
- Most common type of arthritis
  - Affects an estimated 27 million adults in the United States





# The Osteoarthritis Initiative



## *A Research Resource for Biomarker Validation*

- **Need**
  - Objective and measurable standards for osteoarthritis (OA) onset and progression by which new drugs can be evaluated
- **Goal**
  - Create research resources to aid in identification and evaluation of biomarkers as candidates for surrogate endpoints for OA
- **Mechanism**
  - Develop a prospective, natural history cohort
    - ~ 5,000 people, most of whom have or are at high risk of developing OA
    - ~ 20% minority enrollment

# The Osteoarthritis Initiative Consortium

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.

Foundation for the  
National Institutes  
of Health

## NIH Sponsors

- NIAMS
- NIBIB
- NIMHD
- 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

\* GlaxoSmithKline, Merck Research Laboratories, and NIDCR participated between 2001 and 2009 only.

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# Recent Findings from OAI Data

- **Results published**
  - 158 OAI-based publications as of September 2013
- **Analytic methods developed**
  - Facilitate longitudinal comparison of images
- **Predictive markers identified**

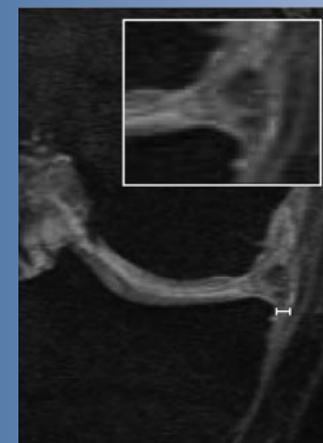
MRI markers  
predictive of  
symptomatic OA



Cartilage defect



Bone marrow lesions



Meniscal extrusion



# Ongoing Efforts



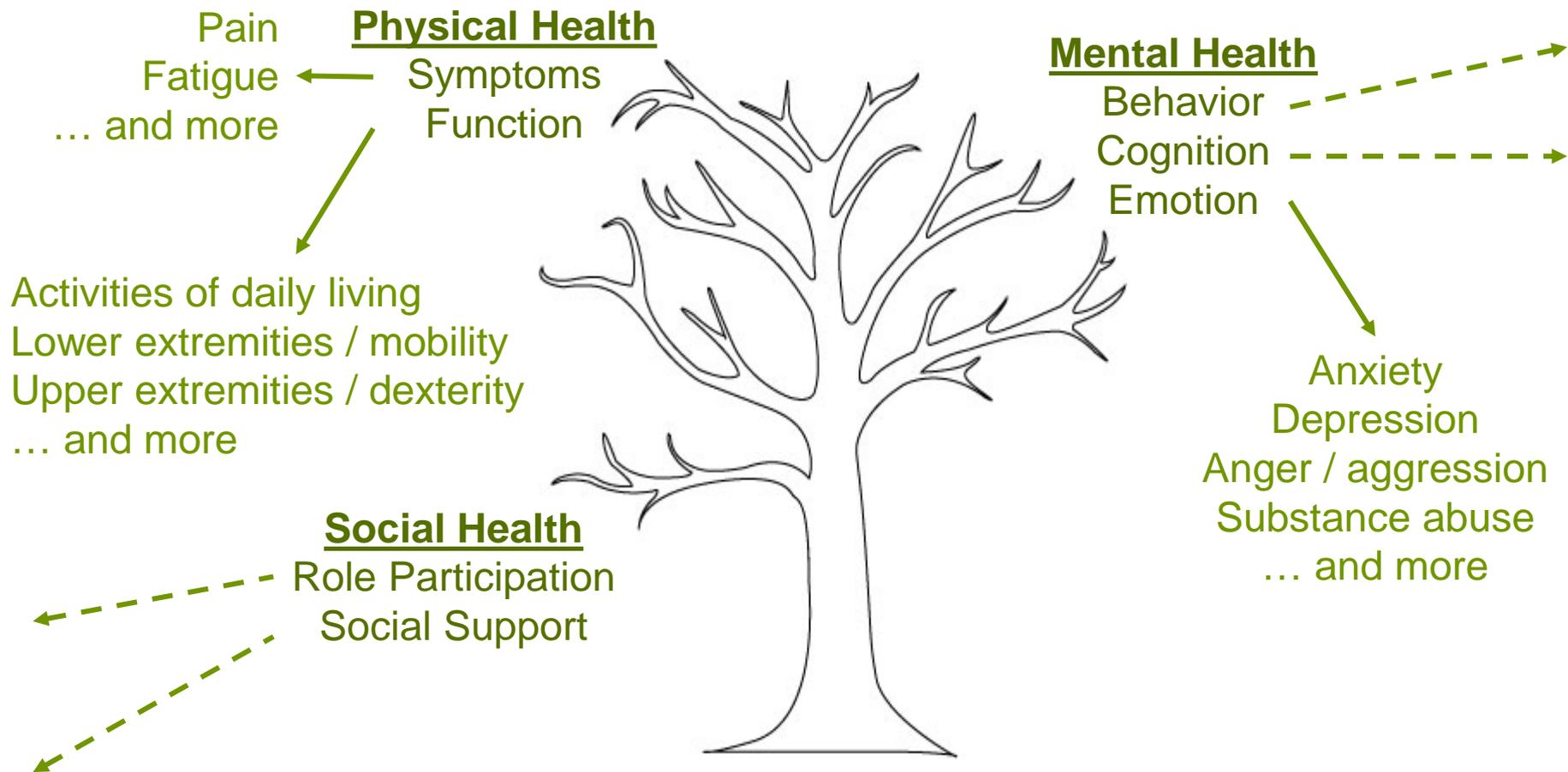
- **FNIH Biomarkers Consortium**
  - **Goal: Discover imaging and biochemical biomarkers of OA progression**
- **NIAMS-funded contracts focused on OAI data / image analysis**
  - **Pivotal Osteoarthritis Initiative Magnetic Resonance Imaging Analyses**
  - **Hip Morphology and Limb Specific Risk Factors for Radiographic Hip OA**
  - **Efficacy of Complementary Alternative Medical Treatments for OA of the Knee on Patient-Centered Outcomes**
- **Basis for investigator-initiated research projects**



- **Patient Reported Outcomes Measurement Information System (PROMIS)**
  - Large item bank measuring patient-reported outcomes
  - Computerized adaptive testing system
  - Relevant to a wide range of chronic diseases
  
- **NIH Common Fund Initiative**
  - Begun in 2004
  - Transitioning to institute support



