# STATE OF THE SCIENCE OF THE USE OF BIOMARKERS TO ESTABLISH PRESENCE AND SEVERITY OF IMPAIRMENTS: A WORKSHOP

## Session 4: State of the Science on Biomarkers to Establish Presence and Severity of Impairments: Part II

## OSTEOARTHRITIS

Virginia Byers Kraus, MD, PhD
7.21.20

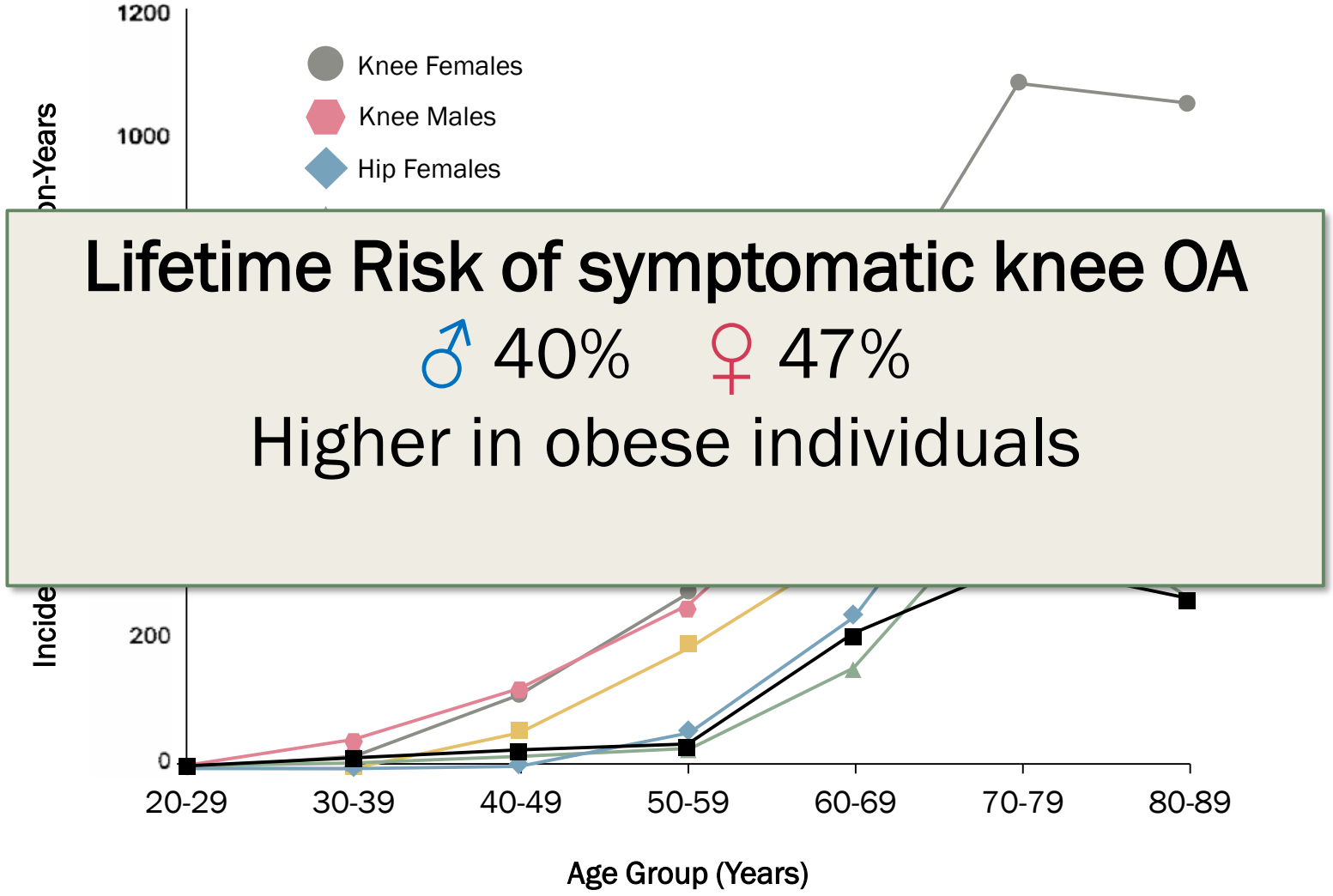
(no conflicts to disclose)

# OVERVIEW

- Overview of Osteoarthritis (OA).
- How do health care professionals diagnose OA?
- What are potential measurable outcomes for OA-related disability?
- What are emerging methods to prognose OA?
- Summary of components for identifying risk of disability in OA.

