EXPEDITED CLINICAL PROGRAMS AND STUDY DESIGNS FOR OA STRUCTURE MODIFYING THERAPIES

May 16, 2019

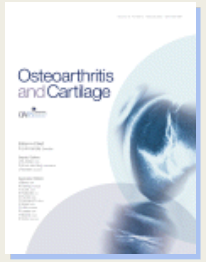
Washington, DC

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Joel A. Block, M.D.

The *Willard L. Wood, M.D. Professor* and
Director, Division of Rheumatology
Rush Medical College
Rush University Medical Center
Chicago, IL
jblock@rush.edu

Editor-in-Chief, *Osteoarthritis & Cartilage*



In the last 12 months, I have had the following relationships related to OA research:

Nature of Financial Relationship		
1. Commercial Interest	2. What Was Received	3. For What Role
Novartis, Pfizer, Abbvie, Jannsen, TissueGene	Research Funds	Clinical Trials
Daiichi-Sankyo, Agios, Omeros	Royalties	Intellectual Property: Cell lines
Zynerba Pharma, Inc., GlaxoSmithKline, Inc. Medivir Inc	Consulting Fees: OA Therapeutics	Consultant
Discgenics, Inc	Consulting Fees	DSMB
** Osteoarthritis Research Society International	Stipend	Editor-in-Chief, *Osteoarthritis and Cartilage*

**** Not Commercial**

Background

- OA is a slowly progressive process, with years (decades) of subclinical activity prior to presentation of symptomatic disease.
- There are no treatments or therapeutic strategies that have been shown to alter the progression of disease in humans
- It is widely believed (and repeatedly published) that “to develop effective therapeutics, predictors & markers of progression are necessary”

Background: OA Biomarkers

US FDA Fast track for accelerated approval (Part 312, subpart E (21 CFR part 312)) requires:

- *qualifying criteria : "**a drug that treats a serious condition** and generally provides a meaningful advantage over available therapies and demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit …"*

Background

- "FDA recognizes that OA can be a serious disease with an unmet medical need for therapies that modify the underlying pathophysiology of the disease and potentially change its natural course to prevent long-term disability."

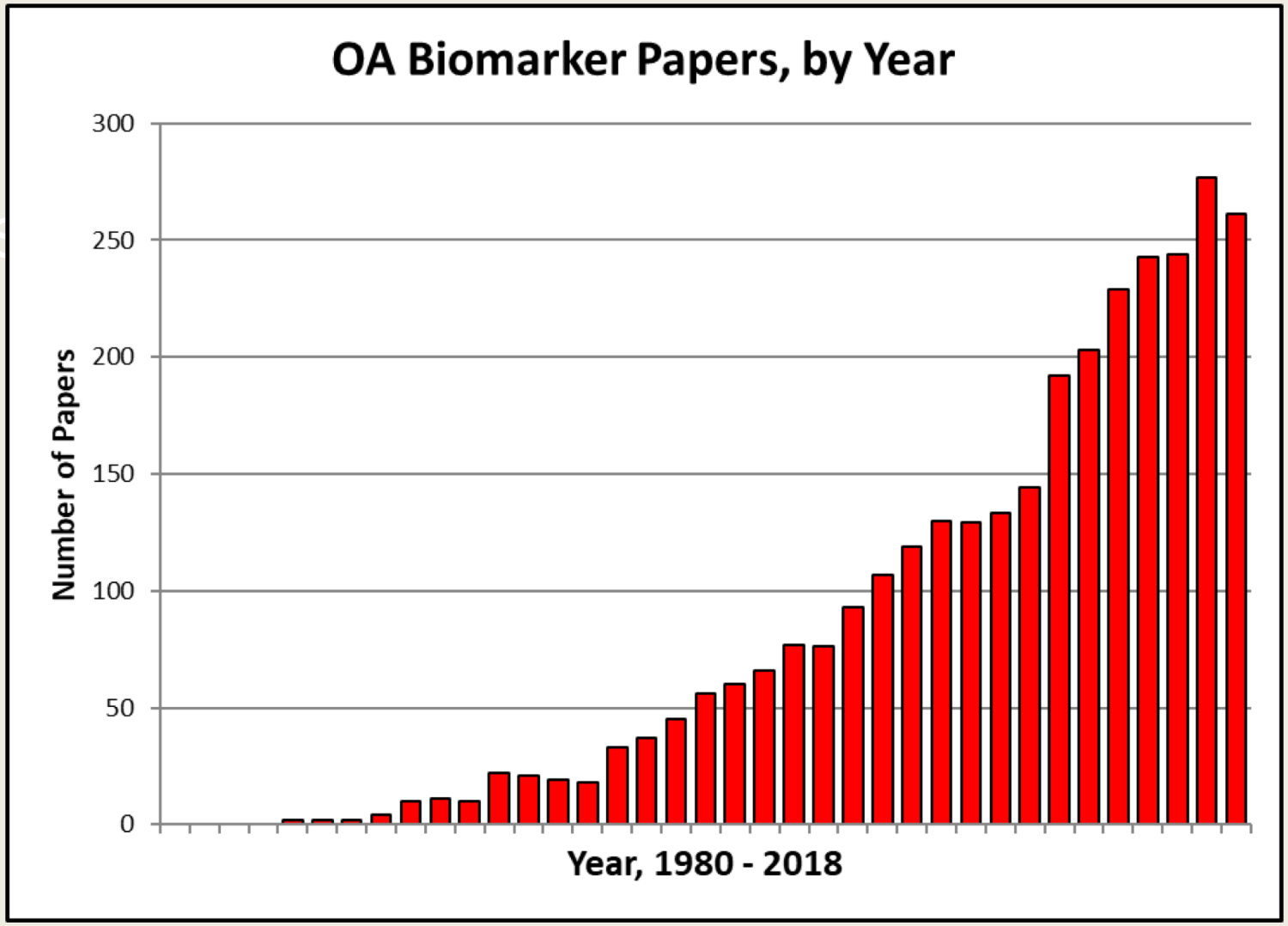
US FDA Draft Guidance, Aug 2018, "Osteoarthritis: Structural Endpoints for the Development of Drugs, Devices, and Biological Products for Treatment Guidance for Industry"

Background: OA Biomarkers

US FDA Fast track for accelerated approval (Part 312, subpart E (21 CFR part 312)) requires:

- *qualifying criteria :* “a drug that treats a serious condition *and generally provides a meaningful advantage over available therapies and demonstrates an effect on a* ***surrogate endpoint*** *that is reasonably likely to predict clinical benefit …”*

OA Biomarkers: History



How far have we come, and Where do we need to go?

<u>Today, our job is to:</u>

1. Define the status of surrogate structural markers in OA

   (What are the meaningful data re: OA surrogate markers - soluble and imaging?)

2. Discuss what it takes to demonstrate structural benefit.

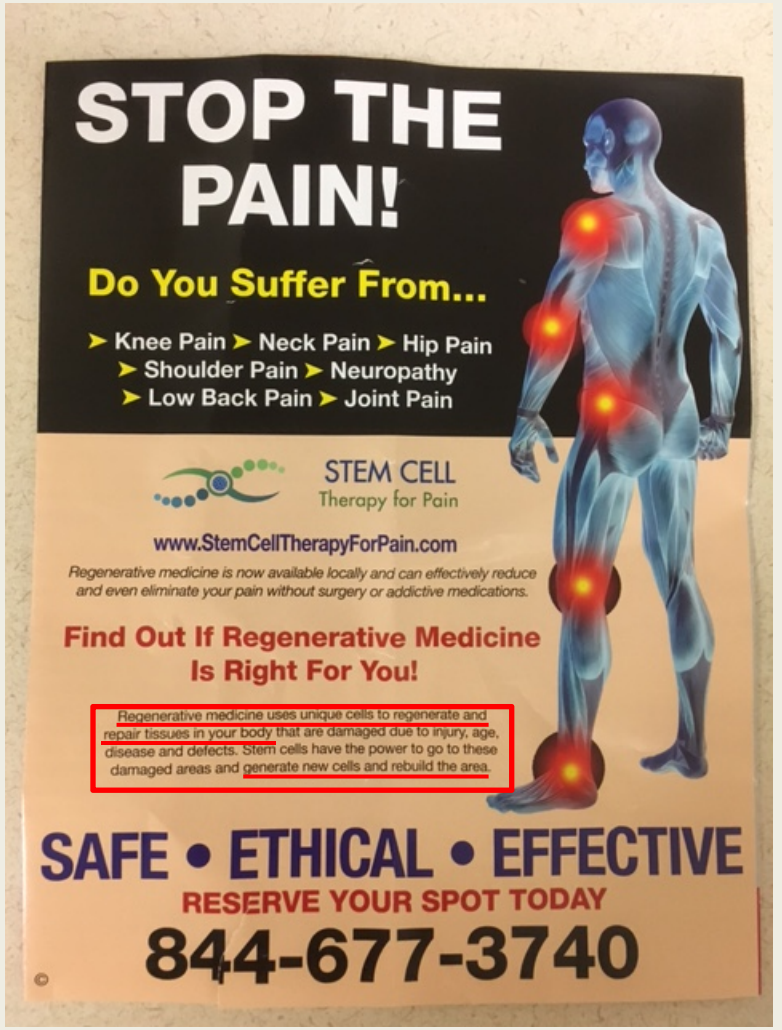
   (Are we now ready for evidence-based endpoints? If not, what do we need?)

3. Consider what is required after approval to prove clinical benefit.

   (What needs to be demonstrated to convince the Agency of a meaningful structure modifier?)

The Alternatives

Received via US Mail
5/13/2019



Chicago Tribune: 4/12/2018

Meeting Agenda

9:00 – 9:15 AM	Welcome and Overview	Joel Block, MD
9:15 - 9:45 AM	Impact of OA	Tuhina Neogi, MD, PhD Leigh Callahan, PhD Ranay Collins Denise Marksberry
9:45 – 10:00 AM	Group discussion	Jeffrey Katz, MD - Moderator
10:00 – 10:15 AM	Break	
10:15 – 10:45 AM	Current status imaging biomarkers	Philip Conaghan, MD, PhD
10:45 – 11:00 AM	Current status soluble biomarkers for OA	Virginia Kraus, MD, PhD
11:00 – 11:30 AM	Group discussion	Joel Block, MD - Moderator
11:30 – 12:00 PM	Applying biomarkers for accelerated approval of OA structure modifying drugs	Nikolay Nikolov, MD
12:00 – 12:30 PM	Group discussion	Marc Hochberg, MD, MPH - Moderator

Meeting Agenda (continued)

12:30 – 1:15 PM	Lunch	
1:15 – 2:15 PM	Post approval study designs for drugs approved on the basis of a surrogate endpoint in OA	Lee Simon, MD
2:15 – 3:30 PM	Group discussion	Philip Conaghan, MD, PhD Moderator
3:30 – 3:45 PM	Final comments	Joel Block, MD

IMPACT OF OA PANEL DISCUSSION

Tuhina Neogi, MD, PhD

Leigh Callaghan, PhD

Ranay Collins

Denise Marksberry

BURDEN OF OSTEOARTHRITIS

Tuhina Neogi, MD, PhD, FRCPC
Professor of Medicine and of Epidemiology
Boston University School of Medicine and
School of Public Health