## ***PROMIS Self-Reported Health Domains*** (Patient Response)





## ***PROMIS Resources***

### **Informatics**

Assessment Center

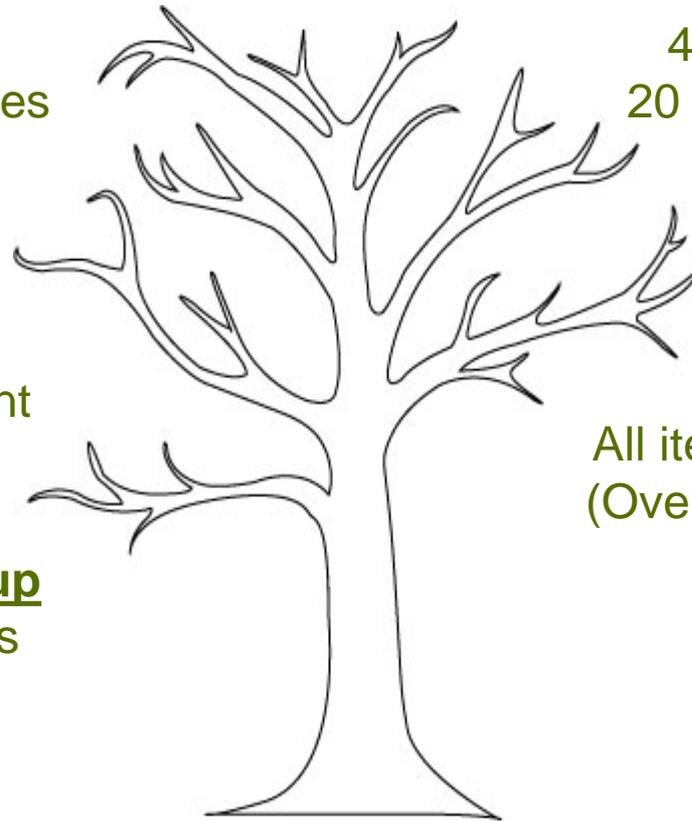
Supports >600 active studies  
in past year alone

### **Advancing Knowledge**

>240 Peer-Reviewed  
publications in 116 different  
journals

### **Cooperative Group**

12 Research Sites  
3 Centers  
150+ Scientists



### **Tools**

40 Adult Measures  
20 Pediatric Measures

### **Translations**

All item banks → Spanish  
(Over 40 other languages)

**NIH funding** (>\$100M)

Numerous RFAs and supplements since 2004 to support Center & Sites



## *Engaging Federal Partners*

- **Food and Drug Administration / Interagency Clinical Outcomes Assessment Working Group**
  - Moving PROMIS into the FDA qualification process and assessing whether it may substitute for the SF-36
- **Centers for Medicare and Medicaid / Centers for Clinical Standards and Quality**
  - Discussing PROMIS instruments as quality performance measures
- **Patient Centered Outcomes Research Institute (PCORI) / NIH-PCORI Task Force**
  - Involved in PCORI's Patient-reported Outcomes (PRO) Infrastructure Workshop (November 2013)
- **Department of Defense (DoD)**
  - Working with PROMIS to implement Pain Assessment Screening Tool and Outcomes Registry (PASTOR)

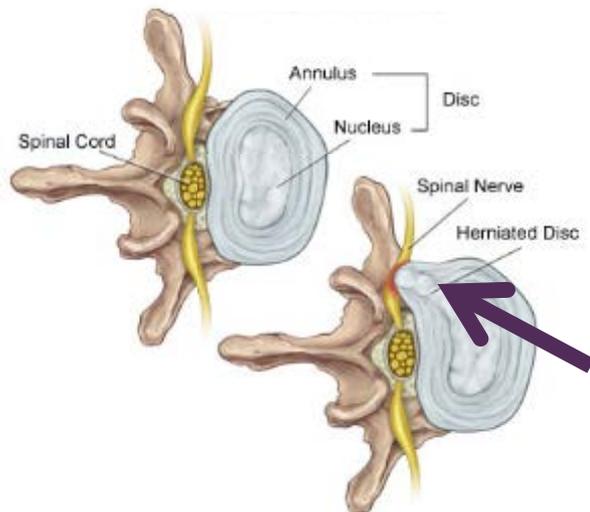
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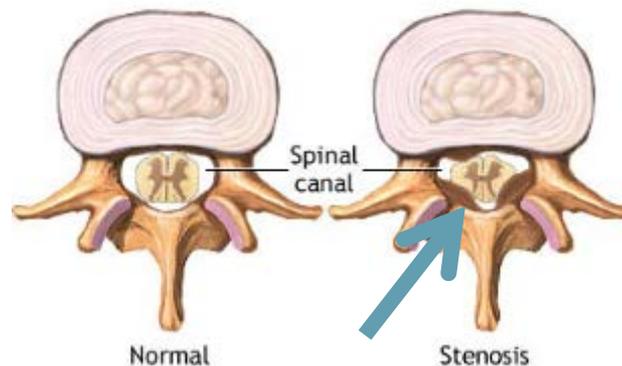
# Spine Patient Outcomes Research Trial (SPORT)

- **Begun in 1999**
  - Is surgery better than non-operative treatments such as physical therapy and medication?
  - Does conservative treatment that delayed surgery harm patients?
- **Three common causes of surgery for low back pain**

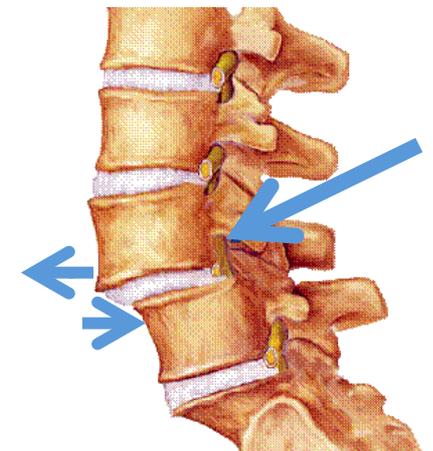
**Intervertebral disc herniation**



**Degenerative spondylolisthesis**



**Spinal stenosis**



# SPORT: Robust Cohorts Leading to Many Publications

Condition	# of Participants		Key Publications (years of follow-up, cohort)
	RCT	Obs.	
Intervertebral disc herniation	501	743	<ul style="list-style-type: none"><li>• Weinstein et al, <i>JAMA</i> 2006 (2-yr, randomized trial)</li><li>• Weinstein et al, <i>JAMA</i> 2006 (2-yr, observational study)</li><li>• Weinstein et al, <i>Spine</i> 2008 (4-yr)</li><li>• Lurie et al, <i>Spine</i> 2013 (8-yr)</li></ul>
Spinal stenosis	289	365	<ul style="list-style-type: none"><li>• Weinstein et al, <i>N Engl J Med</i> 2008 (2-yr)</li><li>• Weinstein et al, <i>Spine</i> 2010 (4-yr)</li></ul>
Degenerative spondylolisthesis	304	303	<ul style="list-style-type: none"><li>• Weinstein et al, <i>N Engl J Med</i> 2007 (2-yr)</li><li>• Weinstein et al, <i>JBJS</i> 2009 (4-yr)</li></ul>