# THE FACES OF OSTEOARTHRITIS


# ALL FORMS OF OSTEOARTHRITIS INCREASE WITH AGE




**Lifetime Risk of symptomatic knee OA**

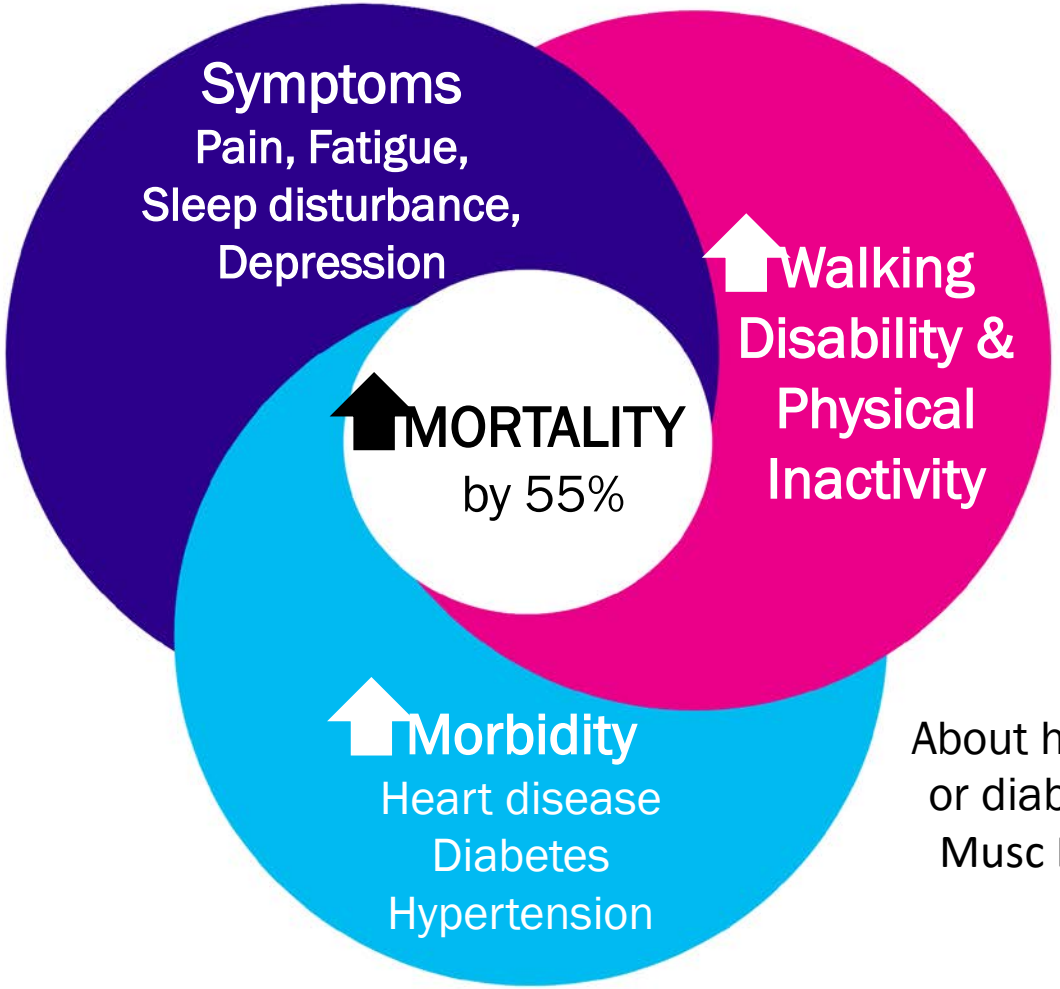
♂ 40% ♀ 47%

Higher in obese individuals

Murphy, et al. *A&R* 2008
Oliveria, et al. *A&R* 1995

Adapted slide from Dr. Tuhina Neogi

# Osteoarthritis is a Serious Disease

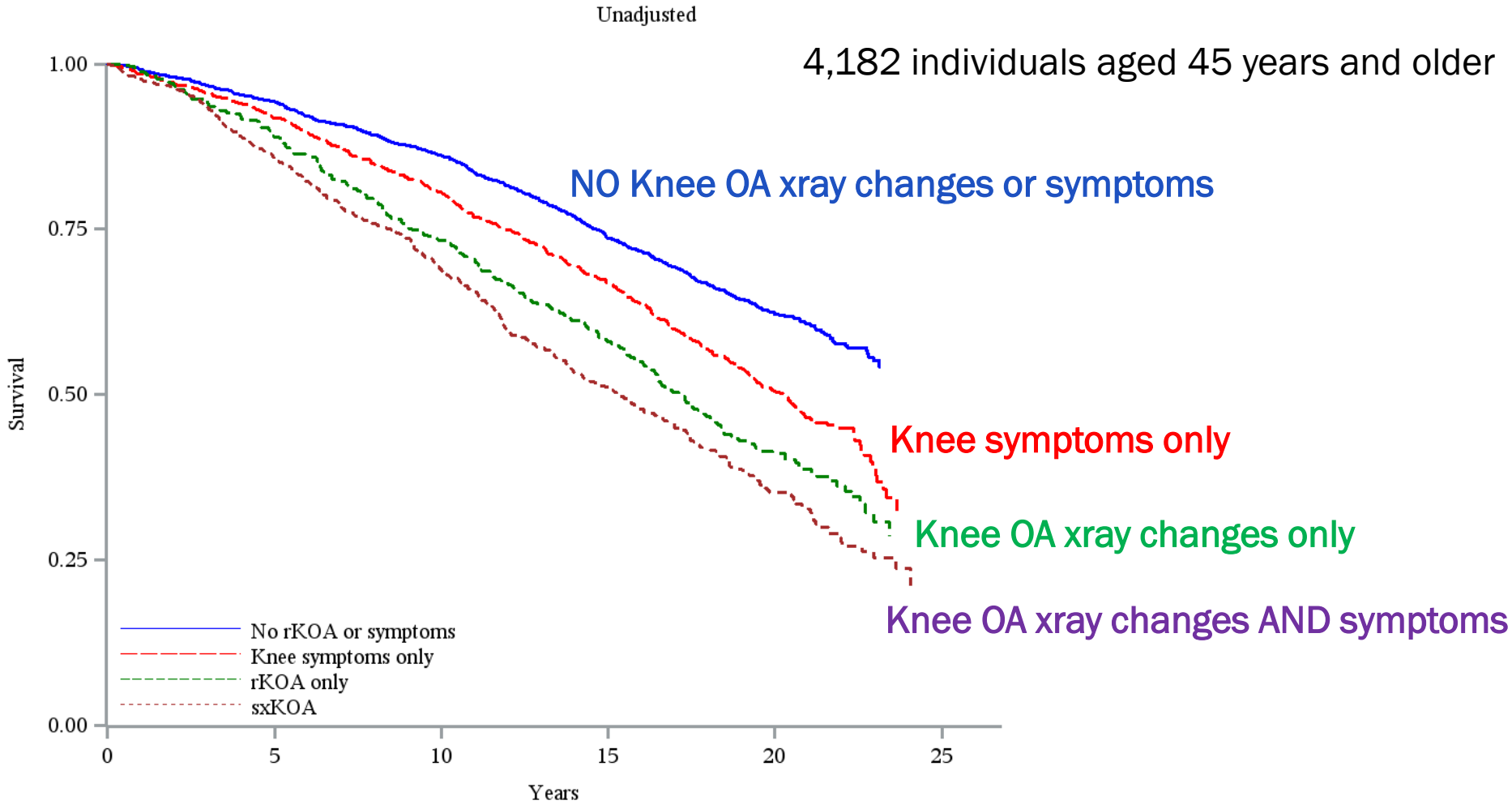



37-47% of association of hip/knee OA with diabetes was explained by walking limitation [Kendzerska, Diabetologia 2018]

About half of all adults with heart disease or diabetes have arthritis [Van Dijk, BMC Musc Disease 2008; Kadam, Ann Rheum Disease 2004]

OARSI White Paper on OA as a Serious Disease: https://www.oarsi.org/research/oa-serious-disease

# Osteoarthritis is a Serious Disease




4,182 individuals aged 45 years and older

NO Knee OA xray changes or symptoms

Knee symptoms only

Knee OA xray changes only

Knee OA xray changes AND symptoms

Cleveland, Alvarez, Schwartz, Losina, Renner, Jordan and Callahan, OAC: 27; 593-602, 2019

# Osteoarthritis Clinical Course

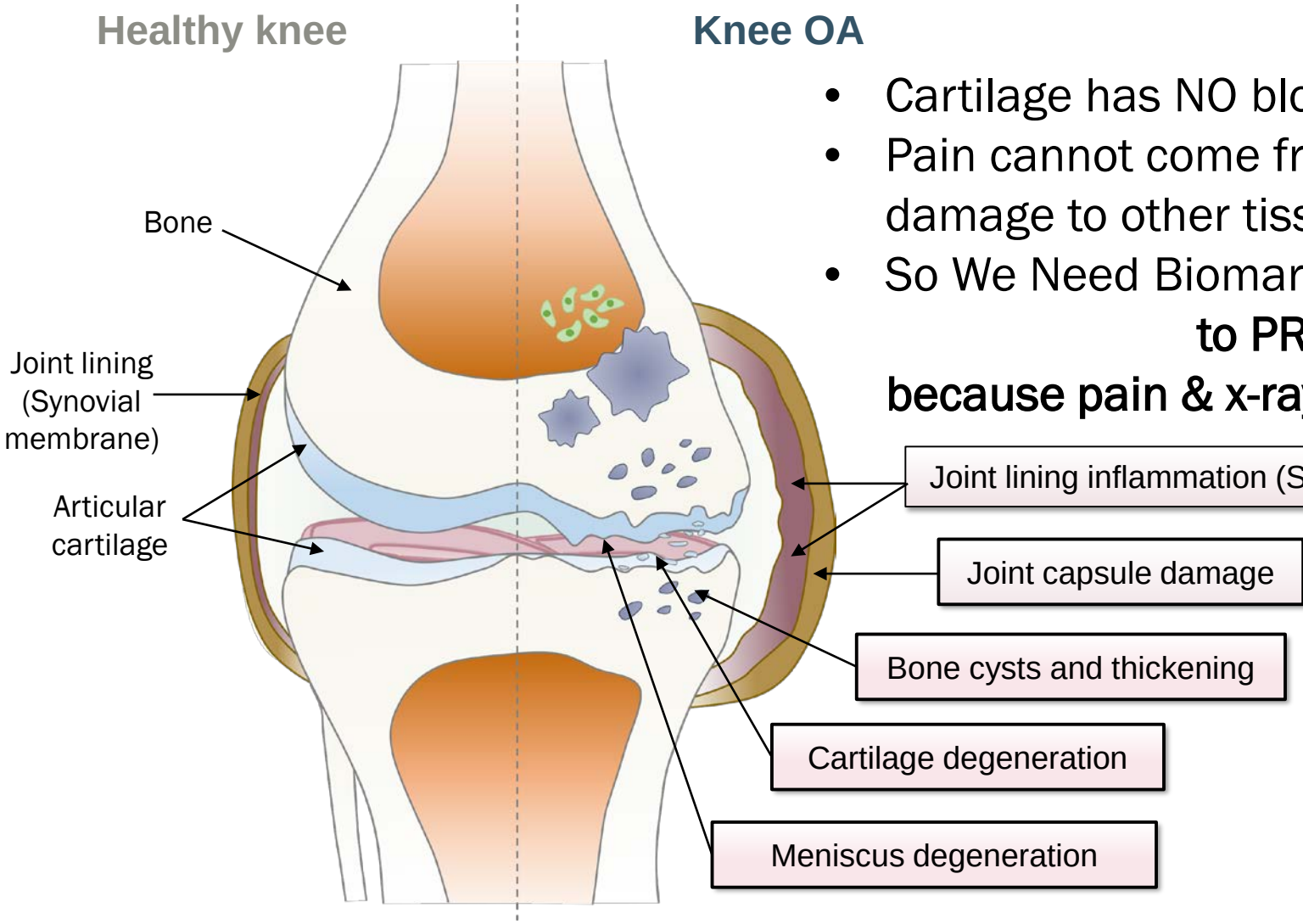
## 302 million worldwide

- Musculoskeletal diseases are now the 2nd most common cause of years lived with disability worldwide
- OA was responsible for 22% of health care visits in the USA in 2010

Kolasinski et al. Arthritis Rheum 2020; 72(2):220–233
Slide adapted from Dr. Tuhina Neogi

Sebbag E, et al. Ann Rheum Dis 2019;78:844–848.
Burden of MSK Diseases in the US, 2014, 3rd Ed. http://bmus.latticegroup.com