BOSTON
UNIVERSITY

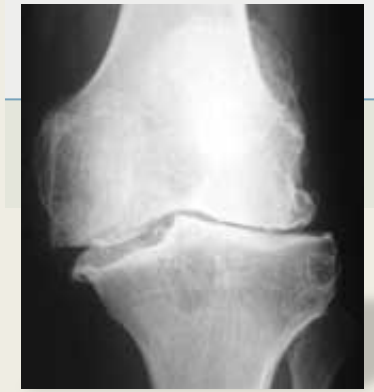
Disclosures

- EMD Merck-Serono
- Novartis
- Pfizer/Lilly
- Regeneron

Osteoarthritis Epidemiology

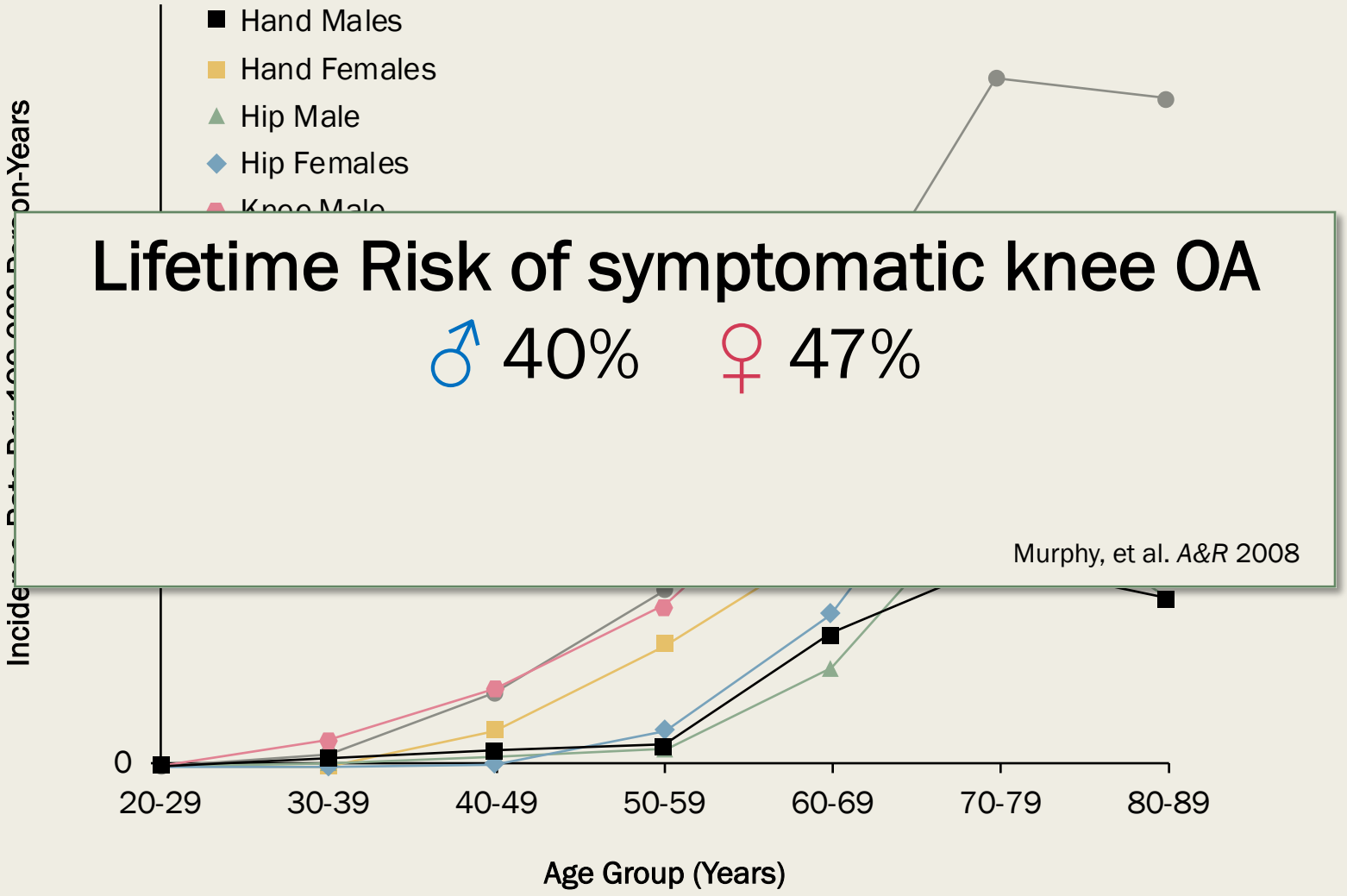
302 million

Joint Site	Radiographic OA	Symptomatic OA
Knee	20-30%	5/10-20%



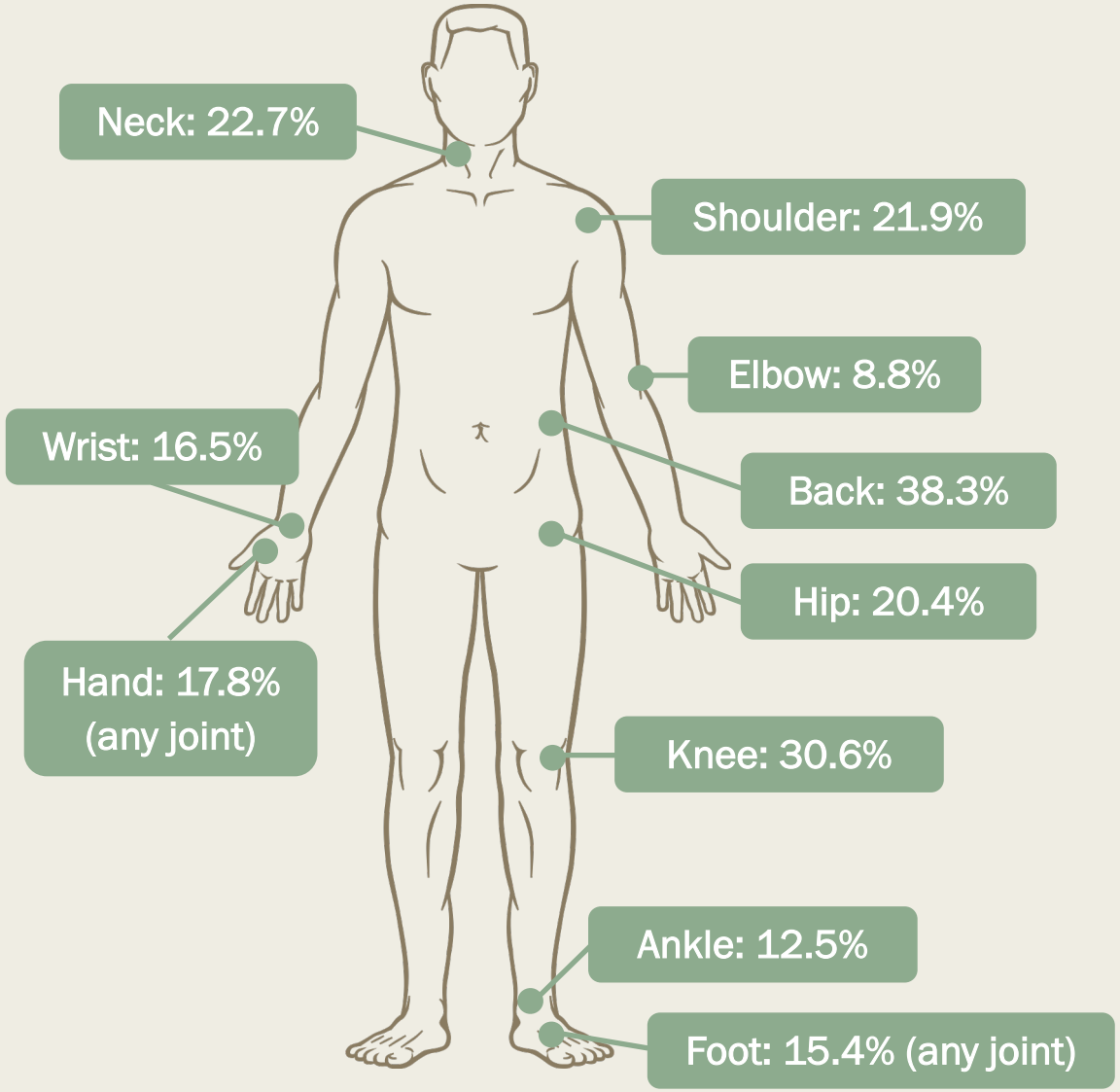
African Americans	Whites
52.4%	36.2%

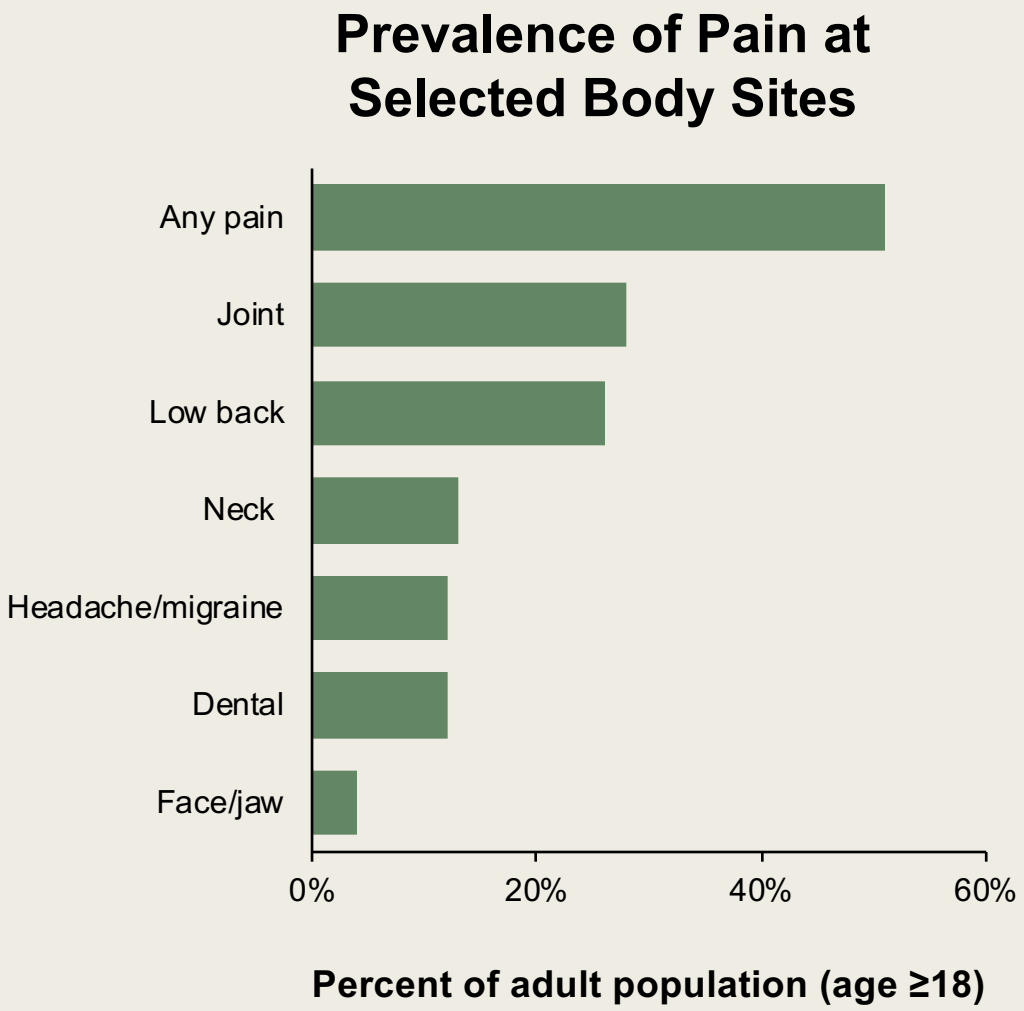
Incidence of OA



Oliveria, et al. *A&R* 1995

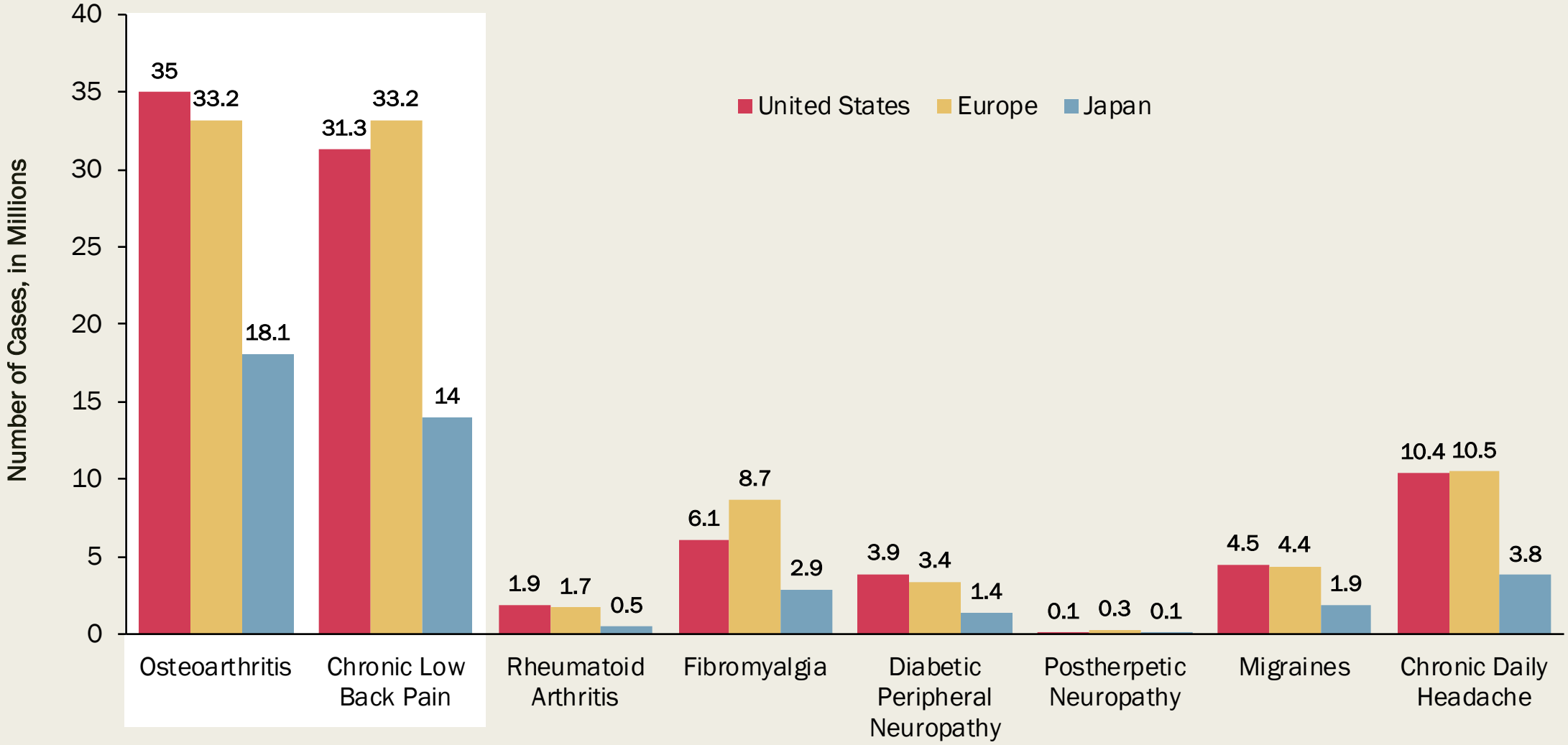
Pain in the Body





NHIS 2007

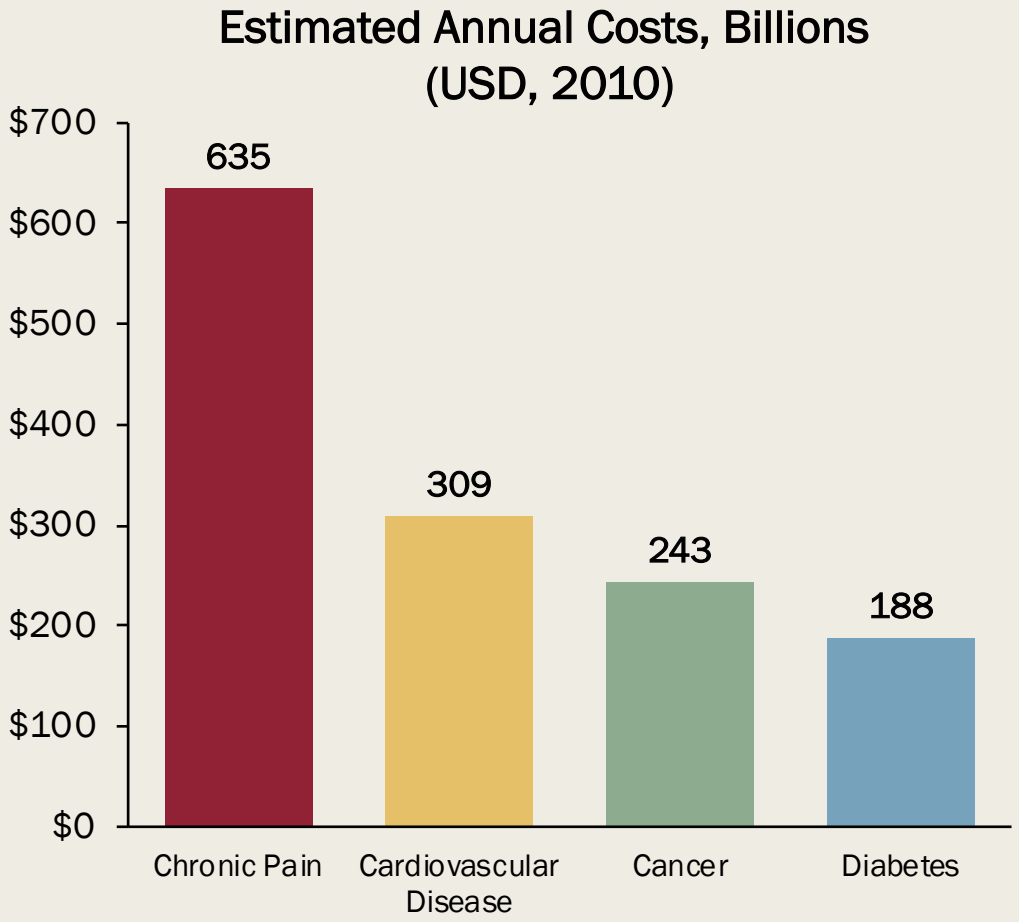
Chronic Pain: Most of it is OA and Back Pain

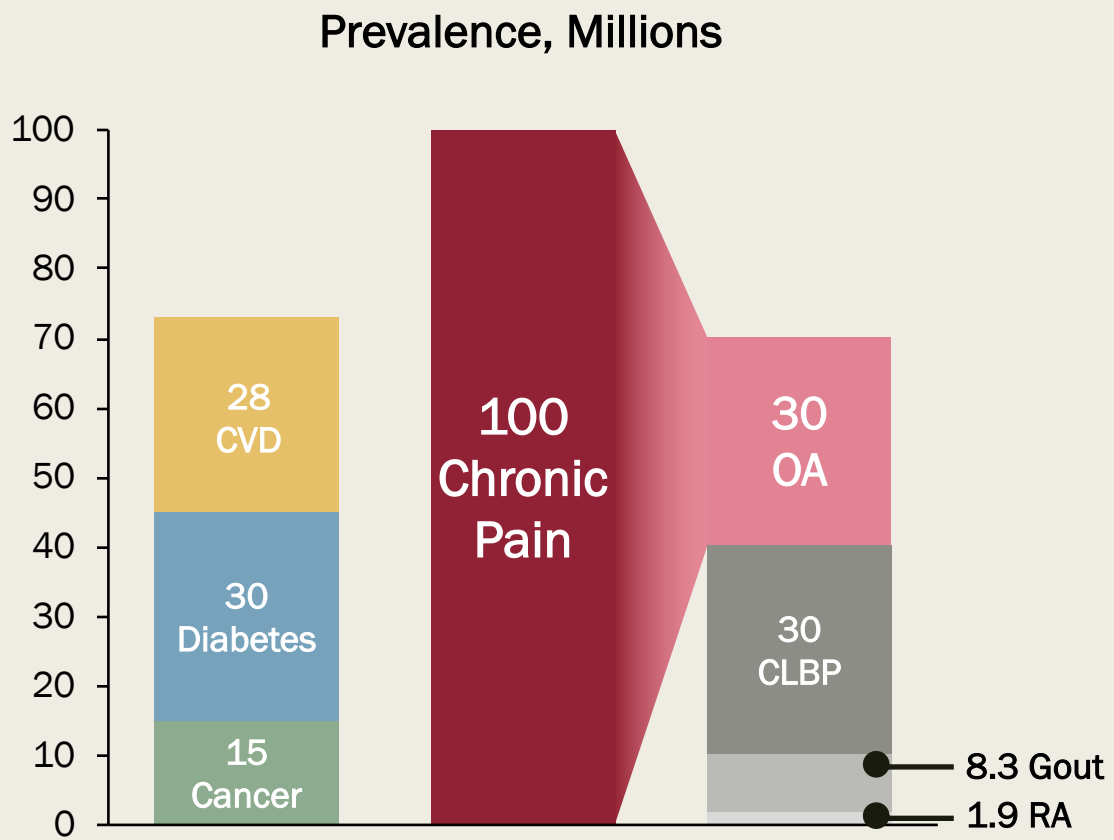


*Estimated projections.