# SPORT Results for All Groups

- **At 2 and 4 years, surgical patients had better function and were more satisfied with their progress than those who did not have surgery**
  - **Similar results observed 8-years post treatment for intervertebral disc herniation**
  - **8-year data will be available soon for spinal stenosis and degenerative spondylolistheses**
- **Surgery remains an option for patients with worsening symptoms or who did not improve with conservative treatment**
  - **People are not subjecting themselves to further harm if they adopt a “wait-and-see” approach before committing to surgery**



# SPORT Back Pain Treatment Calculator Guides Decisions

- **Rich database led to treatment calculator showing possible patient results after surgical or non-surgical treatment for low back pain**
  - **Website: <http://caligari.dartmouth.edu/SpinalOutcomes/>**
  - **Answer questions about**
    - **Diagnosis**
    - **Activity level**
    - **Overall health**
    - **Age and sex**
    - **Pain**
- **Next step: Refine calculator to include**
  - **Individual patient characteristics**
  - **longer-term outcomes data from SPORT**
  - **Information about complications following surgery or the need to have a second procedure**
  - **Results from other related studies**



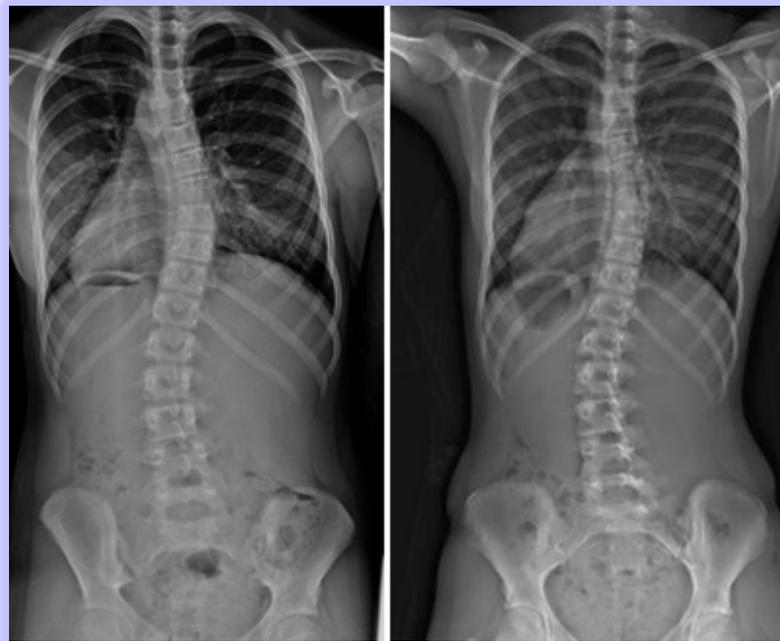
# Bracing in Adolescent Idiopathic Scoliosis Trial (BrAIST)

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**r**  
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**I**  
**S**  
**T**

- **Scoliosis**
  - Curvature of the spine
  - More common in girls than in boys
  - Treatments: waiting, bracing, surgery
- **Multi-center clinical trial**
  - Led by Dr. Stuart Weinstein at University of Iowa
  - Begun in 2006
  - 383 patients (155 randomized cohort, 228 observation cohort)
- **Monitoring patients who have mild curves in the spine**
  - Do curves get worse?
  - Do braces help?

# Bracing Significantly Reduces Risk of Curve Progression and Need for Surgery

Weinstein et al, *N Engl J Med* 2013



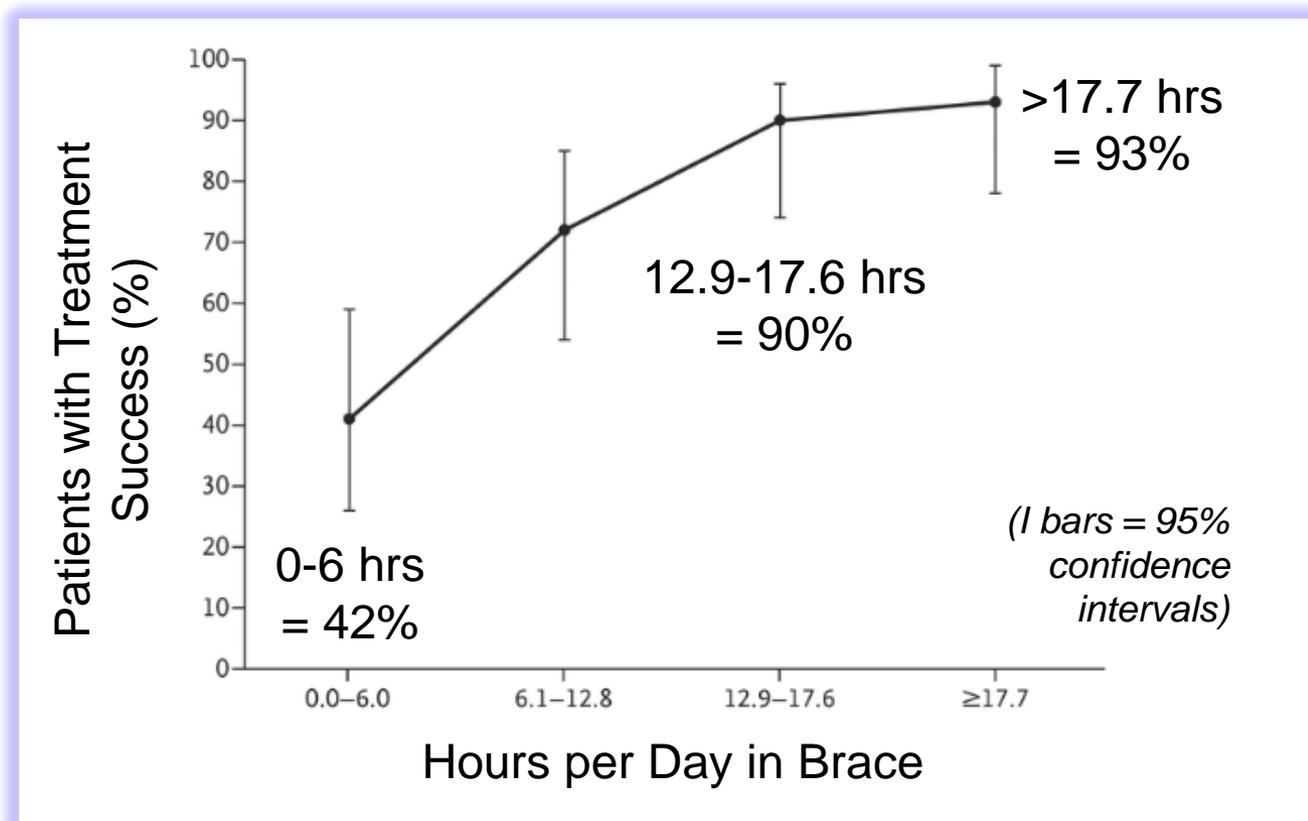
Before and after bracing x-rays of a girl with adolescent idiopathic scoliosis.