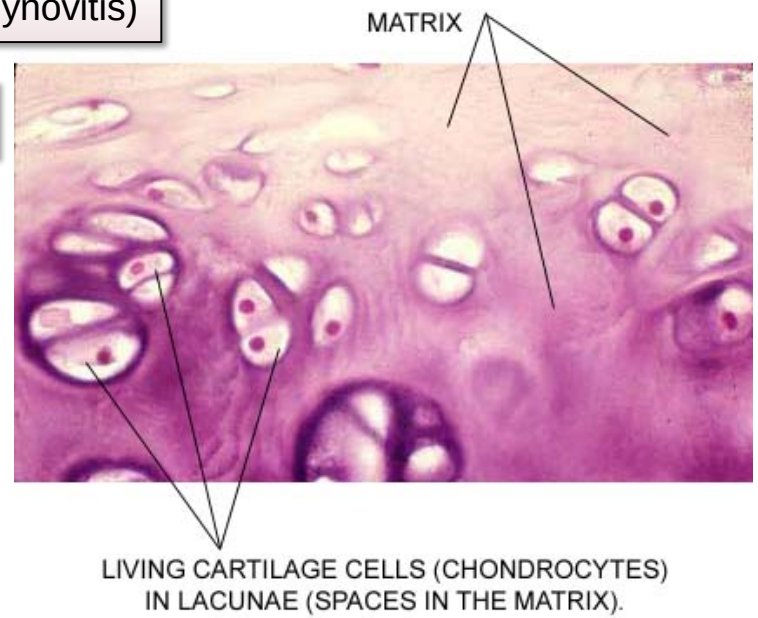
# OA is a whole-joint disease affecting all tissues




- Cartilage has NO blood or lymphatic vessels or nerves.
- Pain cannot come from cartilage, just from collateral damage to other tissues due to the breakdown of cartilage.
- So We Need Biomarkers To Detect OA EARLY

**to PREVENT DISABILITY**

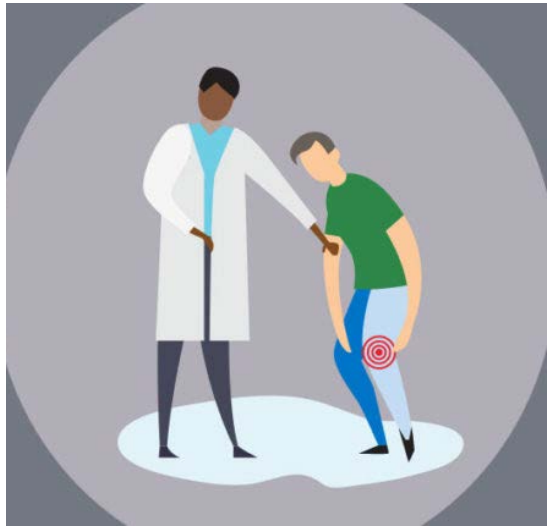
**because pain & x-ray or MRI images do not detect it early!**




Graphic from https://jb004.k12.sd.us/my%20website%20info/human%20anatomy/CHAPTER%205/VIRTUAL%20HISTOLOGY%20LAB/VL%20PAGE%209.htm

Slide adapted from Dr. Jeymi Tambiah)

# How do Health Care Professionals Diagnose OA?



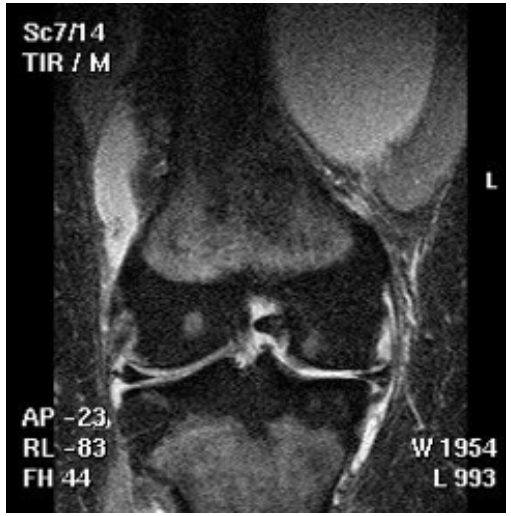
**History & Physical Exam**
for which joints affected, tenderness, swelling, redness and flexibility;
age, weight, injury

**XRAY IMAGING**
Joint space narrowing
Osteophyte ‘spurs’

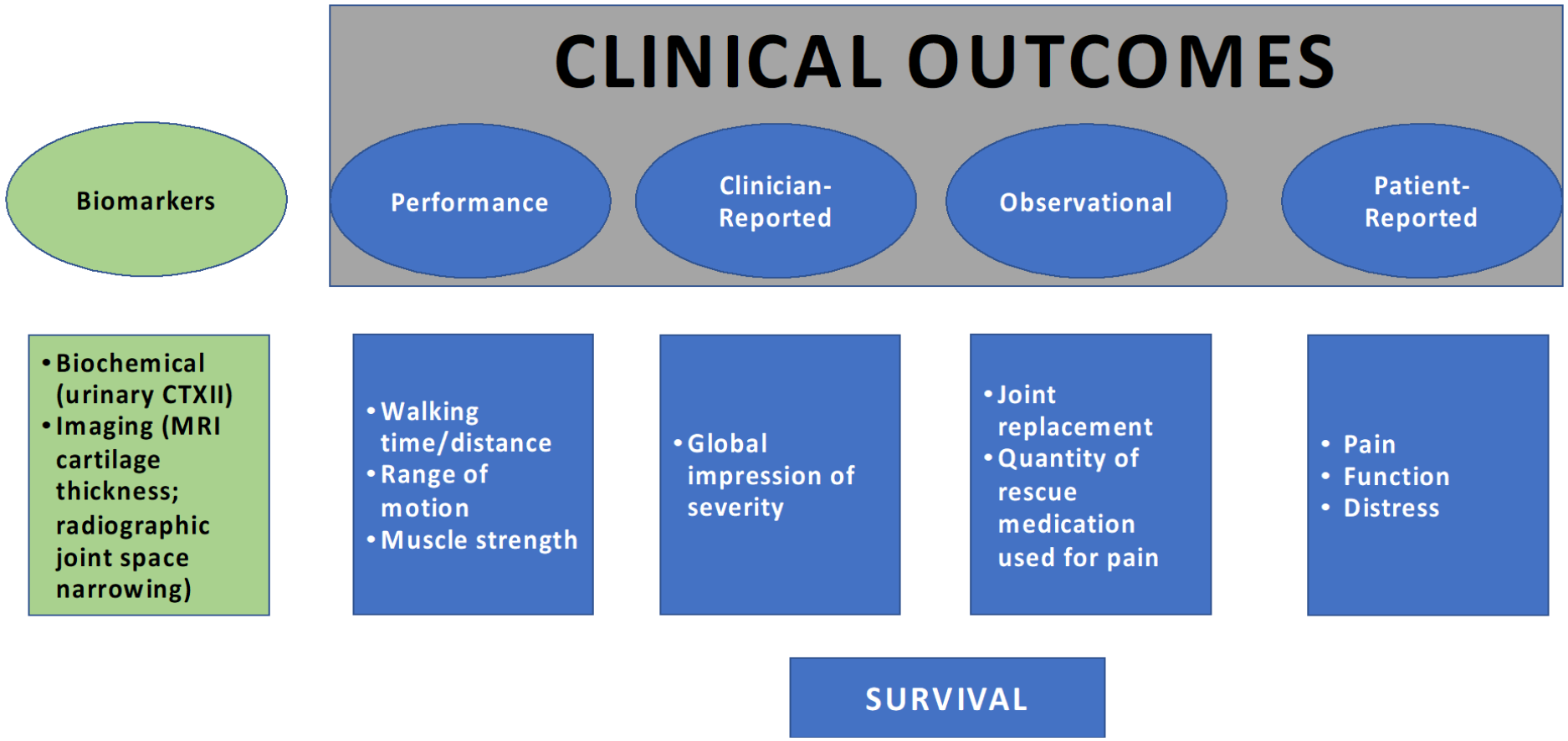
**Blood Tests**
negative for
Rheumatoid Factor and
Anti-Nuclear Antibody
(ANA)