Decision Resources. *Chronic Pain*. November 2011.

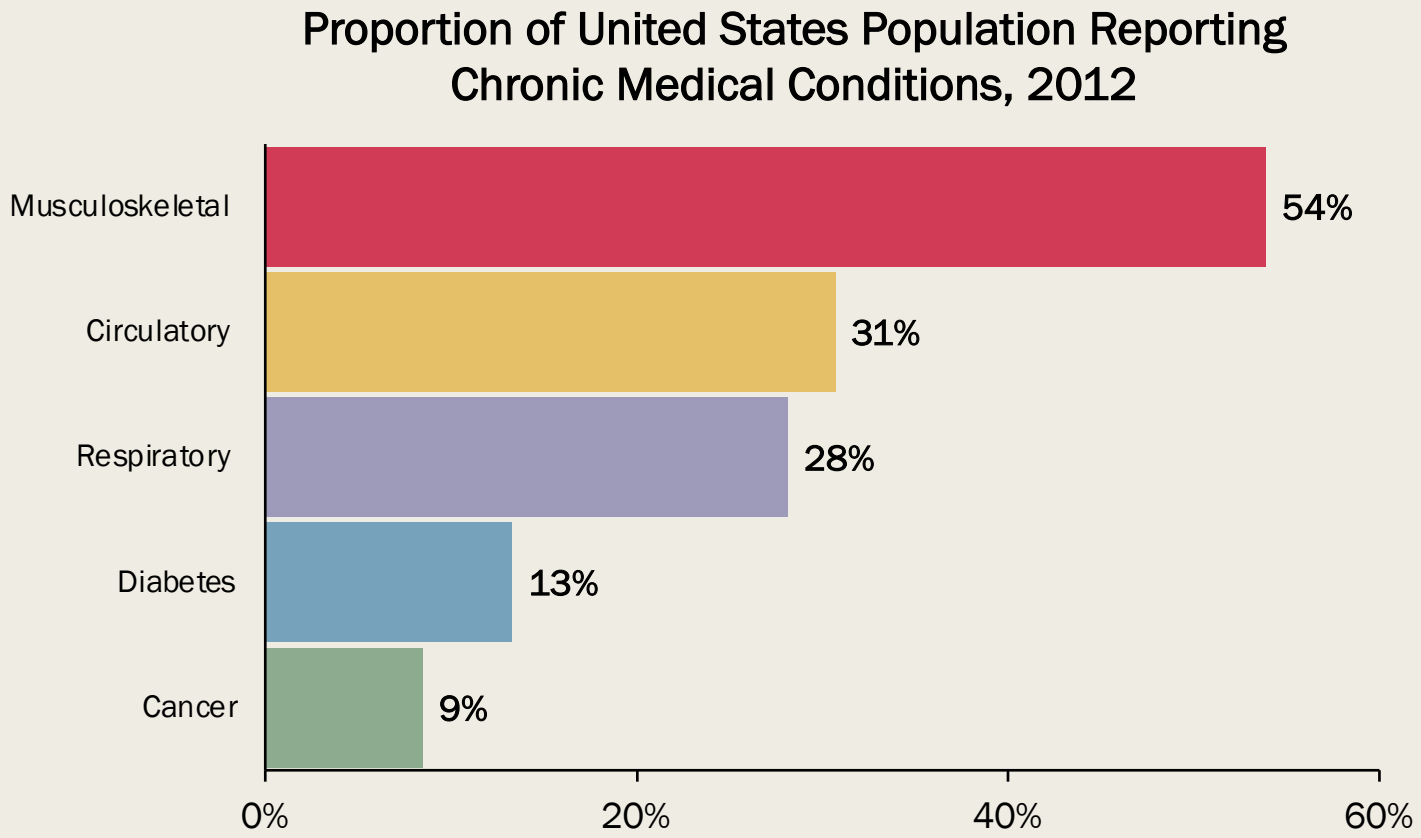
Chronic Pain is More Prevalent and Costly than other Common Diseases





Prevalence of MSK Diseases

1 in 2 (127 million) adults are affected, twice the rate of chronic heart and lung diseases



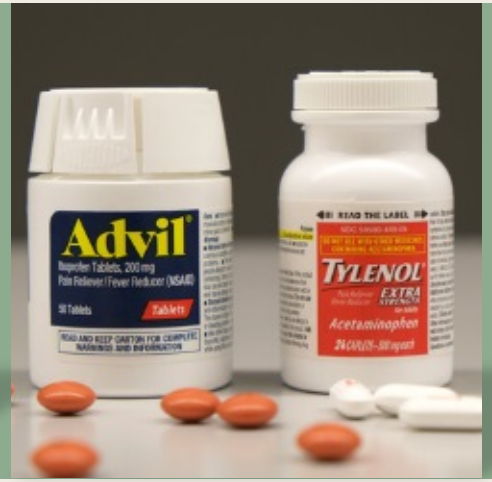
National Center for Health Statistics, National Health Interview Survey, 2012

Clinical Knee Osteoarthritis

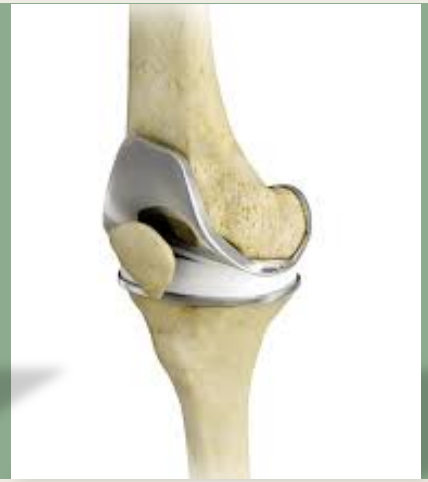
Pain is primary clinical symptom

People are living longer with knee OA

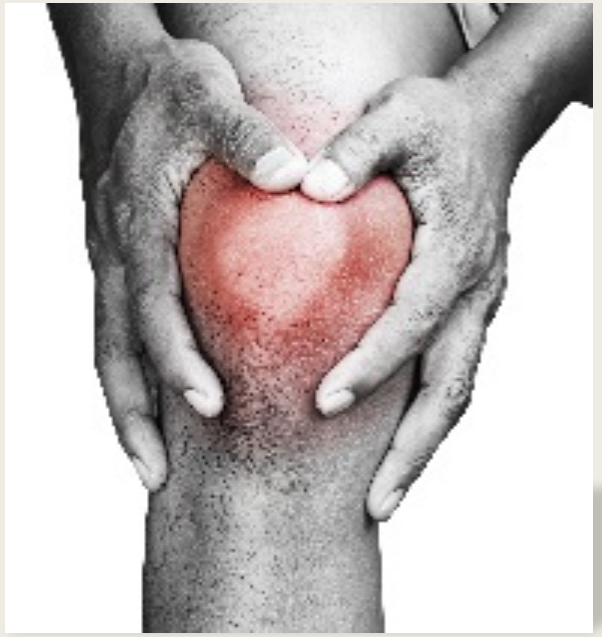
Limited management options



Joint replacement: “definitive treatment”