*Images courtesy of Lori Dolan, University of Iowa / BrAIST database*

BrAIST

# More Hours of Brace Wear Associated with Higher Success Rates

Weinstein et al, *N Engl J Med* 2013



**Successful treatment** = reaching skeletal maturity without a curve progressing to 50 degrees (the point at which surgery is recommended)

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- **Childhood Arthritis and Rheumatology Research Alliance (CARRA)**
  - Self-actuated network
  - More than 390 pediatric rheumatologists and researchers
  - Over 92 institutions in North America
- **CARRA Registry**
  - More than 9250 patients
  - Basis for more than 30 research projects
    - Standards of care for juvenile dermatomyositis
    - Early, aggressive therapy for juvenile idiopathic arthritis
    - Trial of rilonacept for systemic juvenile idiopathic arthritis
    - Atherosclerosis prevention in pediatric lupus erythematosus

# Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE)



A collaborative effort between NIAMS and the Childhood Arthritis and Rheumatology Research Alliance (CARRA) to study the effects of a common cholesterol drug (atorvastatin) against artery fat buildup in children with lupus



# APPLE Conclusions



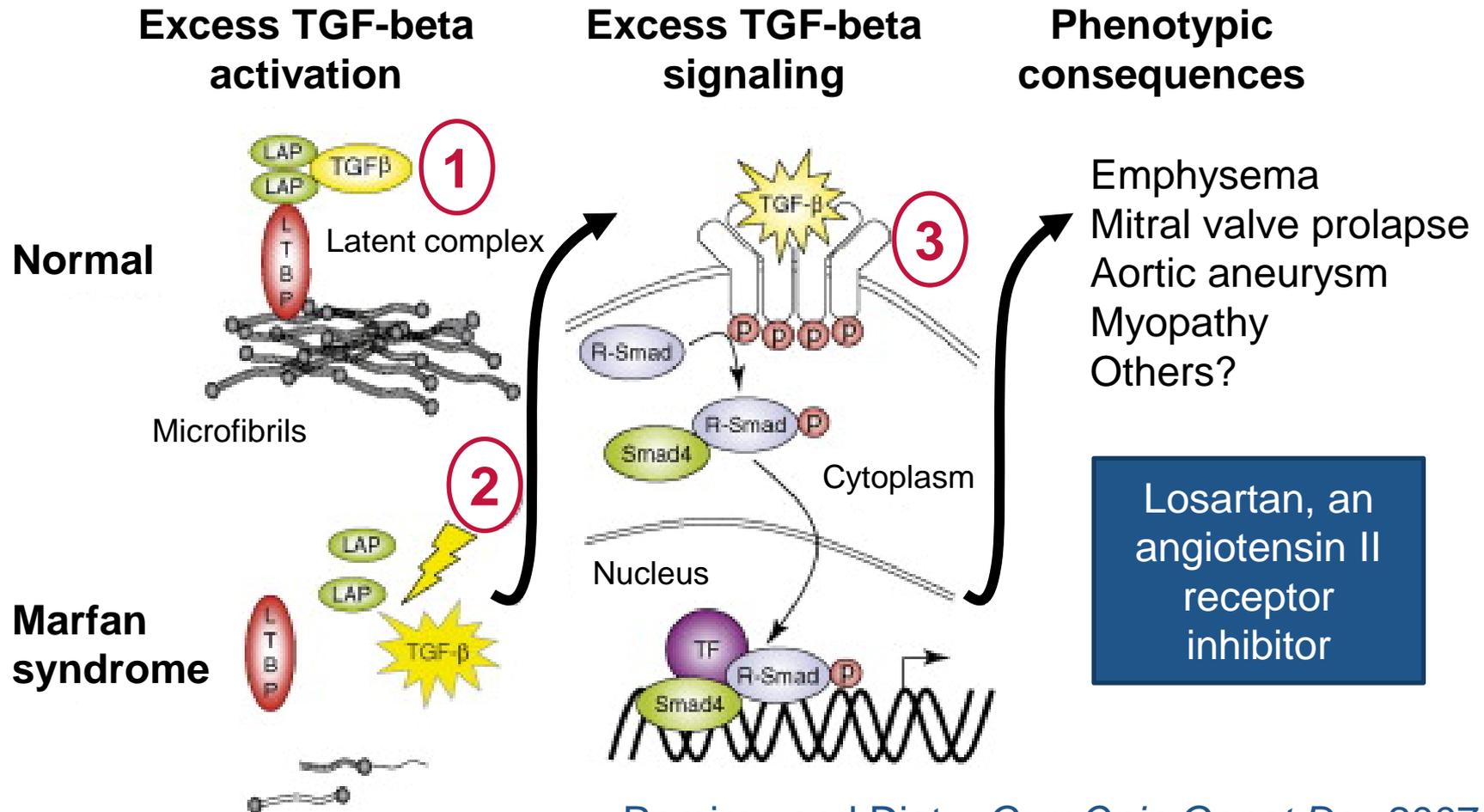
- **Preclinical atherosclerosis starts in children and adolescents with systemic lupus erythematosus**
- **Statins should not be routinely prescribed to children with lupus**
  - **Finding will spare children the cost and potential side effects of a drug that is not proven to be beneficial**
  - **Low dose, intermediate duration statin therapy was safe in this population**
  - **Statins may benefit patient subgroups with severe disease**
- **A well-functioning network can successfully complete a complex trial in a rare pediatric disease**

# Overview

- Trans-NIH efforts
- Multi-center clinical studies
- **Basic and translational research**

# Proposed Mechanism of Marfan Syndrome

Consortium for Translational Research in Marfan Syndrome P01 AR049698 (FY '02-14)