**Joint Fluid Exam**
for crystals, and/or infection (cell count and culture)

**MRI IMAGING**
Cartilage loss
Inflammation
Meniscus tears
Bone marrow lesions



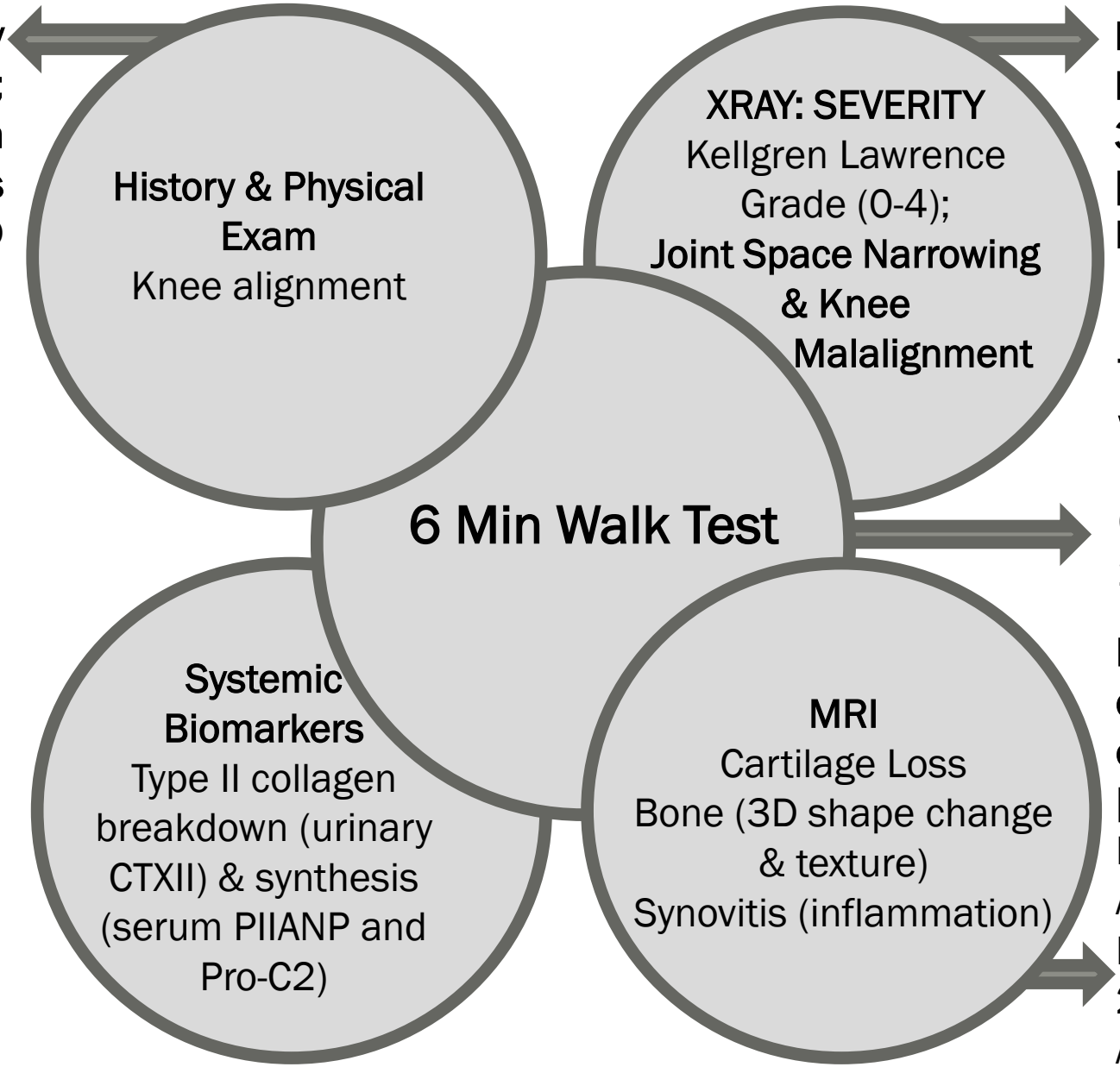
# What Are Potential Measurable Outcomes for OA-related Disability?




Kraus et al. 2019, Osteoarthritis Cartilage, Apr;27(4):571-579; Adapted from Patrick et al. 2014

# What are Emerging Methods to Prognose Risk of Worsening OA?

**Age, gender and weight poorly predict risk of progression; Knee malalignment in an overweight individual predicts progression** [Felson et al. ARD 2004)]



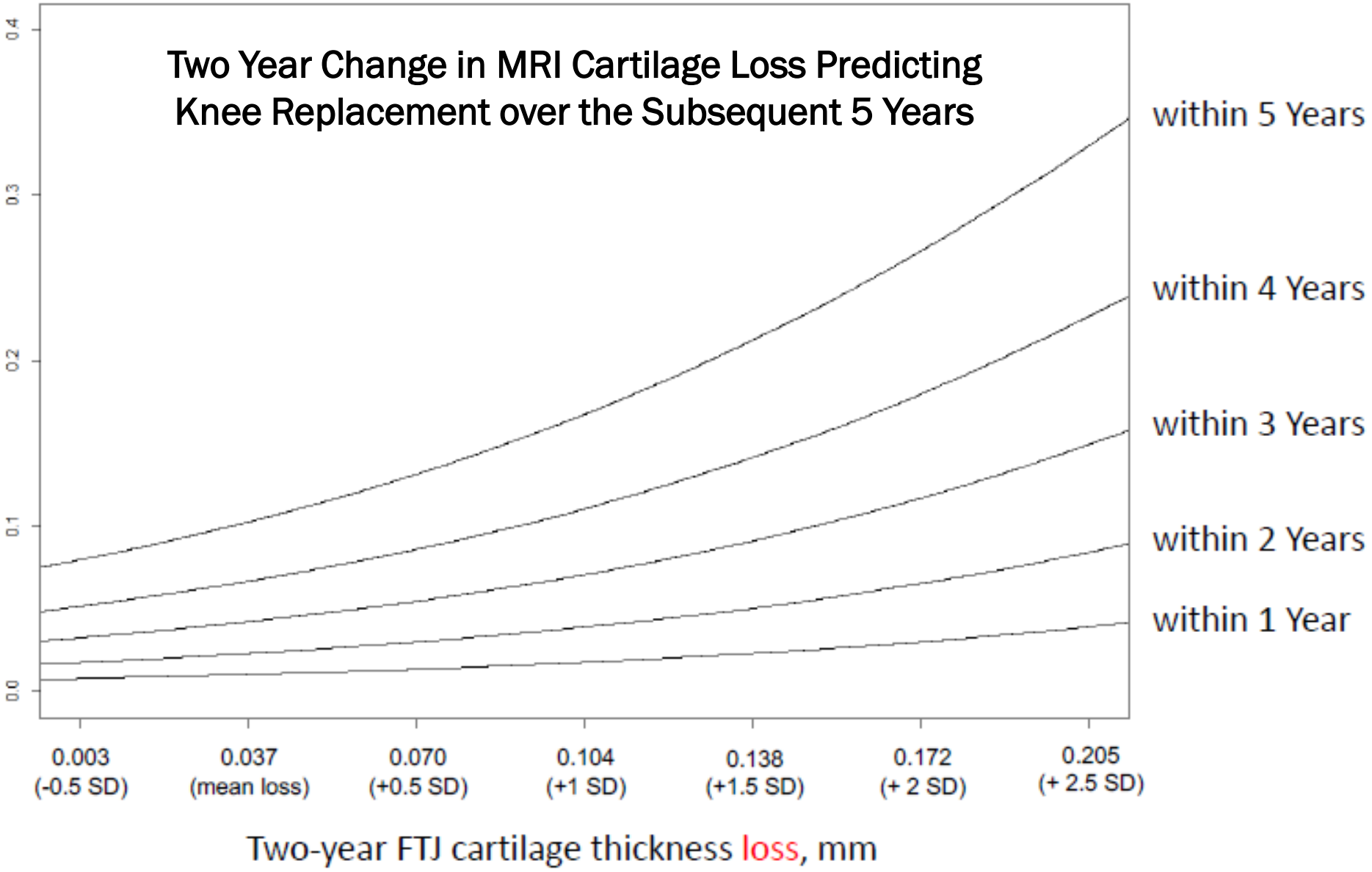

**Pain and risk of Joint Replacement (17% for grade 3, 44% for grade 4)** [Neogi et al. BMJ 2009; Eckstein OARSI 2019]

**Transition to "moderately worse" or "much worse" in 6 months** [Eyles et al. Arthritis Care Res (Hoboken) 2016;68(9):1268-77]

**Progression of pain and xray changes and increased risk of joint replacement** [Demehri et al. Curr Opin Rheum 2015; Pelletier et al. Ann Rheum Dis 2013; Hunter et al Osteo Cartilage 2015; Barr et al. Ann Rheum Dis 2015]