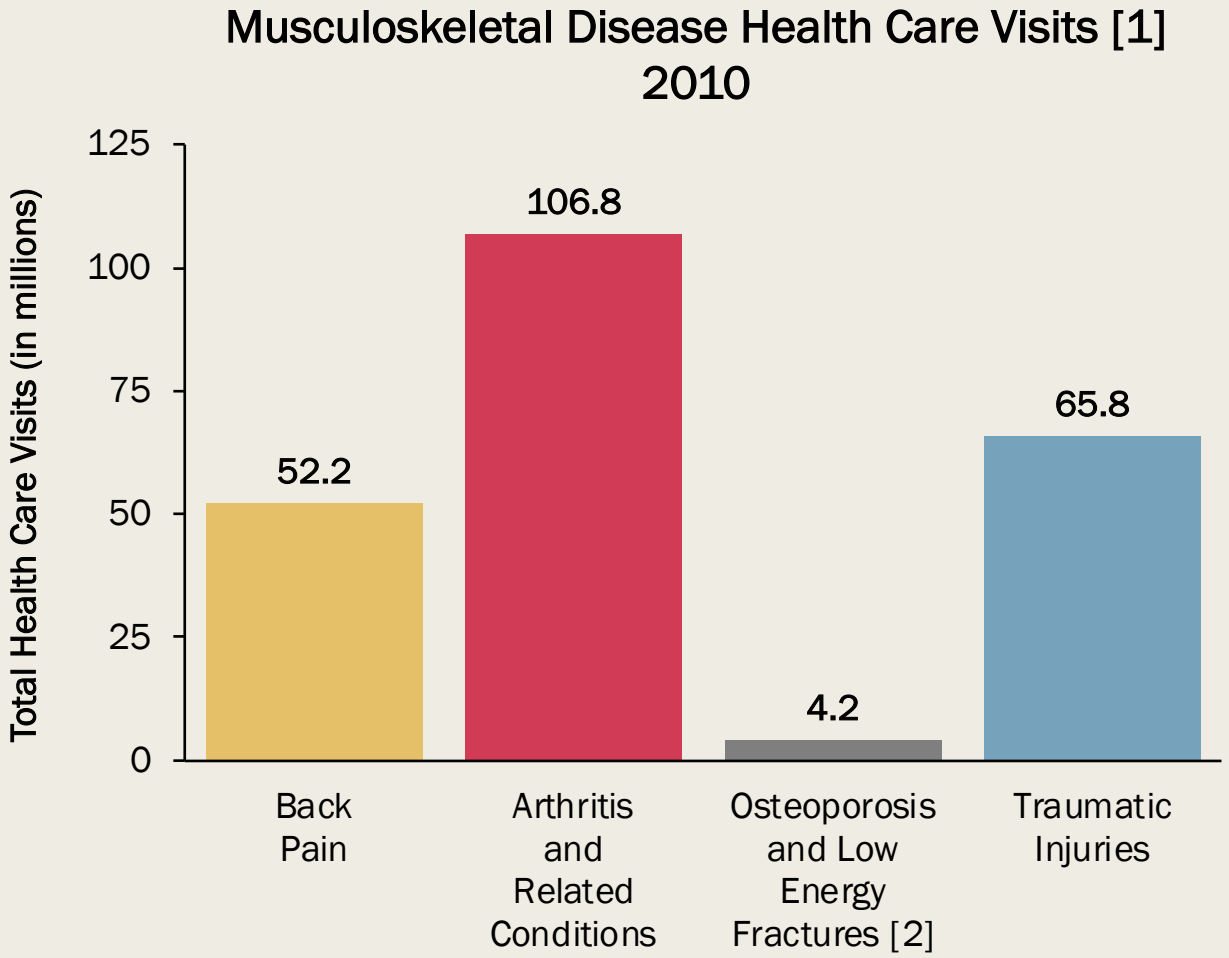
Osteoarthritis Clinical Course



Musculoskeletal diseases are now the 2nd most common cause of years lived with disability worldwide

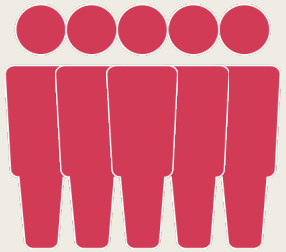
Burden to Health Care System

- Joint Pain and Arthropathies are #1 reason for outpatient visits (NACMS 2015)
- OA was 3rd most common reason for hospitalizations (NIS 2015)
  - *921,000 hospitalizations*
- Knee replacement surgery: 97% for knee OA
  - *3.5 million by 2030*



[1] Includes hospital discharges, ED, outpatient, and physician visits.
[2] Includes only hospital discharges and ED visits.
Source: National Center for Health Statistics, NHDS, NAMCS, 2010.

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

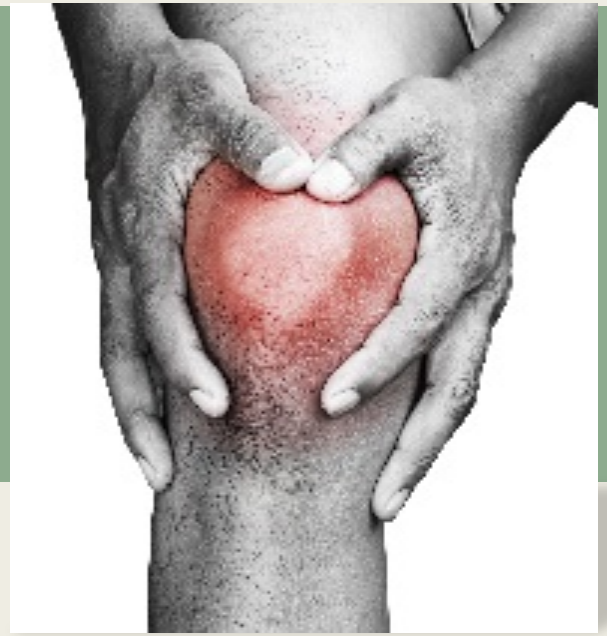
Disability

Quality of Life

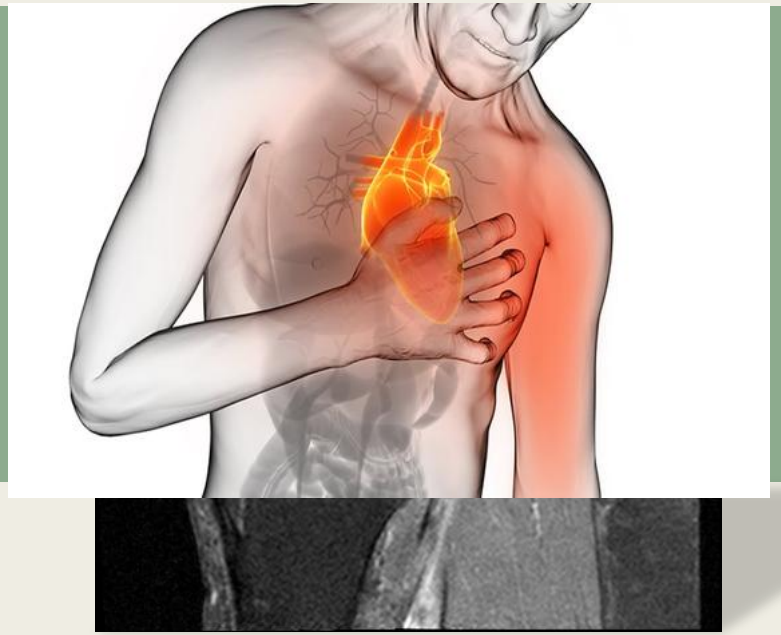
Opioid Epidemic

Urgent Need for More Options

Symptom management alone is insufficient



Need therapies to address the underlying disease pathology

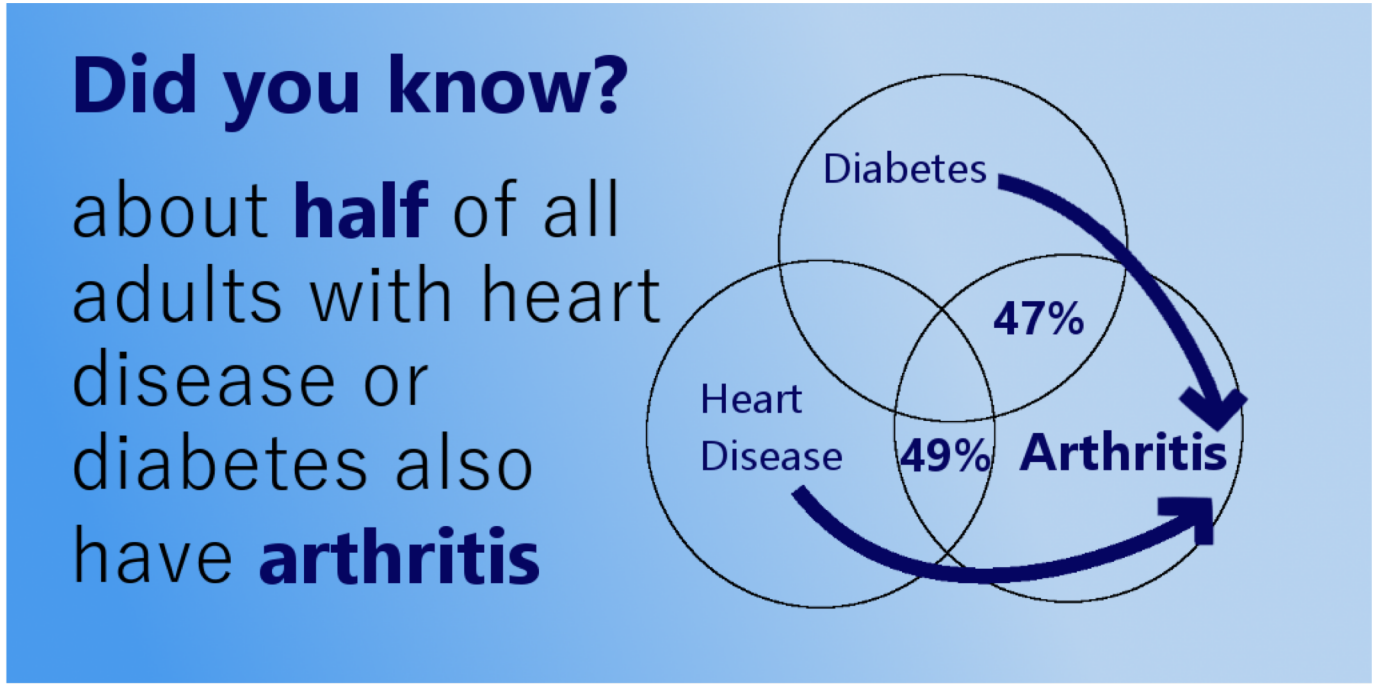


BURDEN OF OSTEOARTHRITIS: COMORBIDITY AND MORTALITY

Leigh F. Callahan, PhD
Mary Link Briggs Distinguished Professor of Medicine
Associate Director, Thurston Arthritis Research Center
University of North Carolina, Chapel Hill

OA and Comorbidity

- People with OA have on average 2.6 moderate-to-severe comorbidities
- 31% of people with OA have five or more other chronic conditions



Between 59 and 87% of people with OA have at least one other chronic condition, especially cardiovascular disease, diabetes and high blood pressure

Van Dijk; BMC Musc Disease 2008
Kadam, Ann Rheum Disease 2004

23.7 MILLION

US ADULTS ARE LIMITED BY ARTHRITIS IN THEIR DAILY ACTIVITIES

making it difficult to complete daily tasks like getting the mail, groceries and cleaning.

Over half of these adults are under age 65 (13.8 million).

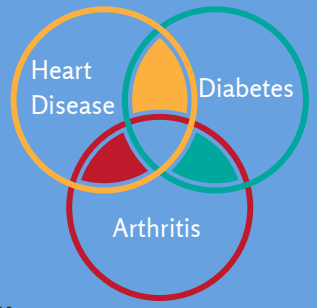
OA accounts for 2.4% of all years lived with disability (YLD)

10TH LEADING CONTRIBUTOR TO GLOBAL YLD

PAIN FROM ARTHRITIS IS ONE OF THE KEY BARRIERS TO MAINTAINING PHYSICAL ACTIVITY

Inactivity makes it harder to manage obesity, diabetes and heart disease.

59%-87% of adults with OA have at least one other significant chronic condition with the most common being cardiovascular disease, diabetes and hypertension.



Around 60% of adults with OA also have obesity.

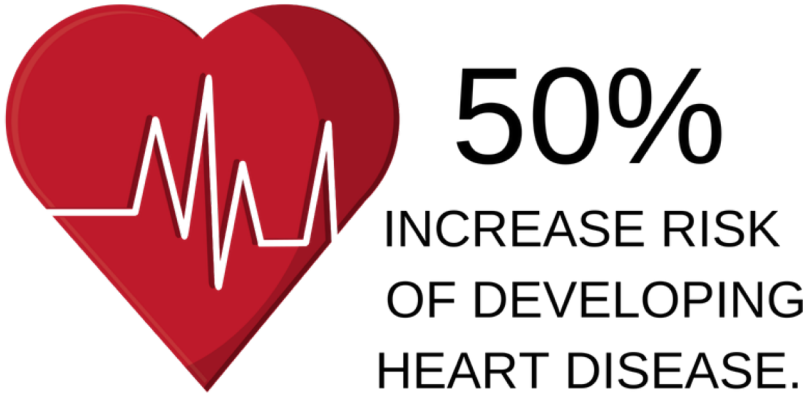
50% INCREASE RISK OF DEVELOPING HEART DISEASE.