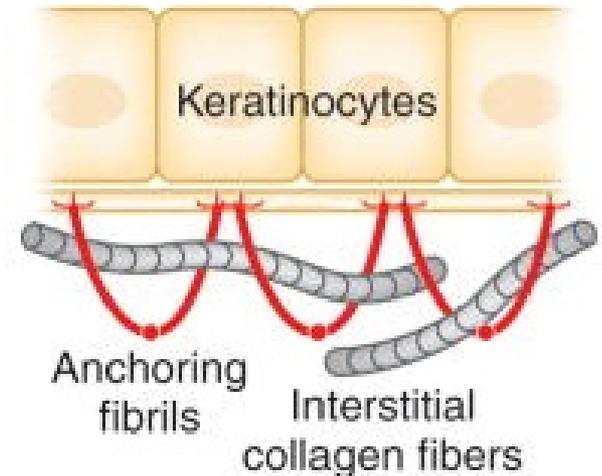
## Gene Transfer for Recessive Dystrophic Epidermolysis Bullosa

- **Recessive dystrophic epidermolysis bullosa (RDEB)**
  - Severe inherited blistering skin disease caused by absence of a protein known as type VII collagen
  - Patients develop large, severely painful blisters and open wounds from minor trauma to their skin
  - Patients often die in late-teens or early-20s from metastatic skin cancer originating in chronically scarred skin
- **Gene Transfer for RDEB**
  - Phase I clinical trial
  - Create a graft from the patient's own skin cells that have been genetically engineered to express this missing protein

# Lack of Type VII Collagen Changes Skin Structure

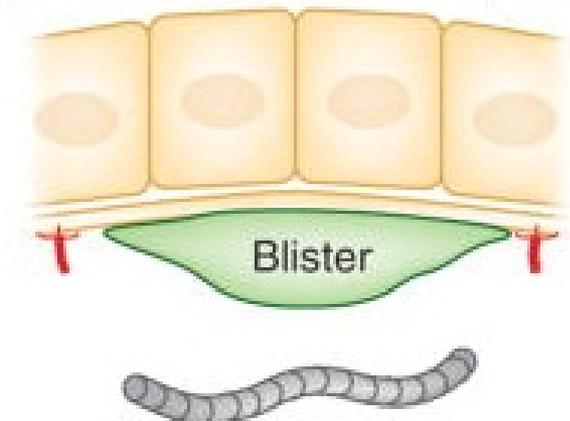
- **Normal skin**

- Keratinocytes synthesize type VII collagen molecules (red), which assemble into anchoring fibrils
- Fibrils entrap the interstitial collagen fibers in the dermis, securing the stable association at the dermal-epidermal junction



- **RDEB**

- There are only a few rudimentary anchoring fibrils, allowing formation of blisters below the lamina densa as a result of minor trauma



## Gene Transfer for Recessive Dystrophic Epidermolysis Bullosa

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## Gene Transfer for Recessive Dystrophic Epidermolysis Bullosa

### Preliminary Results



OR Post-Prep



OR Post-Graft

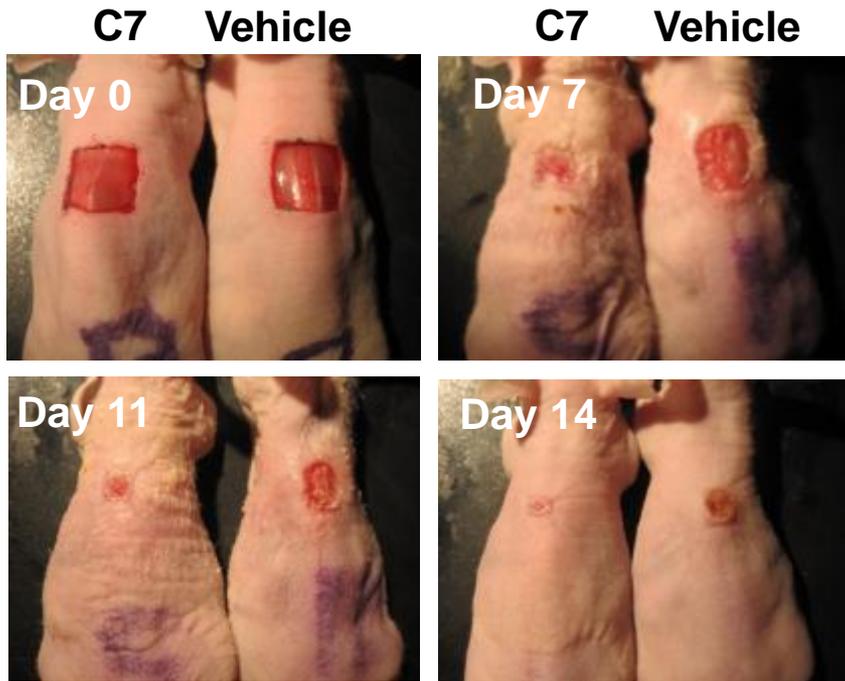


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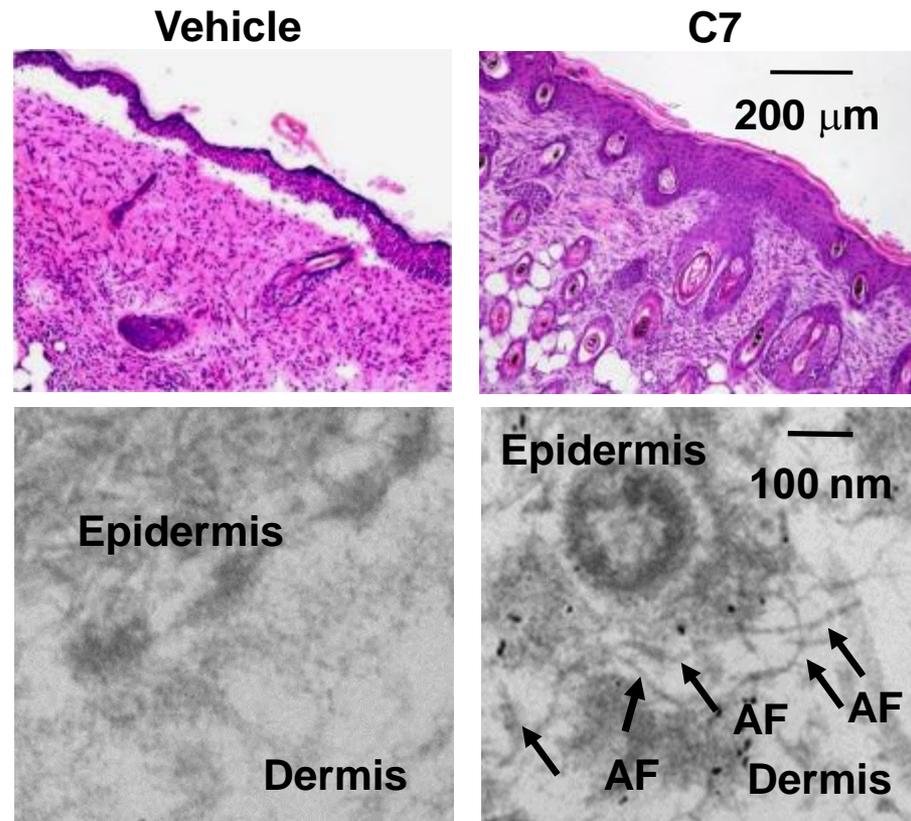