# What are Emerging Methods to Prognose Risk of Worsening OA?

Probability of Knee Replacement



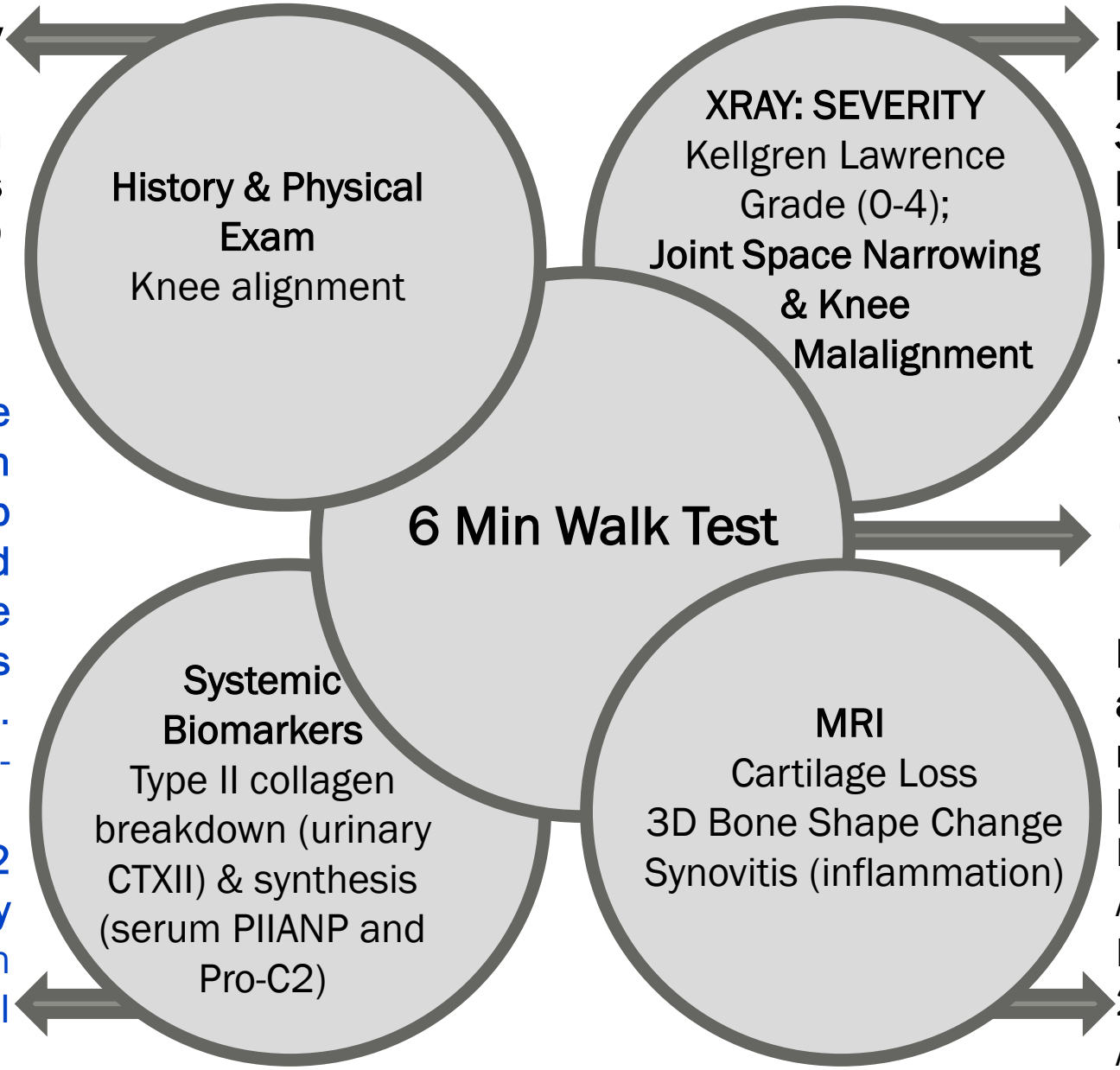

Kwoh CK et al. IWOAI 2018 (kindly provided by Dr. Phil Conaghan)

# What are Emerging Methods to Prognose Risk of Worsening OA?

**Age, gender and weight poorly predict risk of progression; Knee malalignment in an overweight individual predicts progression** [Felson et al. ARD 2004)]

**High baseline CTXII (cartilage breakdown) associated with 3 X higher risk of knee or hip replacement (knee or hip) and 9 X higher risk of knee replacement (knee) in 2 years** [Bjerre-Bastos et al. 2019. Osteo & Cartilage 27, S31-S32]

**Low PIIANP or Pro-C2 (synthesis) predict xray progression** [Kraus et al. Ann Rheum Dis 2017; Luo OARSI 2018]




**Pain and risk of Joint Replacement (17% for grade 3, 44% for grade 4)** [Neogi et al. BMJ 2009; Eckstein OARSI 2019]

**Transition to "moderately worse" or "much worse."** [Eyles et al. Arthritis Care Res (Hoboken) 2016;68(9):1268-77]

**Progression of pain and xray and increased risk of joint replacement** [Demehri et al. Curr Opin Rheum 2015; Pelletier et al. Ann Rheum Dis 2013; Hunter et al Osteo Cartilage 2015; Barr et al. Ann Rheum Dis 2015]