MORTALITY IS HIGHER AMONG THOSE WITH OA THAN IN THE GENERAL POPULATION

OA and Comorbidity

- The presence of comorbidities in older adults with OA is associated with more pain and greater limitation in activities of daily living
- Comorbidities may have a significant impact on choice and tolerance of treatments

OA and Comorbidity: Cardiovascular Disease



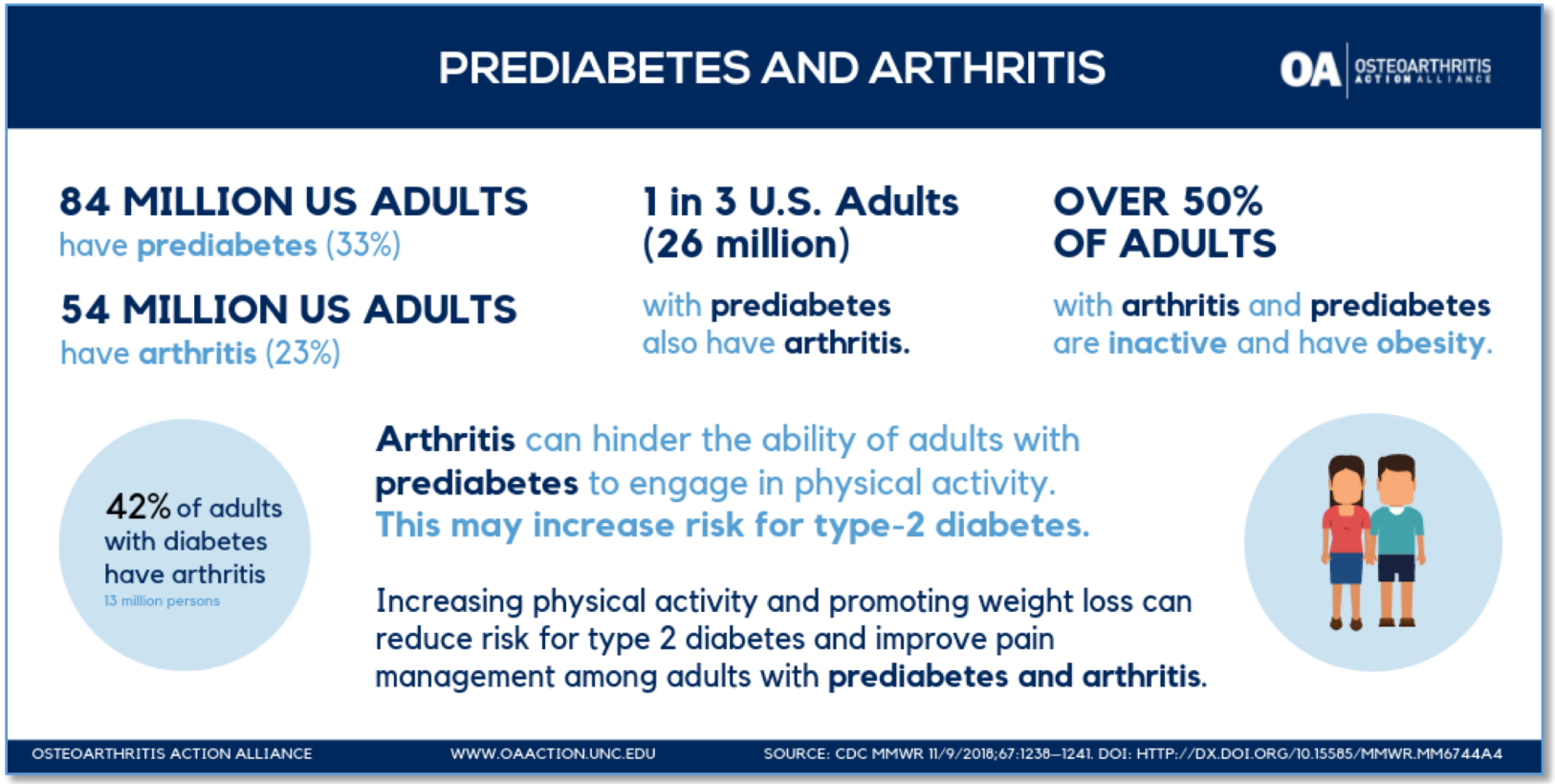
- CVD affects 1 in 3 American adults as the most common cause of death in the Western World
- 61% of people awaiting total knee replacement surgery have CVD
- In primary care, patients with hip and knee OA have twice the rate of CVD
- In people with established CVD, OA is associated with worse physical health and increased burden of symptoms

Mozaffarian, D; 2015
Calvet, J: 2015

OA and Comorbidity: Diabetes

- DM affects approximately 11% of American adults
- People with OA have a 32% increased risk of developing diabetes over a 12-year period
- OA and DM have shared risk factors: older age and obesity
- Walking difficulty is an independent risk factor for developing DM
- OA may impair the ability to exercise and lose weight

Lipscombe, L; 2017 Piva, S; 2015
Tuominen, U; 2007 Hawker, G; 2016
Rahman, M; 2014



OA and Comorbidities Conclusion

- Increased risk of comorbidities in patients with OA
- The comorbidities effect treatment choices
- Comorbidities in OA may be associated with poor outcomes

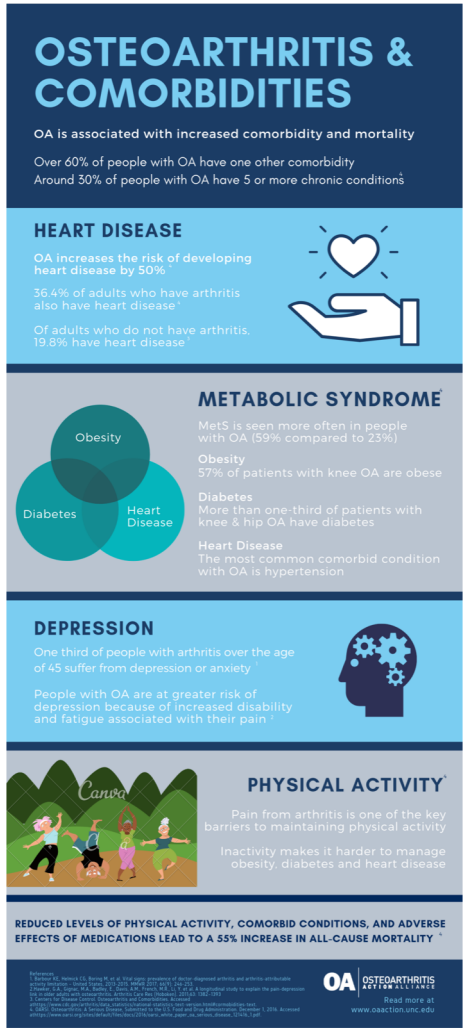


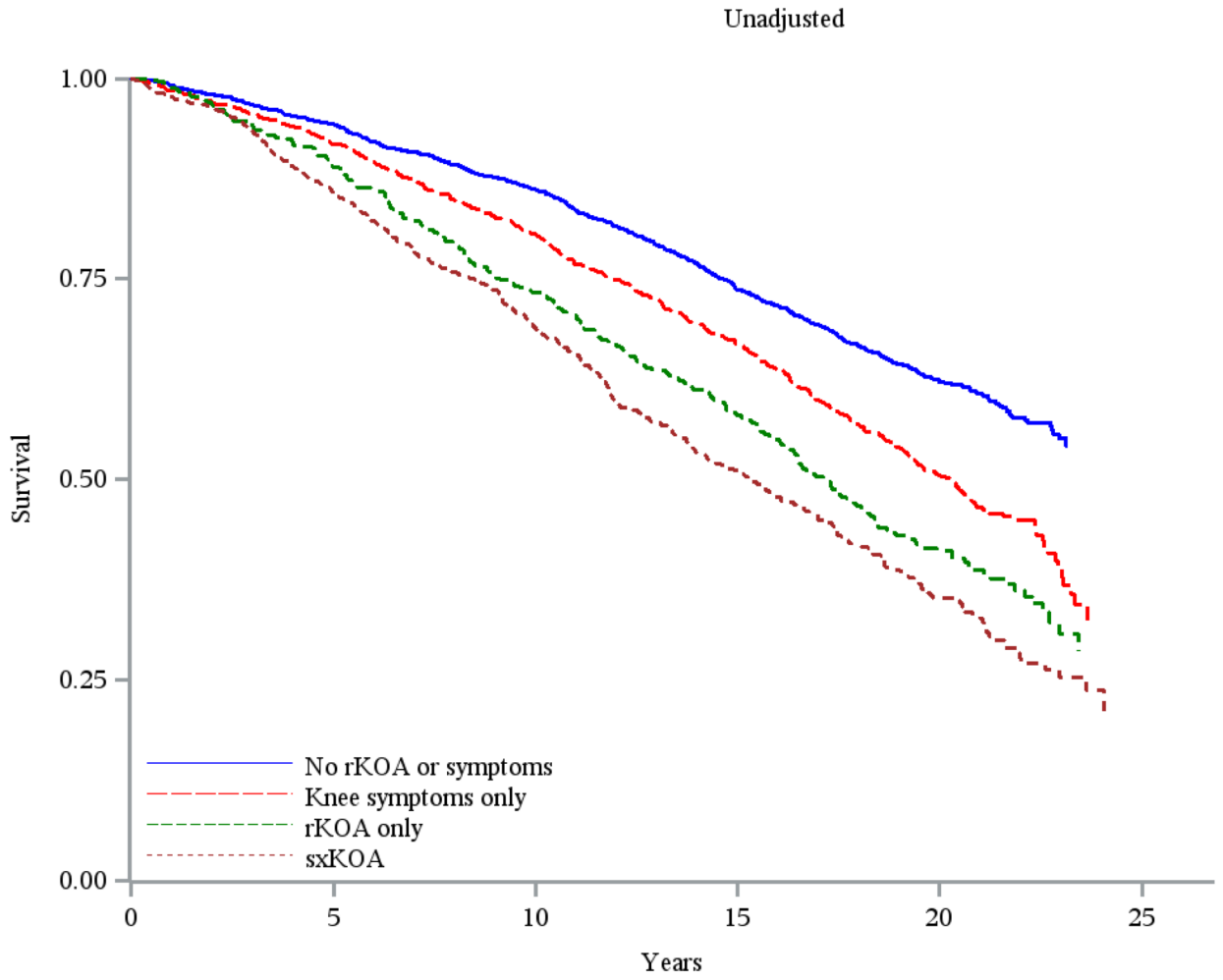
TABLE 2.
Meta-analyses of Osteoarthritis on Mortality

Year	Author	Number of studies	Definition of OA	Estimate of effect (HR, OR, or SMR)	
				All-cause mortality	CVD-specific mortality
2016	Veronese [15]	7 Any OA 4 CVD-specific any OA 3 Knee OA 2 Hip OA 3 Hand OA	Clinical and/or radiologic assessment of hand, hip and knee OA	Any OA: HR = 1.10 (0.97-1.25) Hip OA: HR = 1.08 (0.92-1.26) Knee OA: HR = 1.21 (0.82-1.78) Hand OA: HR = 0.91 (0.79-1.04)	Any OA: HR = 1.21 (1.10-1.34)
2016	Xing [17]	7 Symptomatic OA 6 Radiographic OA	Radiographic hand, knee, hip or spine; with or without symptoms	**Symptomatic OA** HR = 0.91 (0.68-1.23) **Radiographic OA** HR = 1.13 (0.95-1.35)	
2017	Han [16]	13 Any OA 5 CVD-specific any OA 6 Any rOA 5 Any sxOA 6 Knee OA 4 Hip OA 4 Hand OA	Hip, knee, spine, hand	Any OA: HR = 1.06 (0.88-1.28) Any rOA: HR = 1.24 (1.01-1.53) Any sxOA: HR = 0.95 (0.68-1.33) Knee OA: HR = 1.24 (0.87-1.76) Hip OA: HR = 1.06 (0.77-1.20) Hand OA: HR = 1.01 (0.89-1.14)	Any OA: HR = 1.36 (1.10-1.69)
IPD meta-analysis					
2016	PCCOA White Paper [18]	Knee sxOA: 3 US cohorts 2 ROW Hip pain: 2 US cohorts 2 ROW	Symptomatic knee rOA; hip pain	**Knee sxOA:** US: HR = 1.23 (1.07-1.42) ROW: HR = 0.72 (0.39-1.35) **Hip pain:** US: HR = 1.20 (1.04-1.37) ROW: HR = 0.99 (0.87-1.10)	

Note. CVD, cardiovascular disease; HR, hazard ratio; IPD, Individual Patient Data; OA, osteoarthritis; OR, odds ratio; rOA, radiographic osteoarthritis; sxOA, symptomatic osteoarthritis; SMR, standardized mortality ratio; ROW, rest-of-world.

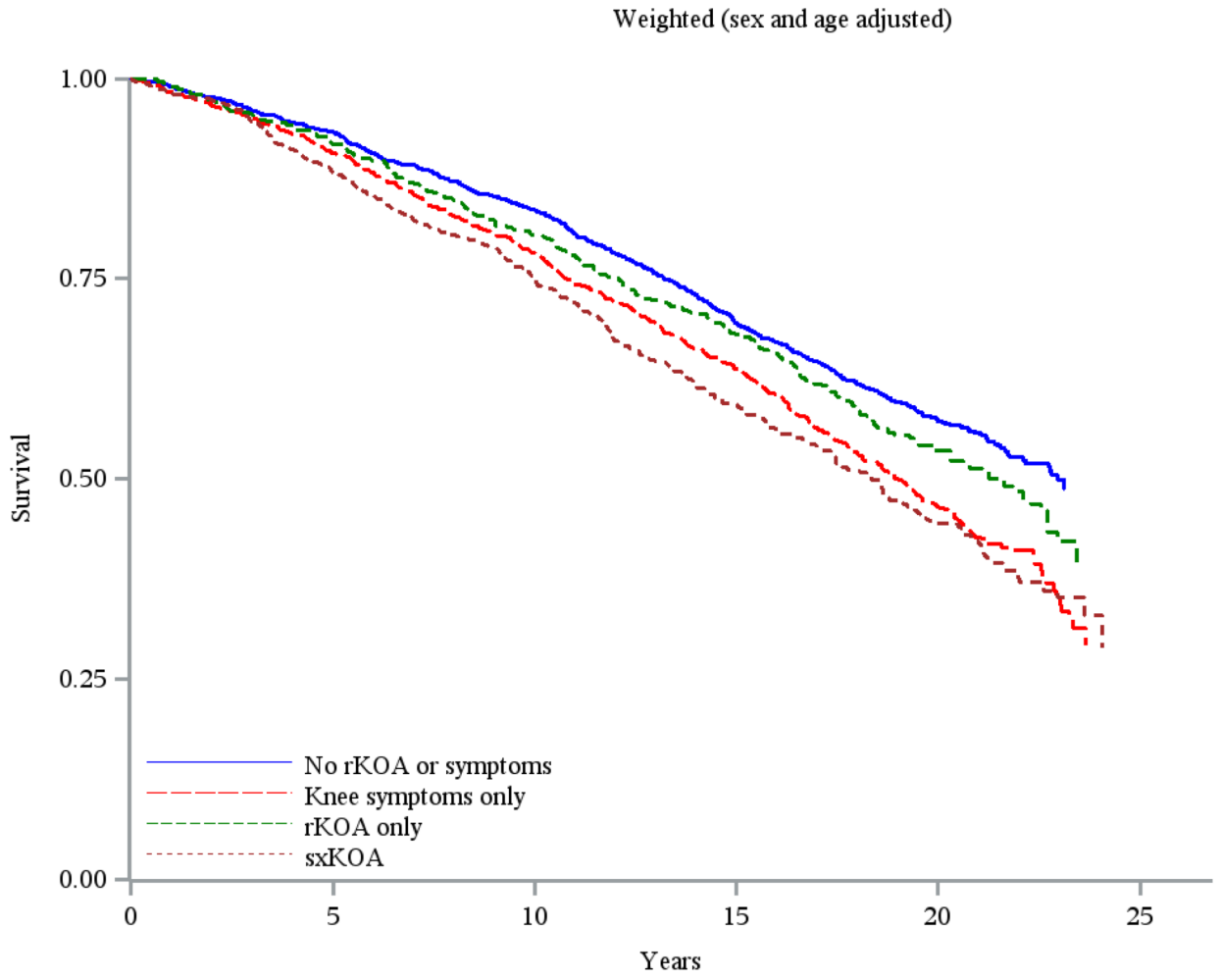
Cleveland and Callahan, NCJM 2017

Kaplan, Meier survival curves for mortality by baseline knee rOA and/or knee pain group