# Recombinant Type VII Collagen (rC7) on Normal and RDEB Mouse Skin

## Topical rC7 Accelerates Wound Closure on Normal Mouse Skin



## Topical rC7 Forms Anchoring Fibrils (AF) in RDEB Mouse Skin

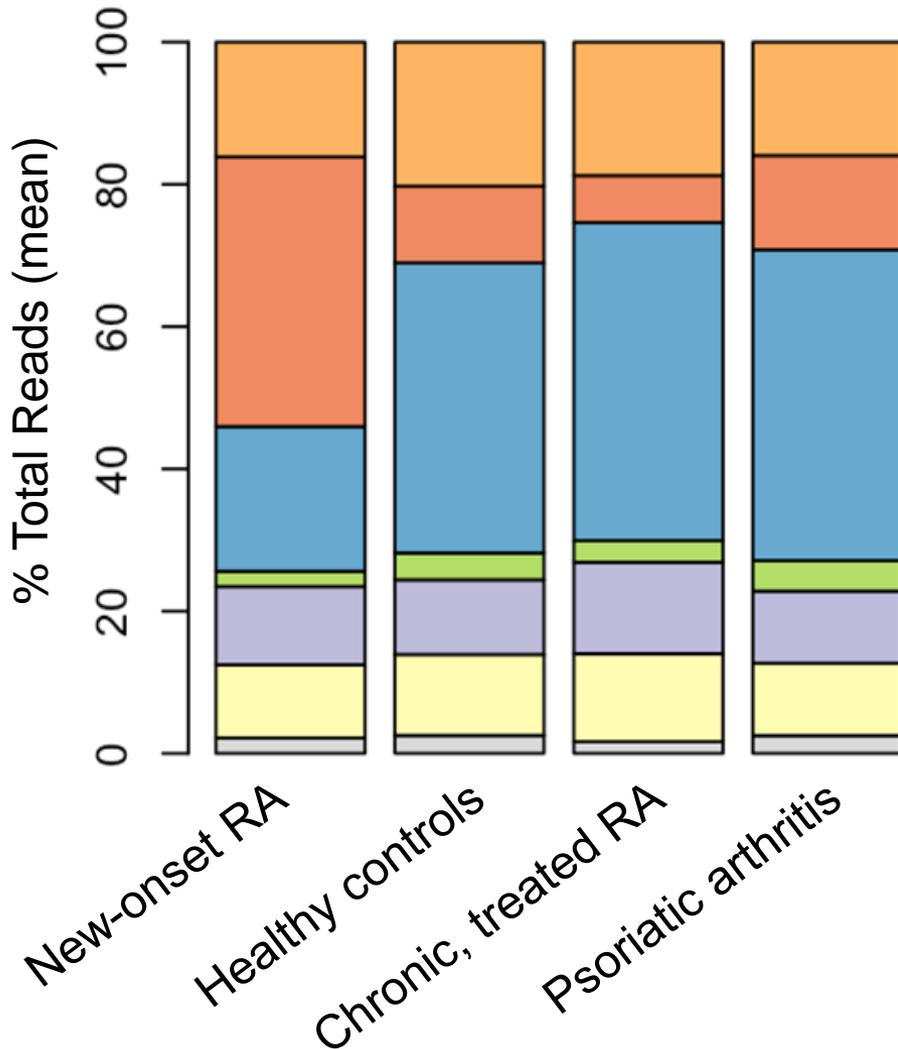


# Rheumatoid Arthritis (RA)

- Causes pain, swelling, stiffness, and loss of joint function
- Occurs when the immune system attacks the synovial membrane that lines the joint
  - Inflamed synovium invades and destroys cartilage and bone within a joint
  - Muscles, ligaments, and tendons that stabilize the joint weaken
- Affects approximately 1.5 million adults in the United States



# Gut Microbiome Implicated in RA



## Relative abundance of gut microbiota changes with RA onset.

People who have new-onset RA have a significant increase in *Prevotellaceae* (red) and a concomitant decrease in *Bacteroidaceae* (blue).

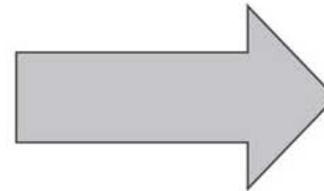
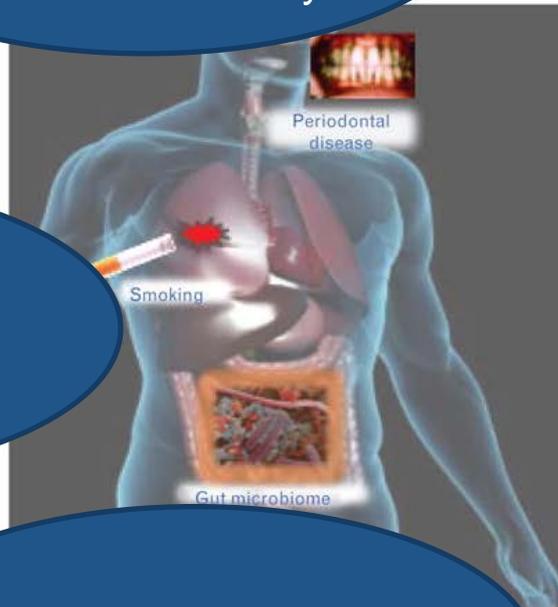
- Veillonellaceae
- Lachnospiraceae
- Ruminococcaceae
- Porphyromonadaceae
- Bacteroidaceae
- Prevotellaceae
- Other