# Many Molecular Biomarkers are Available for Osteoarthritis

## BIPEDS

**B**urden of Disease

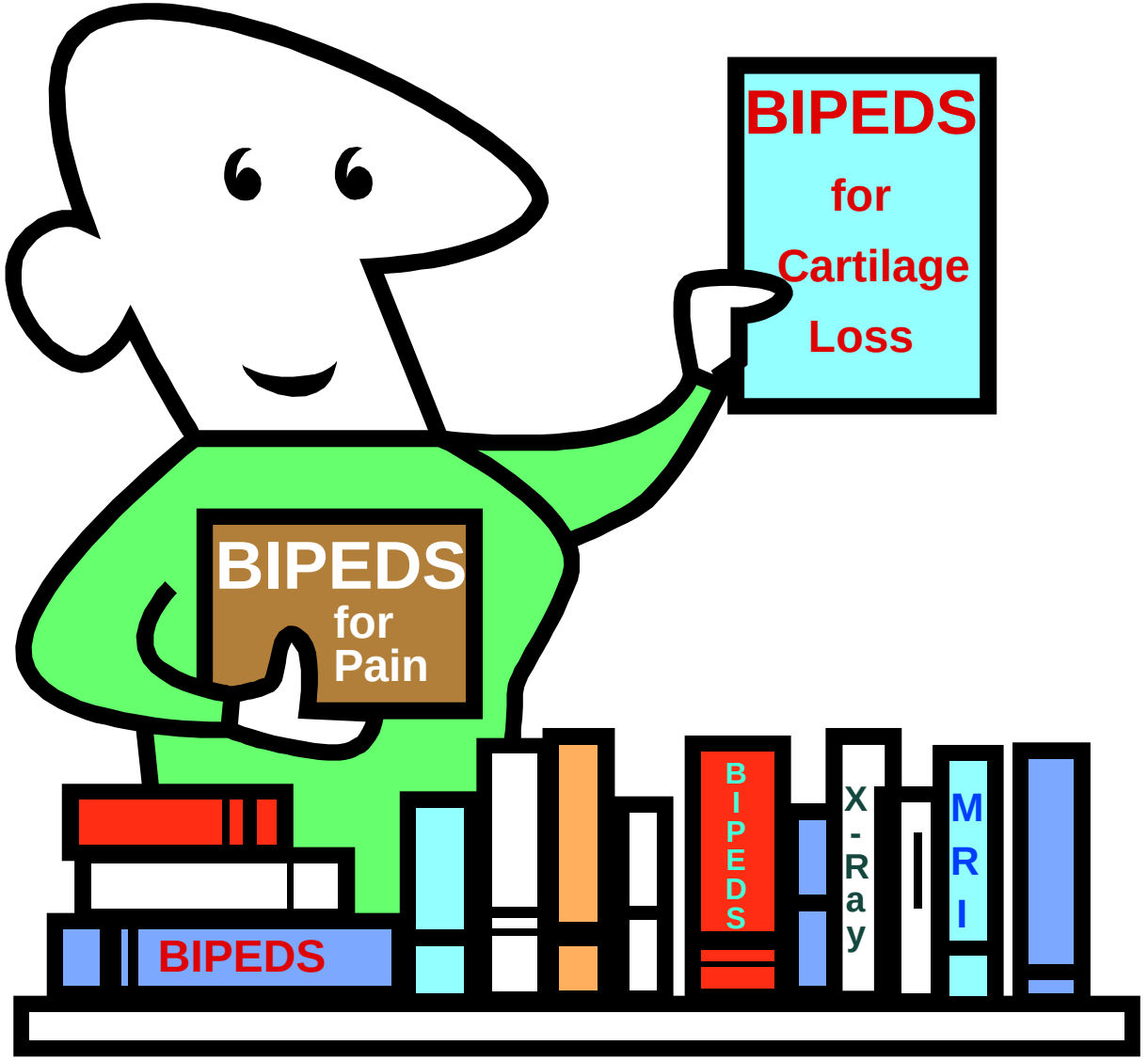
**I**nvestigative

**P**rognostic

**E**fficacy of Intervention

**D**iagnostic

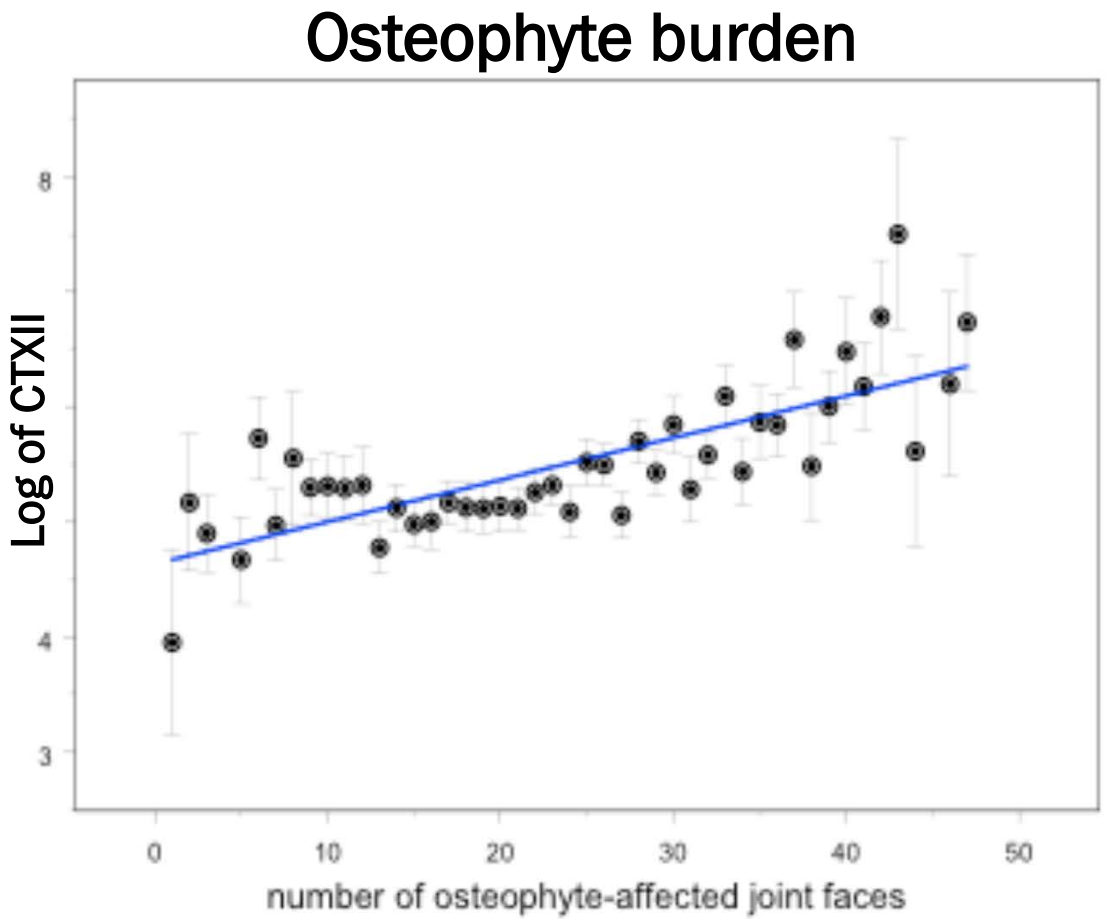
**S**afety

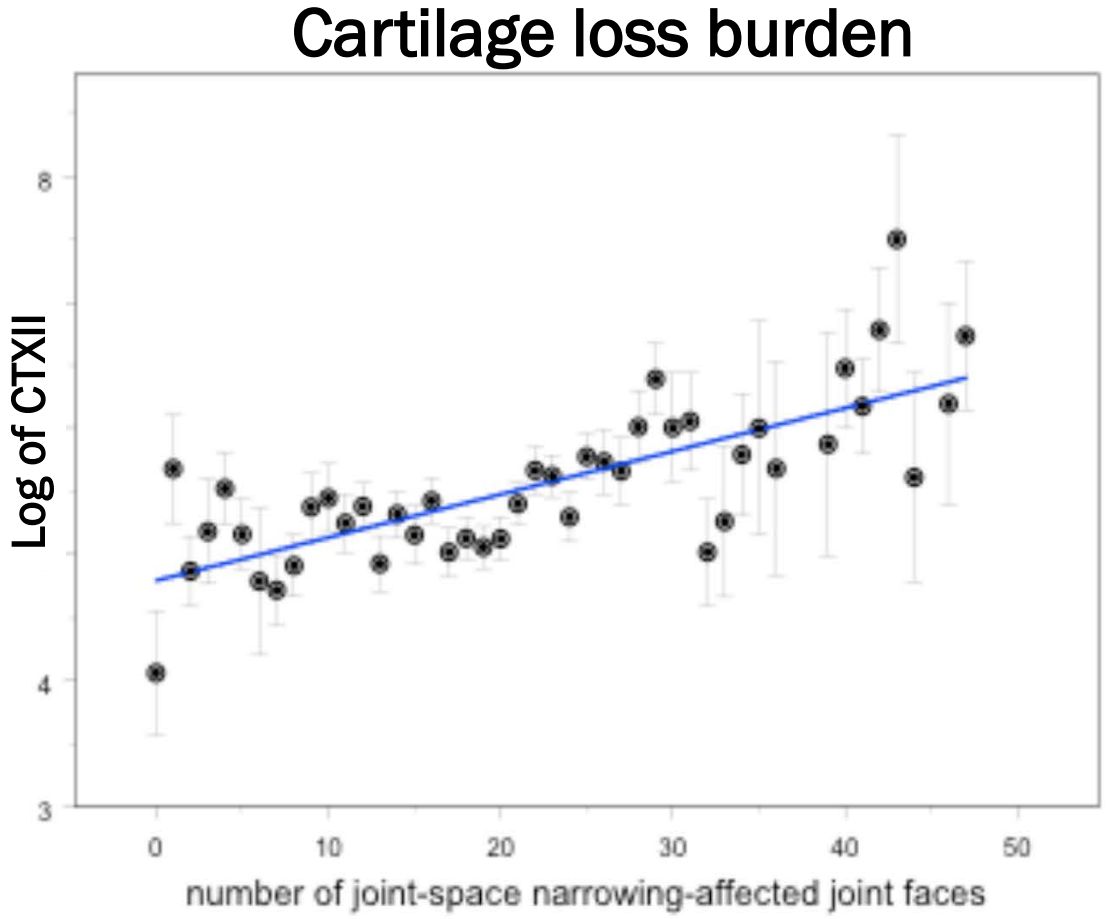



Bauer et al. 2006 Osteoarthritis Cartilage 14(8):723-7. PMID: 16733093
Kraus et al. 2011. Osteoarthritis Cartilage May;19(5):515-42. PMC3568396
Van Spil et al. 2010. Osteoarthritis Cartilage 18(5):605-12. PMID: 20175979

# Urinary CTXII -- a Systemic Biomarker -- Predict Whole Body Burden of OA

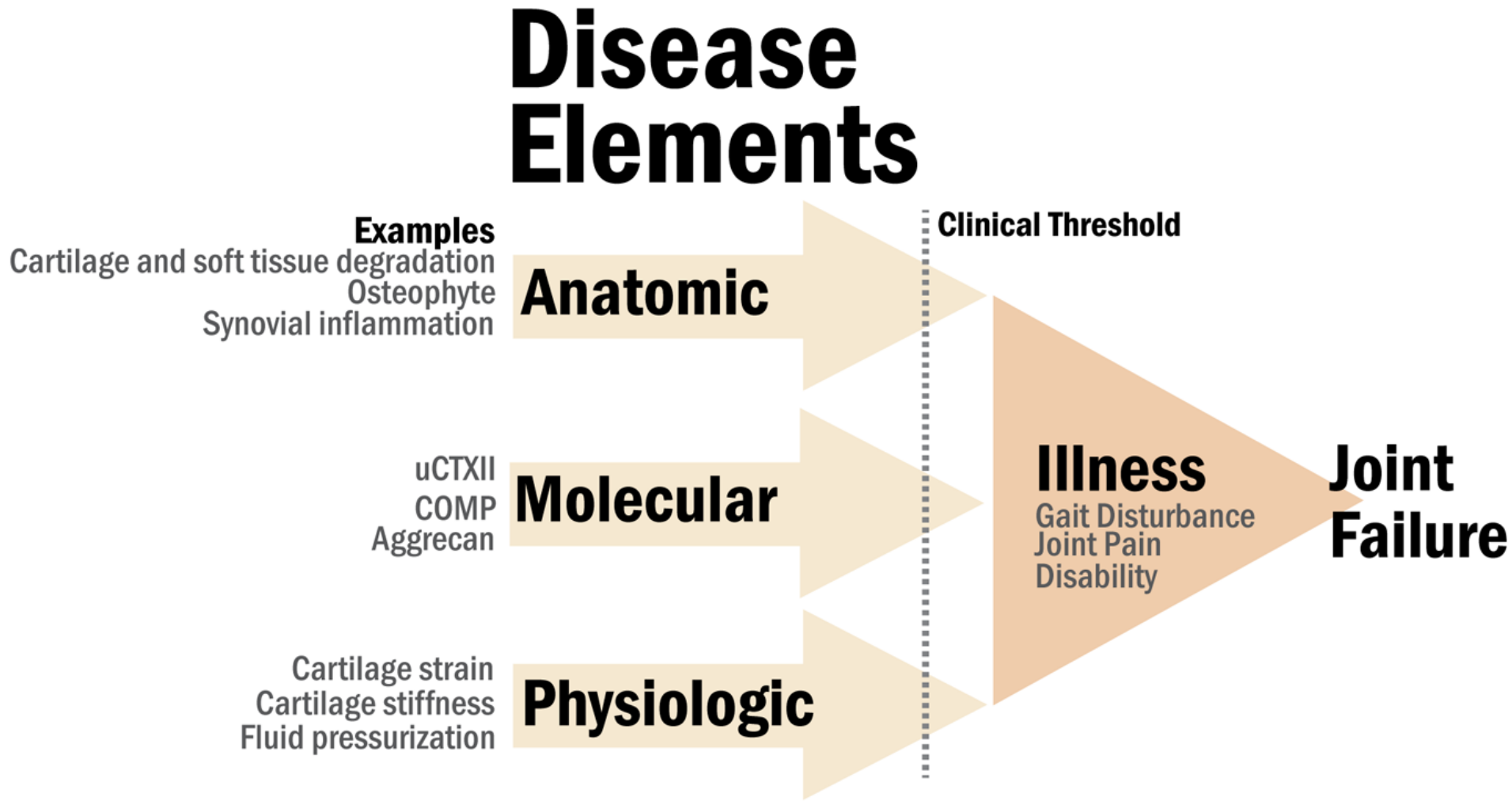
(481 women with xrays of hands, hips, knees and spine)