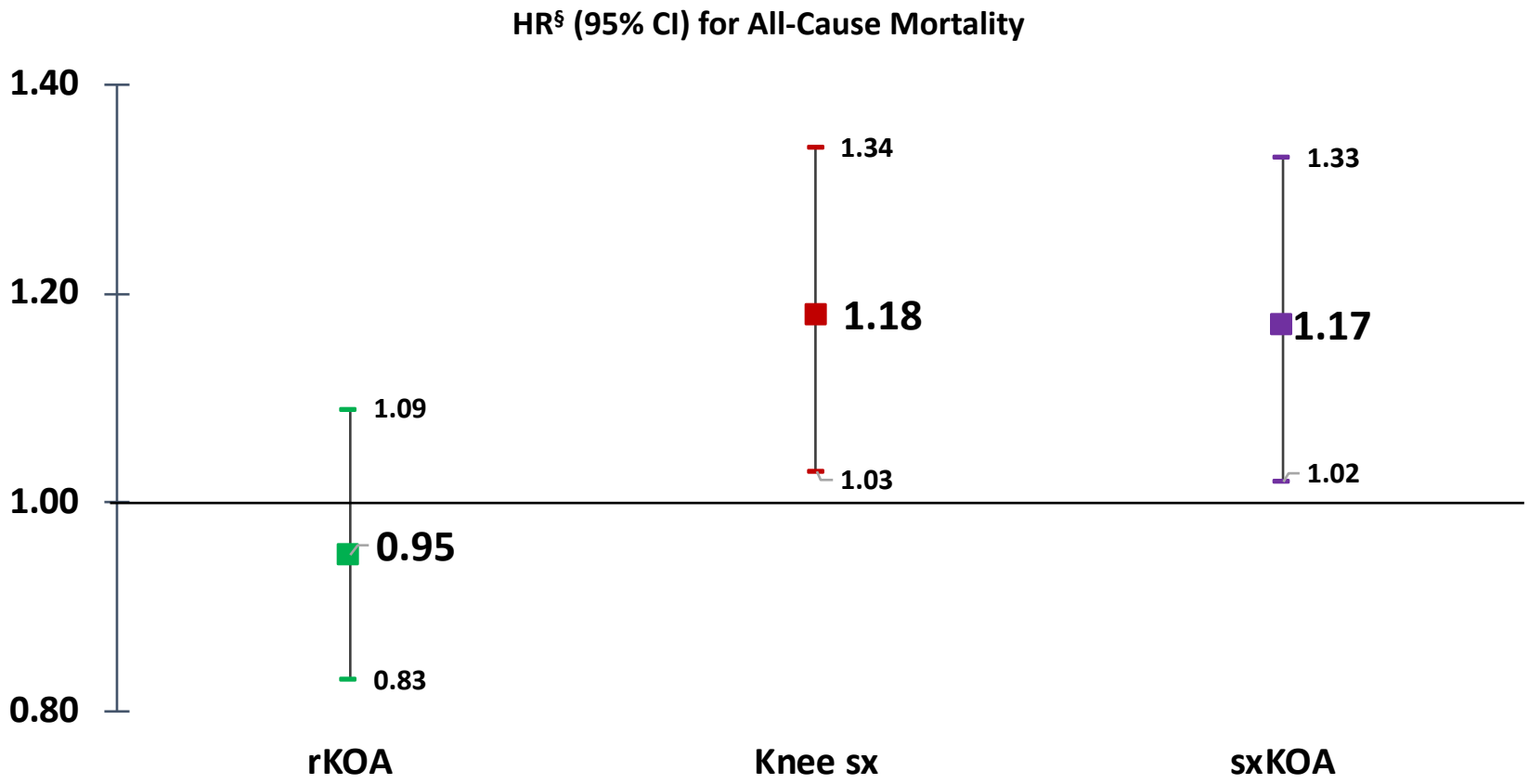
Cleveland, Alvarez, Schwartz, Losina, Renner, Jordan and Callahan, OAC: 27; 593-602, 2019

Kaplan, Meier survival curves for mortality by baseline knee rOA and/or knee pain group



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

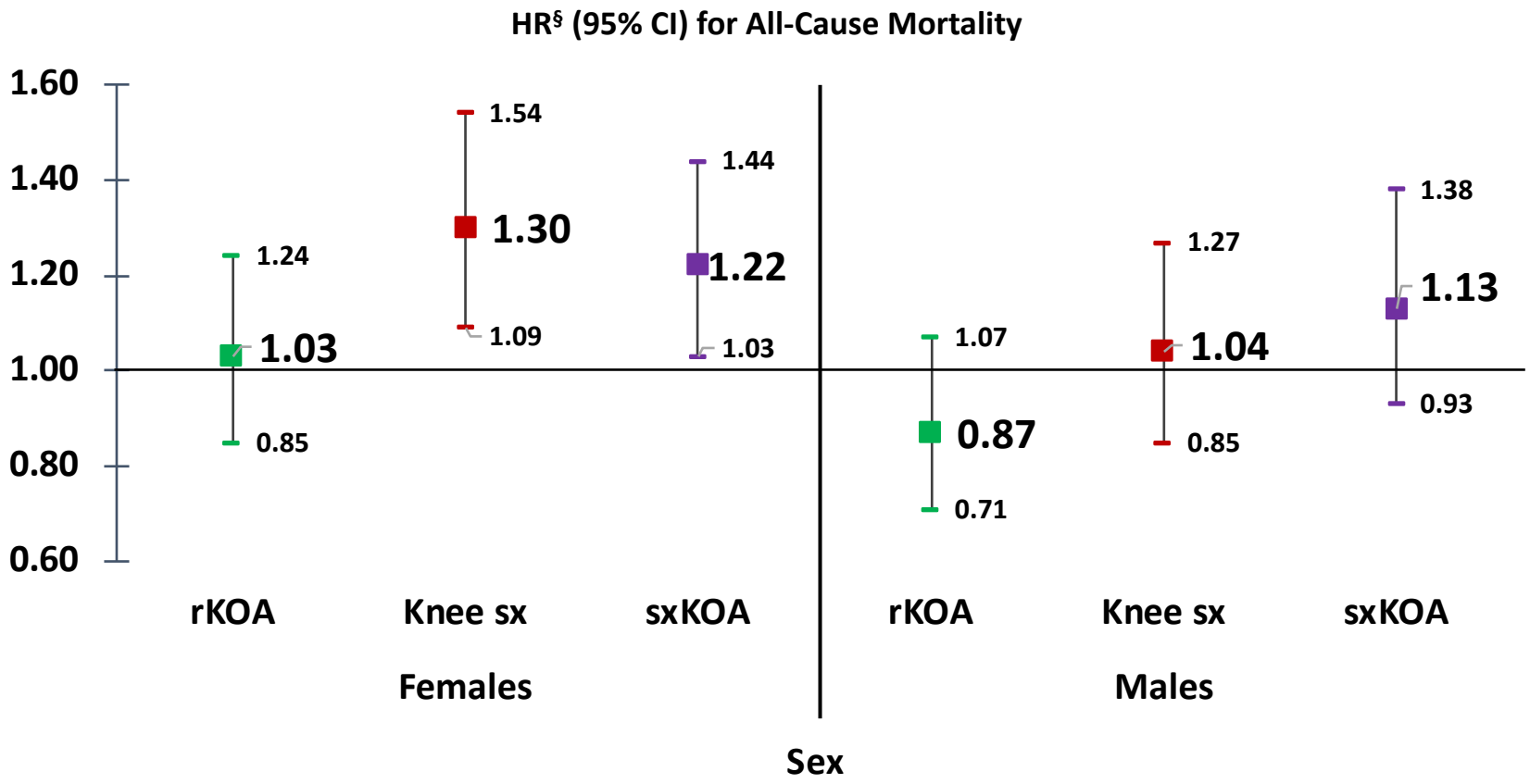
All-cause Mortality



§Adjusted for enrollment wave, age, sex, race, education, knee injury, cancer, non-steroidal anti-inflammatory drugs, hypertension, smoking, liver disease, alcohol use, depression, physical activity, BMI, diabetes, cardiovascular disease

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

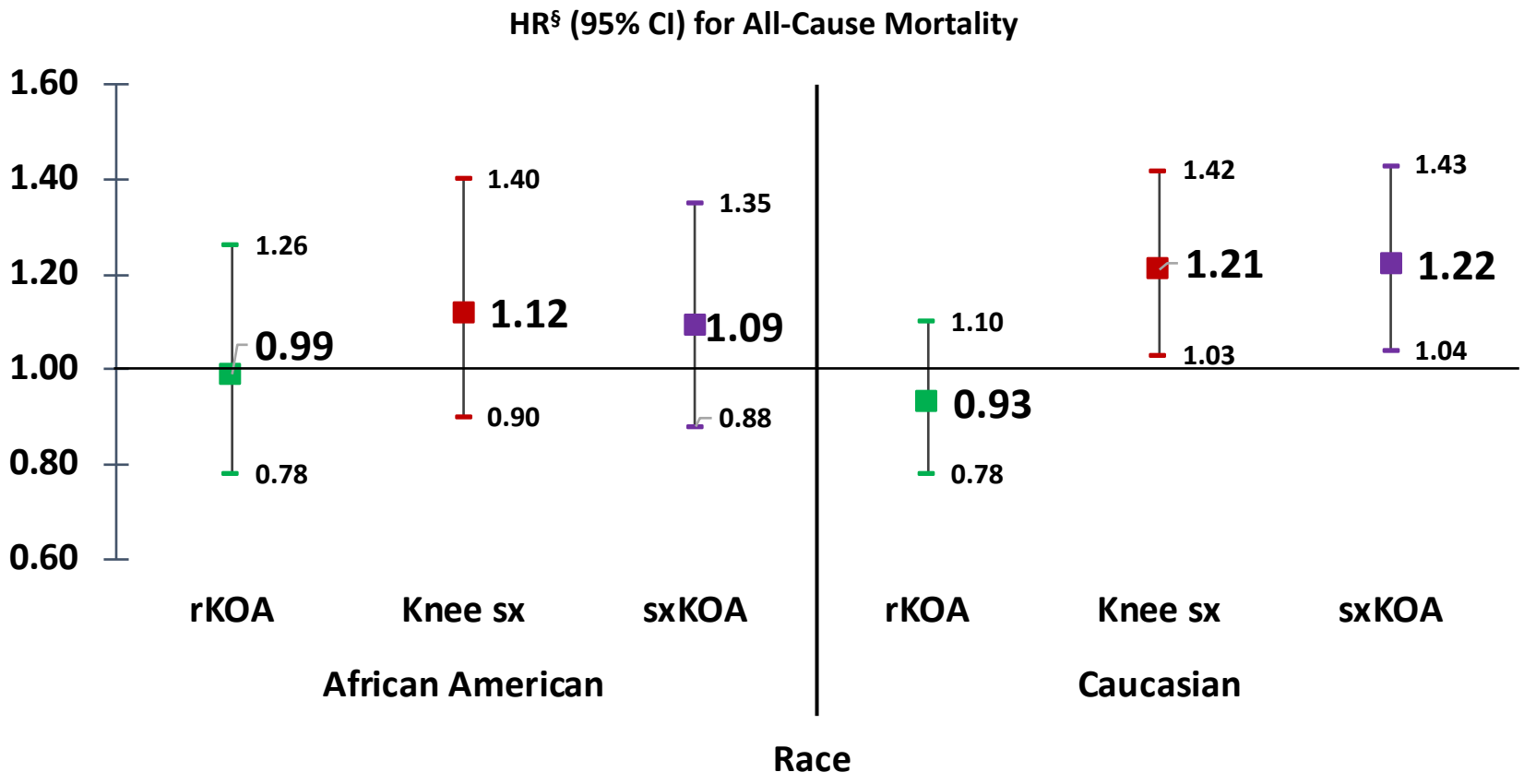
All-cause Mortality, Stratified by Sex



§Adjusted for enrollment wave, age, race, education, knee injury, cancer, non-steroidal anti-inflammatory drugs, hypertension, smoking, liver disease, alcohol use, depression, physical activity, BMI, diabetes, cardiovascular disease