# Microbiome and Mucosal Inflammation as Extra-Articular Triggers for RA

- Periodontitis
- *P. gingivalis*
- Peptidyl arginine deiminase activity

- Smoking
- Lung disease
- Peptidyl arginine deiminase activity

- Gut microbiome
- Antibiotics



**Rheumatoid arthritis**

# Autoinflammatory Diseases

## The Expanding Spectrum

### IL-1 $\beta$ activation disorders



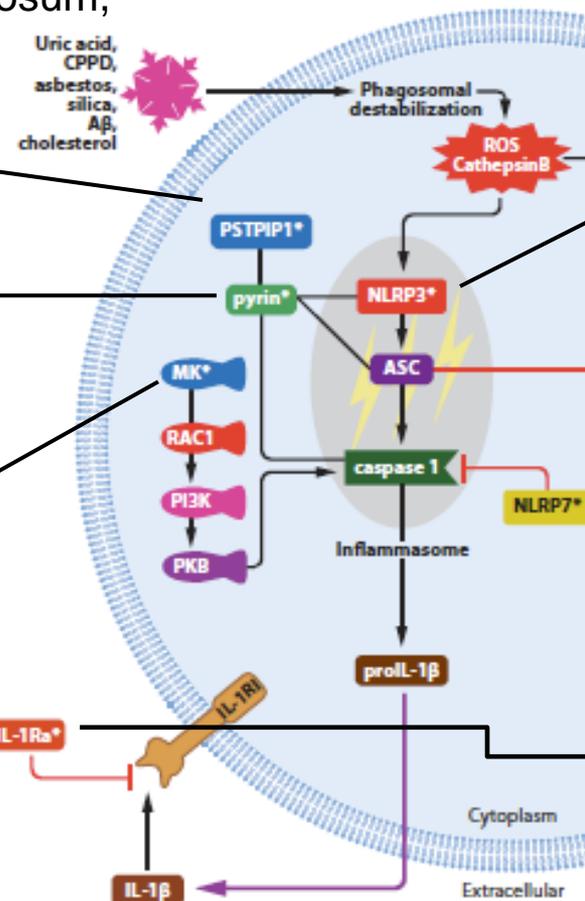
Pyogenic arthritis,  
pyoderma gangrenosum,  
and acne (PAPA)



Familial  
Mediterranean  
fever (FMF)



Hyperimmuno-  
globulinemia D with  
periodic fever  
syndrome (HIDS)



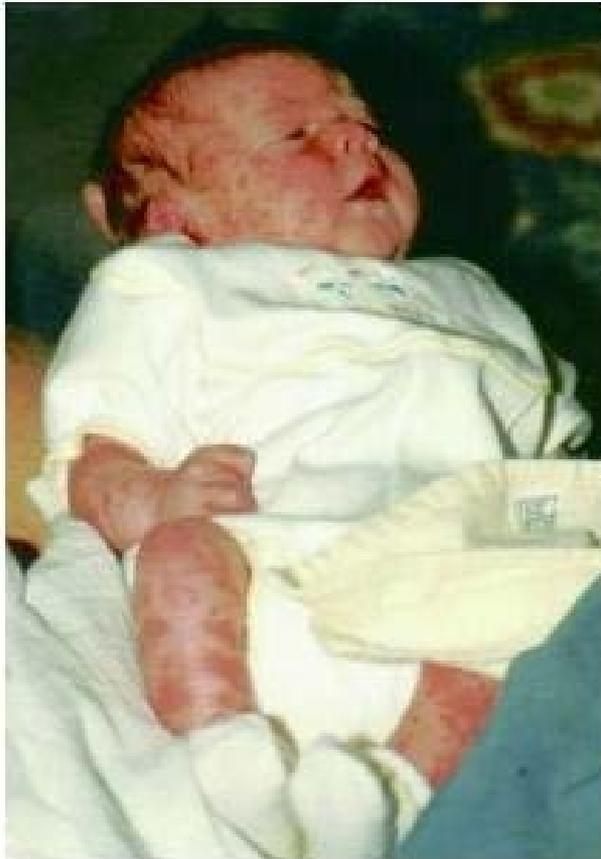
Neonatal-onset  
multisystem  
inflammatory  
disease (NOMID)



Deficiency of the  
interleukin-1 receptor  
antagonist (DIRA)



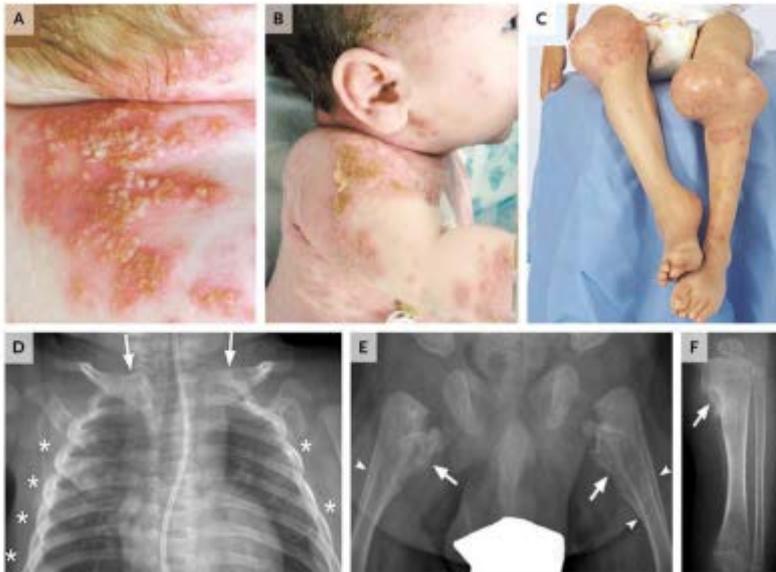
# Meet Alex— Before and After an NIH Clinical Trial



NOMID patient and clinical trial participant Alex (then and now)  
with NIAMS researcher Dr. Goldbach-Mansky

# Deficiency of the Interleukin-1 Receptor Antagonist (DIRA)

## *Inflammatory Skin and Bone Manifestations in Patients with DIRA*

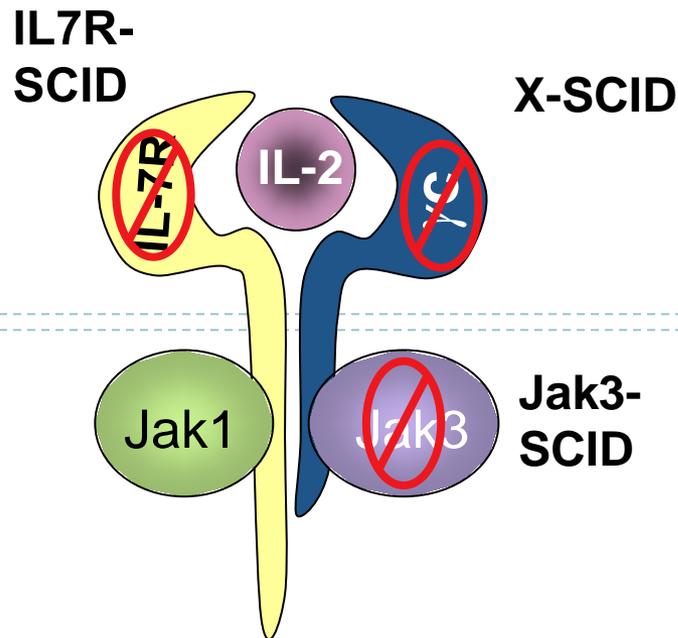


Aksentijevich et al, *N Engl J Med* 2009



Jacob Whelan (center) with his parents, and Raphaela Goldbach-Mansky, M.D. who, along with her team at NIAMS, discovered DIRA, for which Jacob has been undergoing treatment.