Kraus et al. 2010 PLOS One 5:3 e9739

# Summary of Components for Identifying Risk of Disability in Osteoarthritis

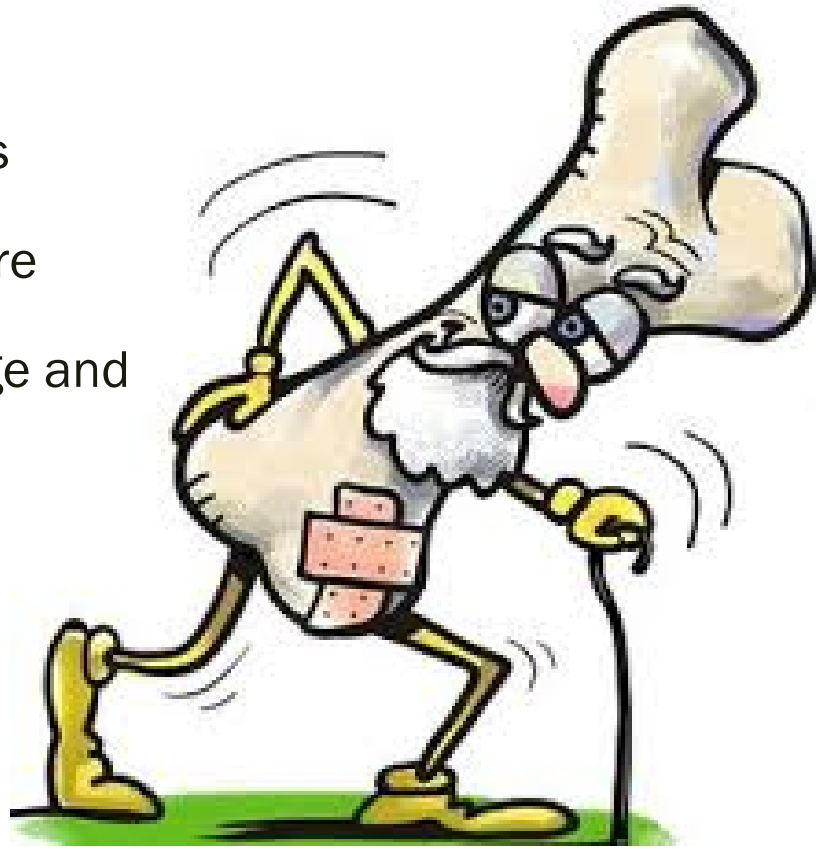



Kraus et al. Osteoarthritis Cartilage. 2015;23(8):1233-41. doi: 10.1016/j.joca.2015.03.036. PMCID: PMC4516635.

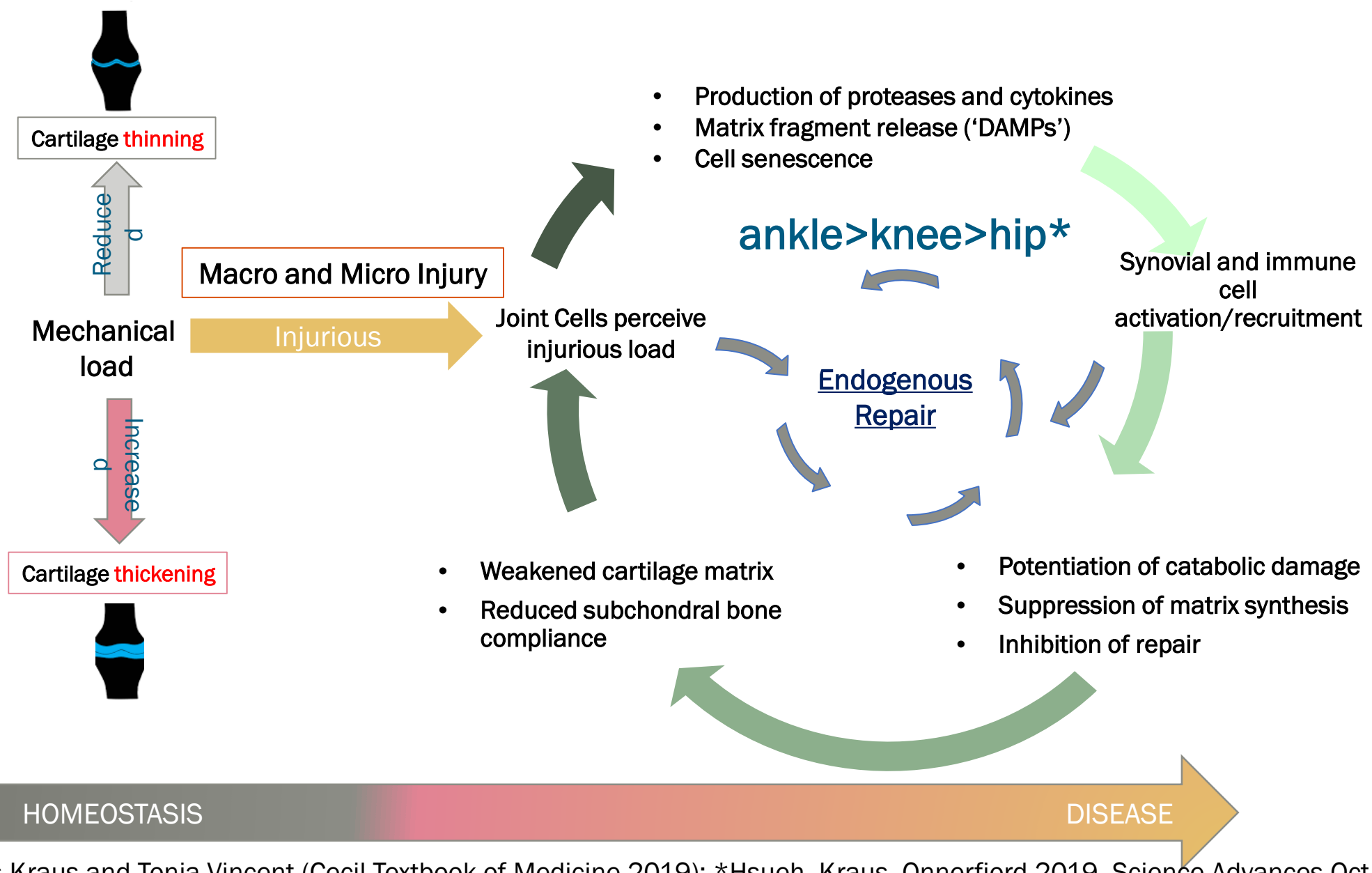
# Remaining Challenges for Molecular Markers of OA

- Pathogenesis of OA remains **complex** and **multifactorial**;
- The heterogeneity of molecular pathways in OA **may require different molecular markers**;
- Unknown relationship of the **magnitude of change** in the biomarker to a clinically meaningful change in clinical outcome.
- Because there are no disease modifying treatments

or drugs for OA, the situation is **likely to get worse** before it gets better due to increasing OA due to increasing age and obesity of the population.



# OA Pathogenesis – Vicious Cycle of Sterile Inflammation



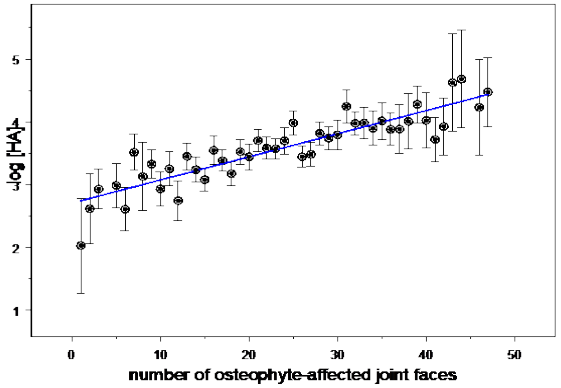

Virginia Byers Kraus and Tonia Vincent (Cecil Textbook of Medicine 2019); *Hsueh, Kraus, Onnerfjord 2019. Science Advances Oct 9:5(10)eaax3203

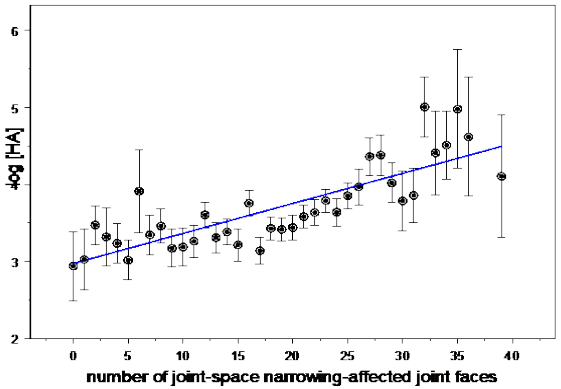
# Systemic Biomarkers Predict Whole Body Burden of OA