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

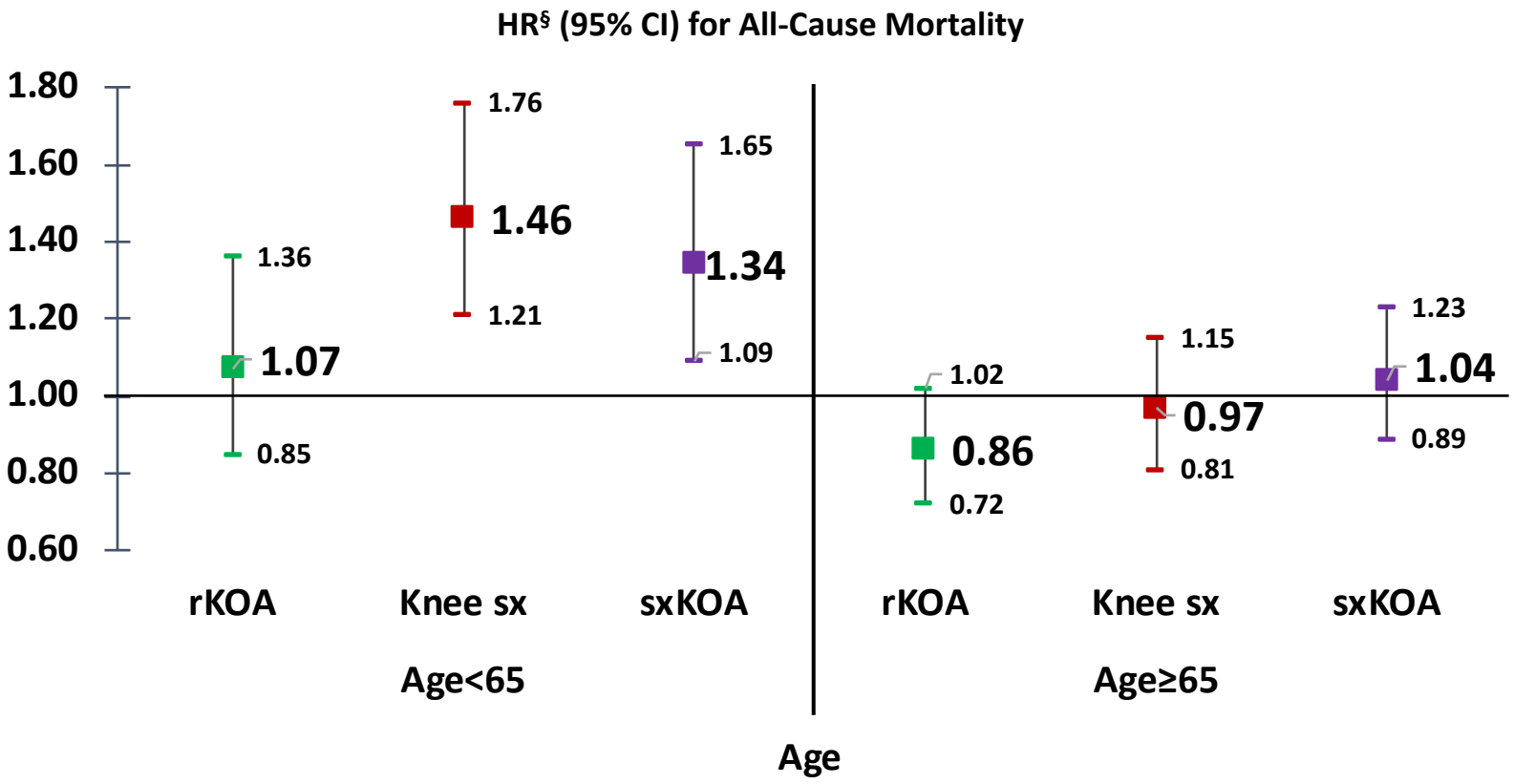
All-cause Mortality, Stratified by Race



§Adjusted for enrollment wave, age, sex, education, knee injury, cancer, non-steroidal anti-inflammatory drugs, hypertension, smoking, liver disease, alcohol use, depression, physical activity, BMI, diabetes, cardiovascular disease

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

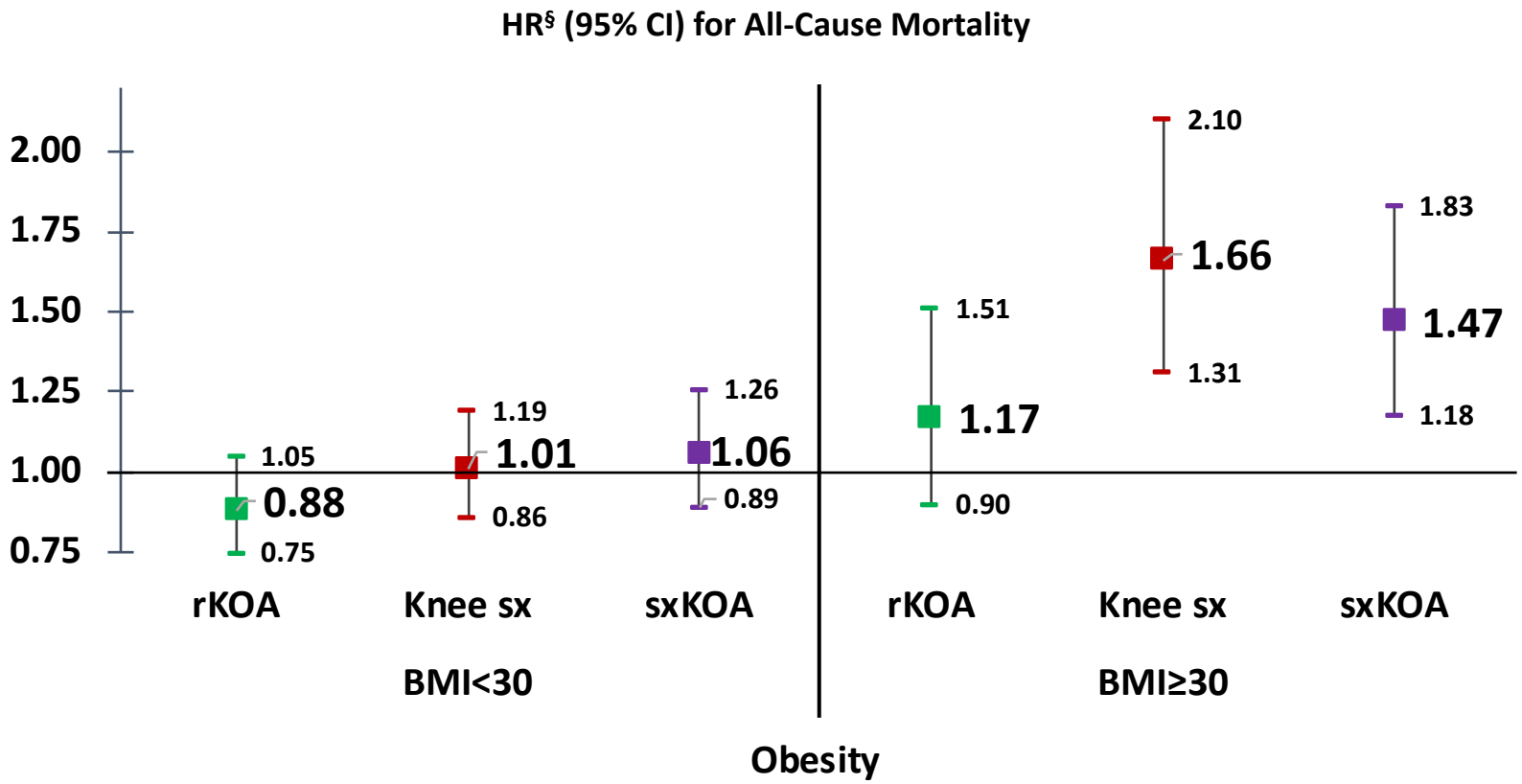
All-cause Mortality, Stratified by Age



§Adjusted for enrollment wave, age, sex, race, education, knee injury, cancer, non-steroidal anti-inflammatory drugs, hypertension, smoking, liver disease, alcohol use, depression, physical activity, BMI, diabetes, cardiovascular disease

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

All-cause Mortality, Stratified by Obesity



§Adjusted for enrollment wave, age, sex, race, education, knee injury, cancer, non-steroidal anti-inflammatory drugs, hypertension, smoking, liver disease, alcohol use, depression, physical activity, diabetes, cardiovascular disease

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

Cardiovascular Mortality in Patients with Knee OA

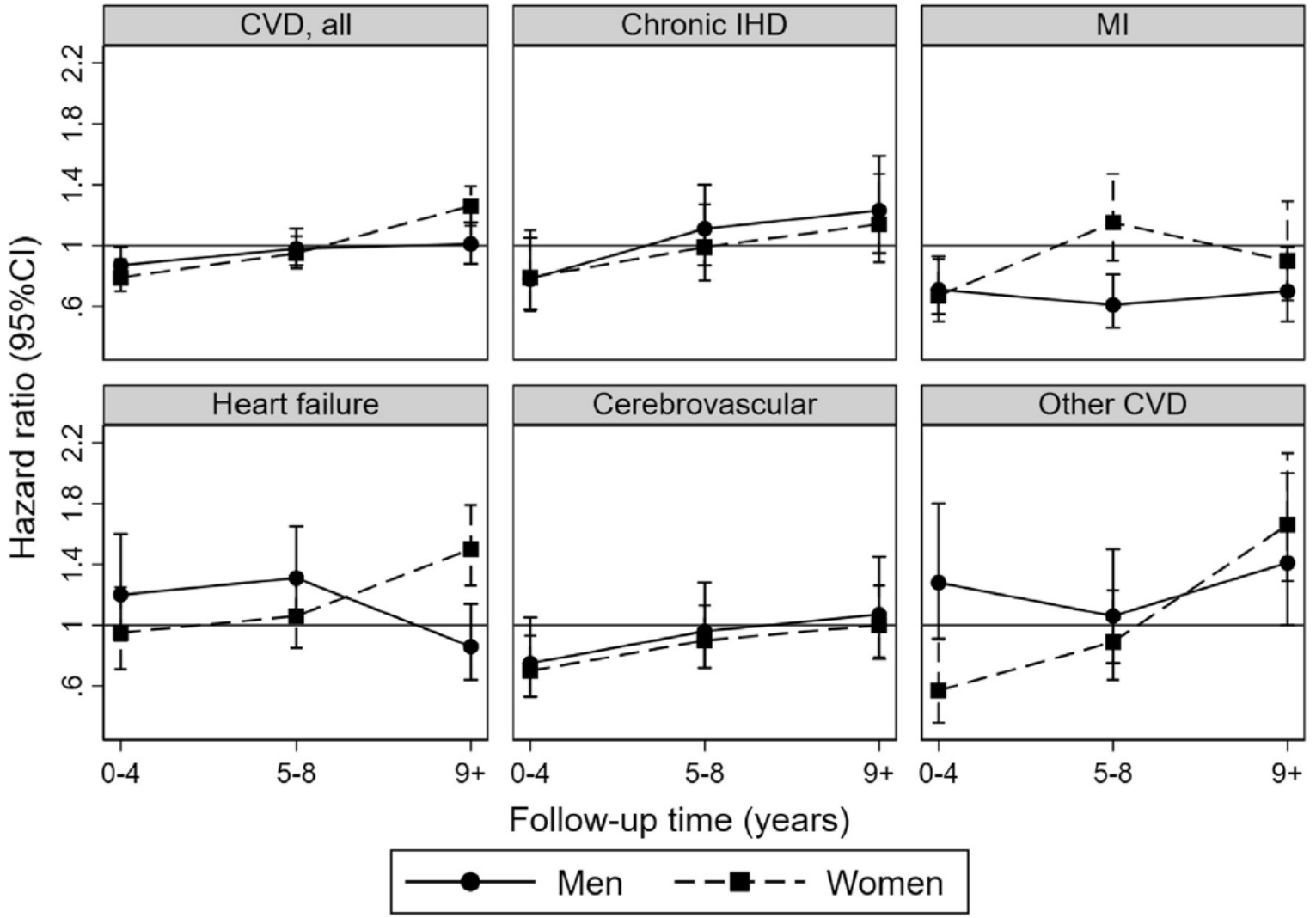


Fig. 1. Cardiovascular mortality in patients with knee OA as compared to the general population, by sex - adjusted hazard ratios with 95%CI from Cox regression model during 3 periods of the follow-up time. *CVD – cardiovascular diseases, IHD – ischemic heart diseases, MI – myocardial infarction.