# Jak Inhibitors – an 18-year Journey from Bench to Bedside

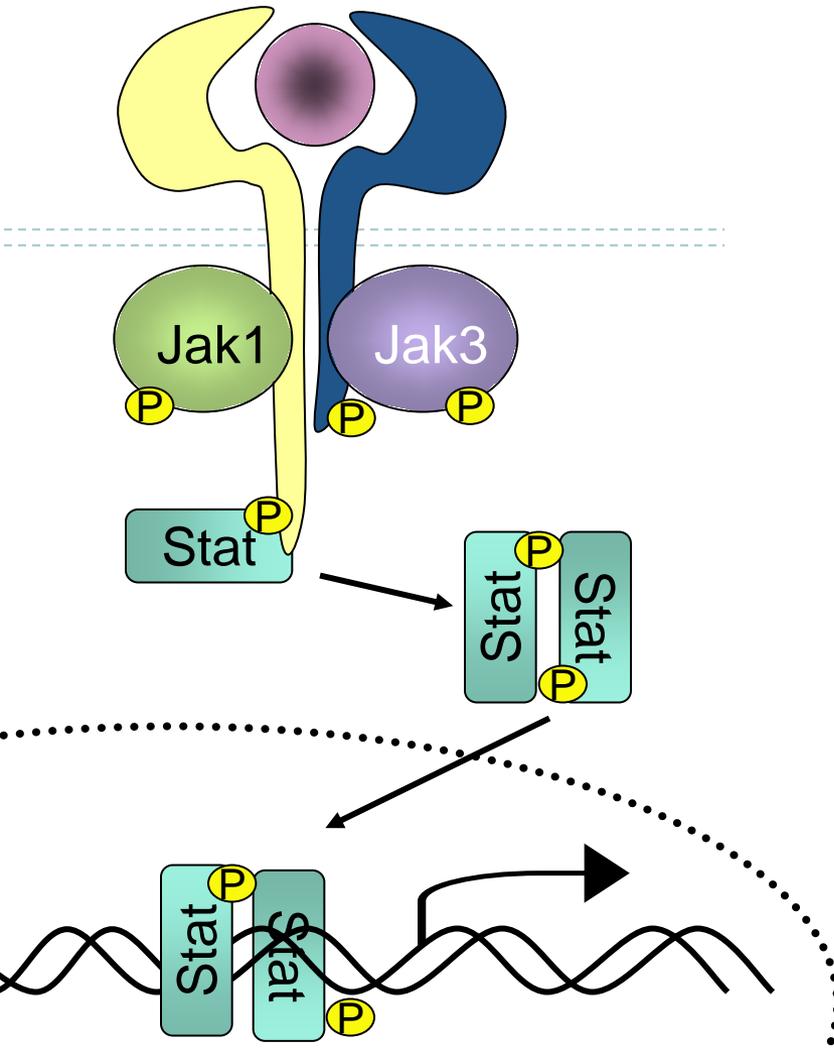


- **1994: Cloning of JAK3 and identification as a mediator of IL-2 signaling**
- **1995: Discovery of Jak3 mutations in SCID**



John O'Shea,  
NIAMS Scientific Director

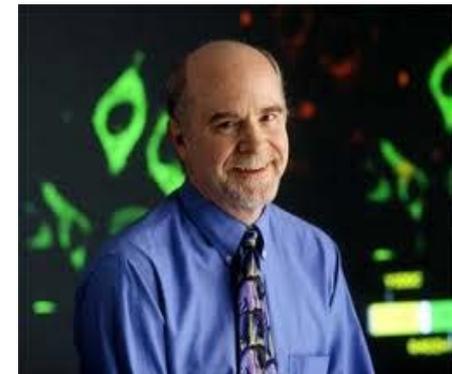
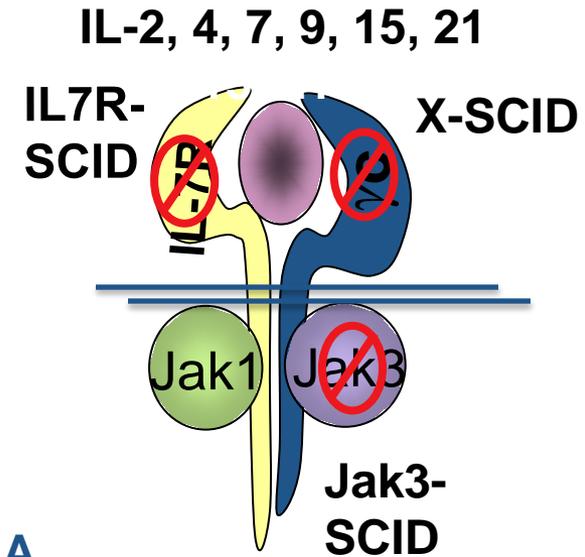
# Type I/II cytokines signal via Janus kinases and STATs



- ~200 “cytokines” in the human genome
- ~60 signal via Jak-Stat pathway
- Diverse roles in cell growth, differentiation, host defense and inflammation
- Four Jaks: Jak1, Jak2, Tyk2 – broad functions
- Function of Jak3?

# Jak Inhibitors – an 18-year Journey from Bench to Bedside

- **1994:** Cloning of JAK3 and identification as a mediator of IL-2 signaling
- **1995:** Discovery of Jak3 mutations in SCID
- **1995-2000:** Development of small molecule JAK3 inhibitors (NIH-Pfizer)
- **2005:** Demonstration that lead compound (CP-690,550) prevents allograft rejection
- **2008:** Efficacy of CP-690,550 in animal models of RA
- **2008-2011:** Phase II/III clinical trials of CP-690,550/ Tofacitinib in Rheumatoid Arthritis: Efficacy comparable to TNF inhibitors, slows erosions
- **2012:** At least 7 JAK inhibitors in trials, FDA approved JAK1/2 inhibitor for myelodysplastic syndrome (ruxolitinib)
- **May 9, 2012:** FDA advisory panel recommends approval of tofacitinib for treatment of RA



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