## Osteophyte

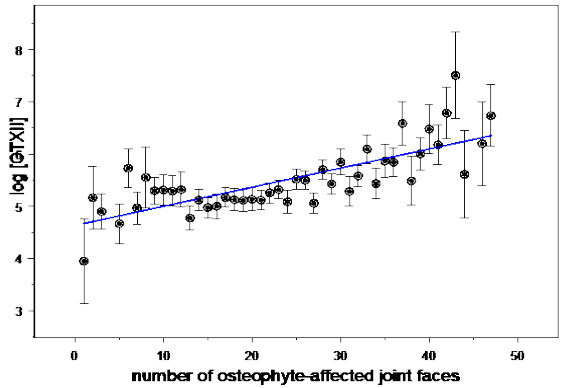
## Joint Space Narrowing

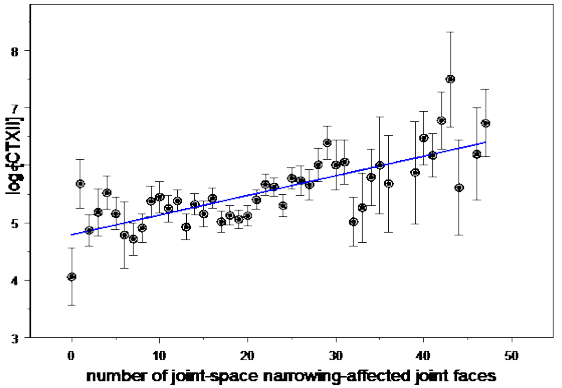
**Ln sHA**
Hyaluronan
(cartilage, synovium)



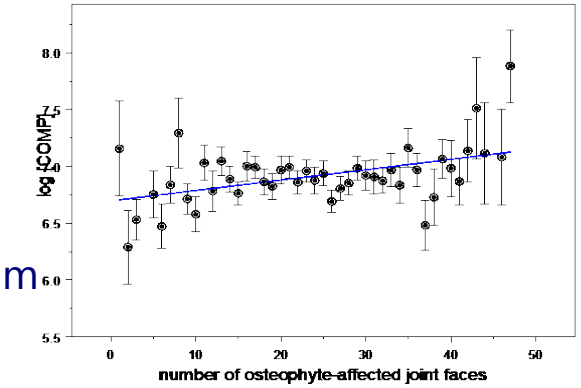



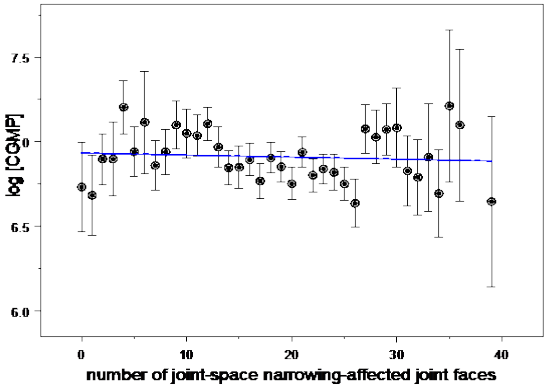

**Ln uCTX-II**
Col2 telopeptide
(cartilage-mineralized)




**Ln sCOMP**
Cartilage Oligomeric
Matrix Protein
(cartilage, tendon,synovium




**GOGO**

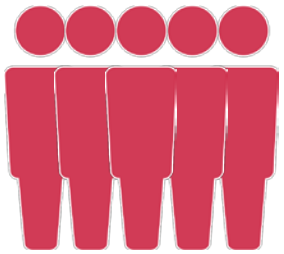
**N=481 Women**

**x-rays: hand, hip, knee, spine**

**Counted up total osteophytes and total sites of joint space narrowing**

VB Kraus, et al. 2010. PLoS ONE 5(3): e9739. doi:10.1371/journal.pone.0009739, PMC2840035.

# Scope of the OA Problem



Prevalence Burden

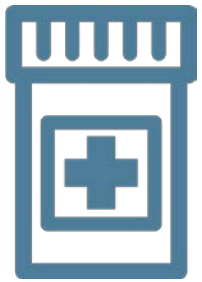
>300 million adults globally

15% adult population

Cost Burden

>$100s billion annually

>900,000 hospitalizations



Lack of Effective Therapies

Disability

Quality of Life

Opioid Epidemic

Kindly provided by Dr. Tuhina Neogi

# Types of Biomarkers - Nomenclature

**Prognostic**

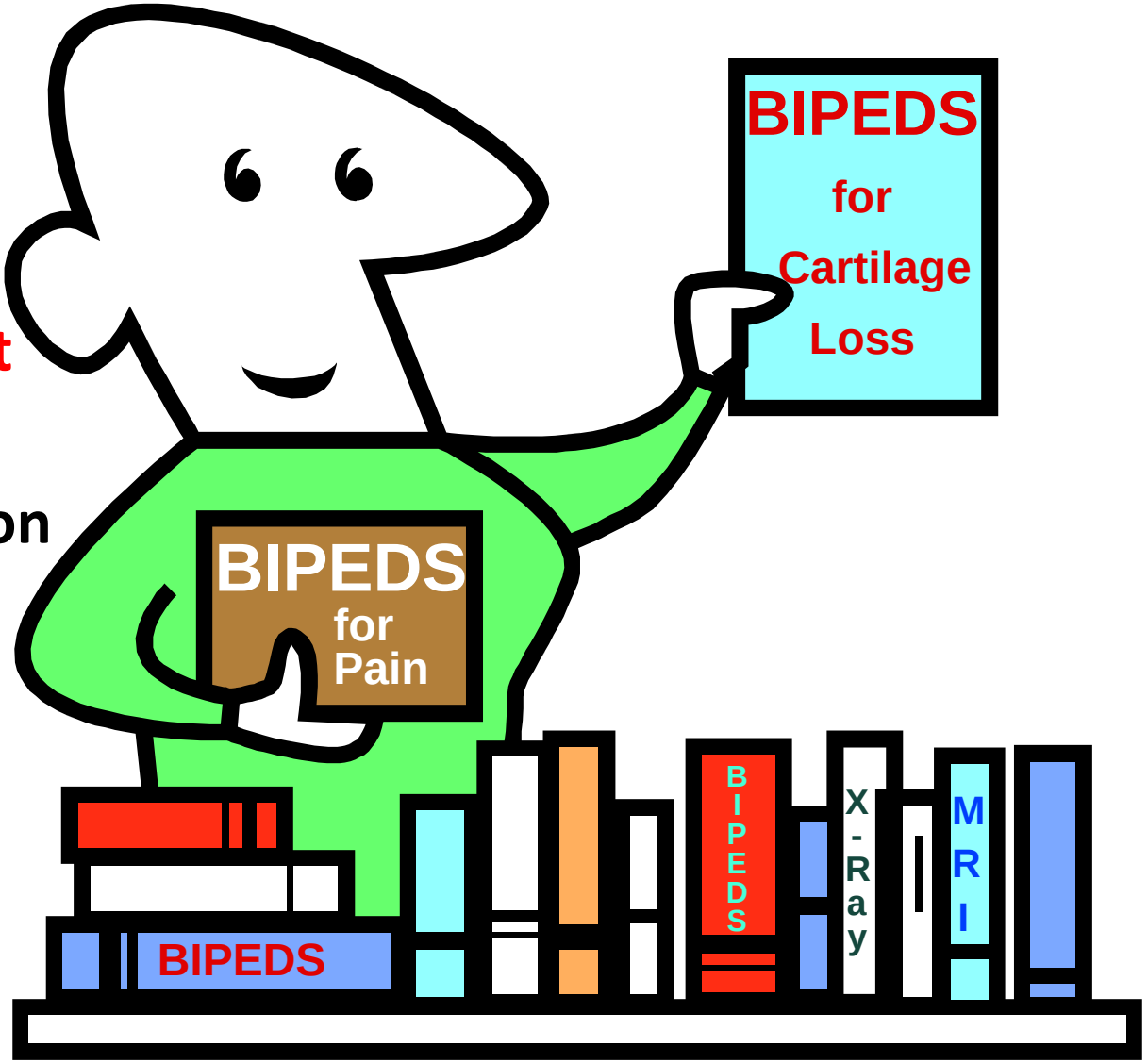
**prognostic-disease progression**

**predictive-treatment response**

**Efficacy of Intervention**

**pharmacodynamic-treatment efficacy**

**surrogate-substitute for a clinical efficacy endpoint**




Bauer et al. 2006 Osteoarthritis Cartilage 14(8):723-7
Kraus et al. 2011. Osteoarthritis Cartilage May;19(5):515-42. PMC3568396