Turkiewicz, Kiadaliri, Englund, OAC, 2019

Cardiovascular Mortality in Patients with Hip OA

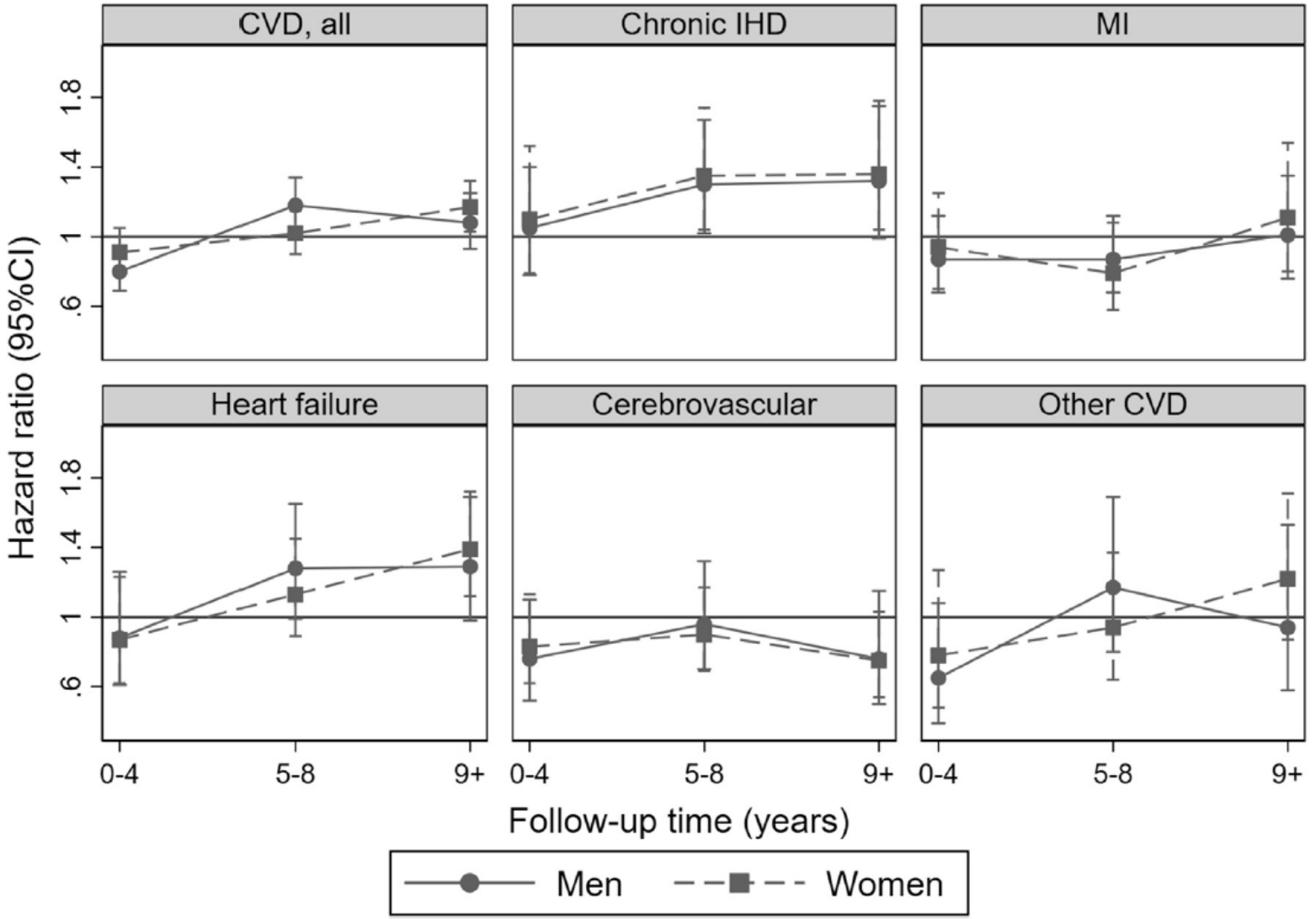


Fig. 2. Cardiovascular mortality in patients with hip OA as compared to the general population, by sex - adjusted hazard ratios with 95%CI from Cox regression model during 3 periods of the follow-up time. *CVD – cardiovascular diseases, IHD – ischemic heart diseases, MI – myocardial infarction.

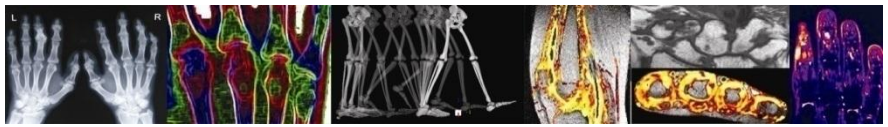
Turkiewicz, Kiadaliri, Englund, OAC, 2019

OA and Mortality Conclusion

- Increased all-cause and CVD mortality has been noted in individuals with knee pain and symptomatic knee OA compared to the general population
- Increased all-cause and CVD mortality has been noted in individuals with hip pain or hip OA compared to the general population
- Increased CVD mortality has been noted in individuals with any OA compared to the general population

OA Disease Progression: Current status of imaging biomarkers

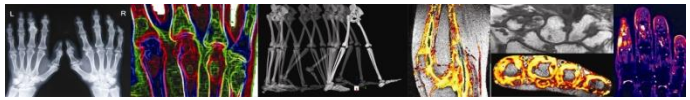
Philip Conaghan MBBS PhD FRACP FRCP
Director, Leeds Institute of Rheumatic & Musculoskeletal Disease, University of Leeds
Deputy Director, NIHR Leeds Biomedical Research Centre
Leeds, United Kingdom



Disclosures

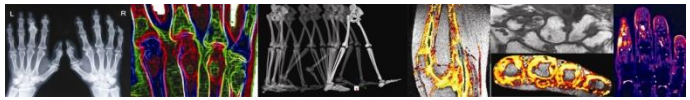
Advisory boards or speakers bureaus for:

- AbbVie, BMS, EMD Serono, Flexion, Galapagos, GSK, Lilly, Novartis, Pfizer, Samumed

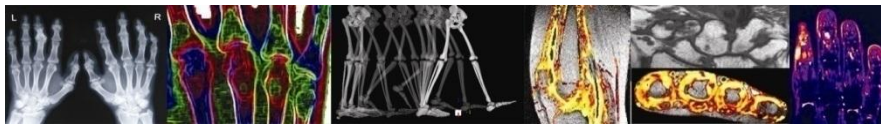


This presentation

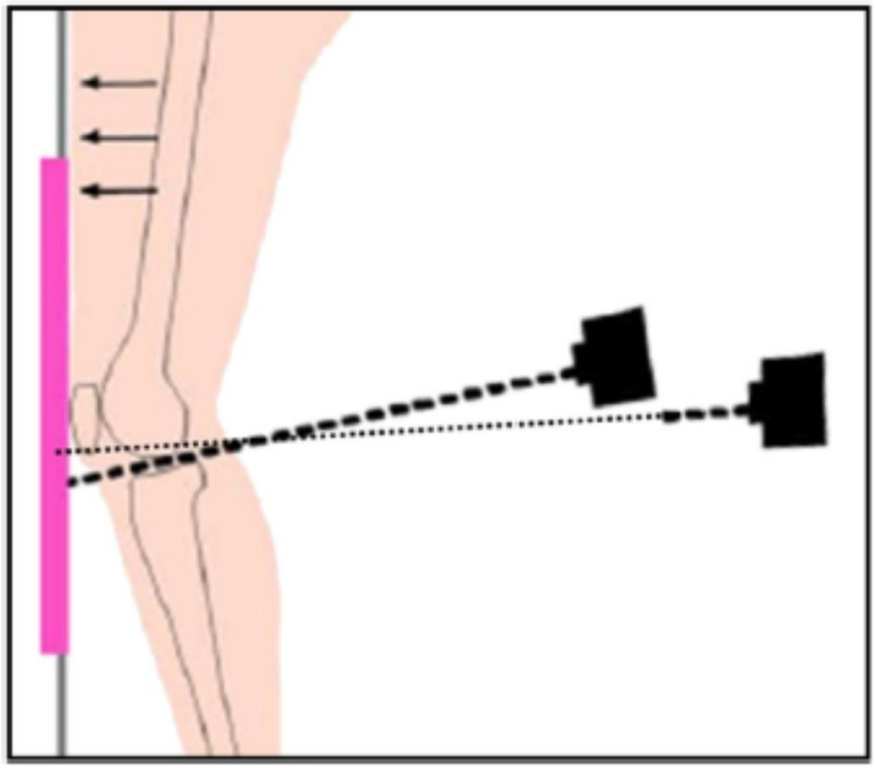
- Focus on knee OA
- Focus on most advanced MRI quantitative endpoints: cartilage thickness, bone shape (not detailed review), especially predictive validity for patient important outcomes
- Heterogenous disease but….understanding of multiple tissue relationships has got better
- Structure-pain understanding is improving
- Suggest a new way of thinking about OA progression based on imaging of structure

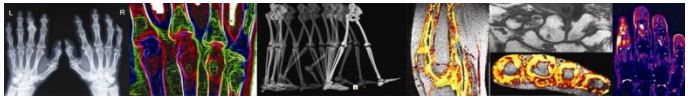


X-ray lessons



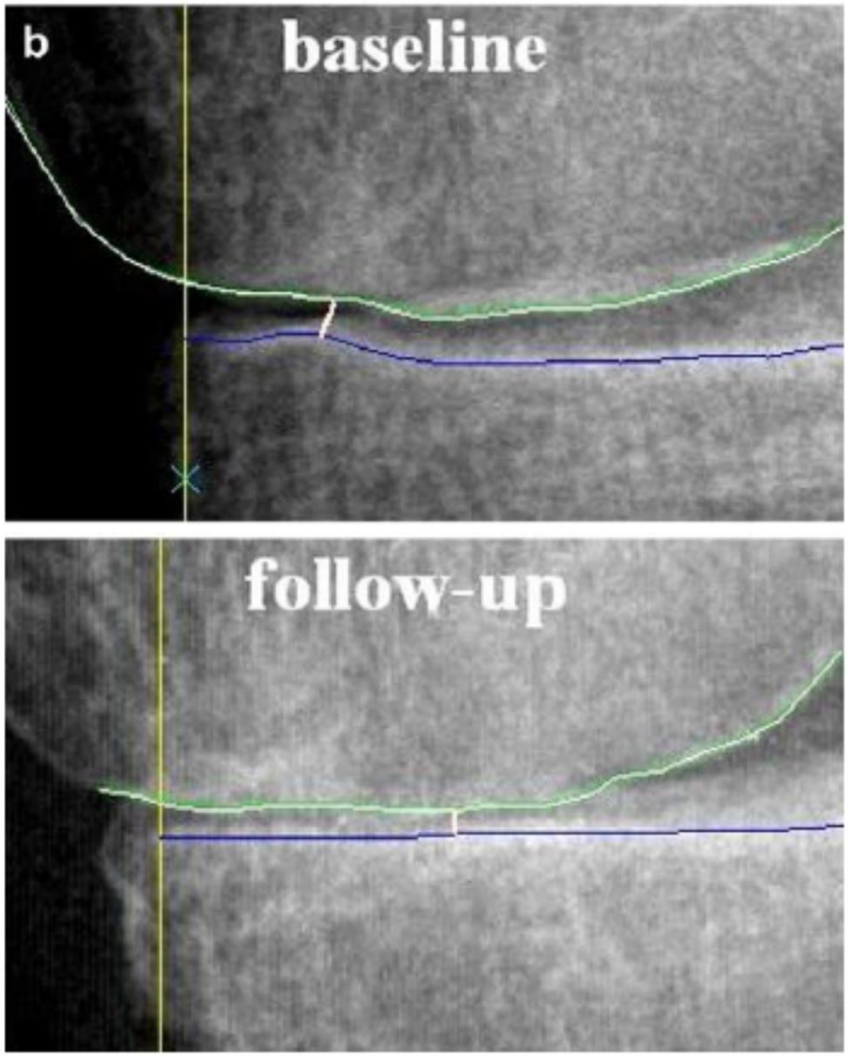
X-ray positioning

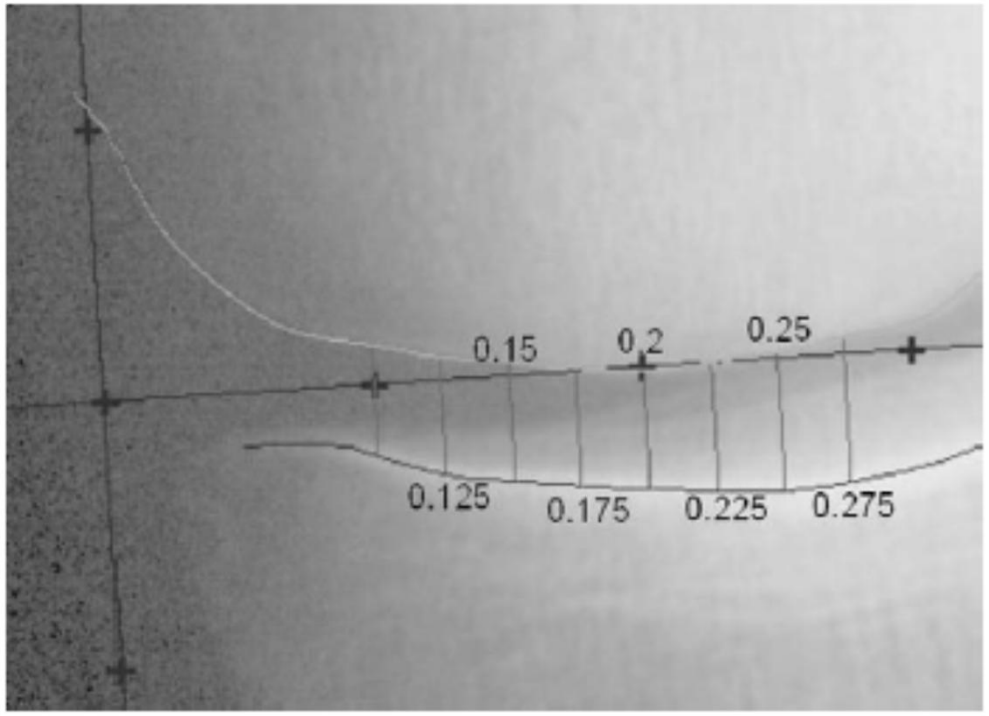


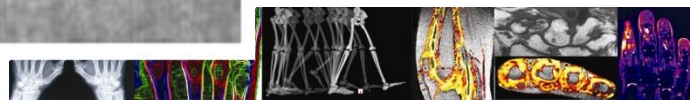


Hunter DJ et al
Osteoarthritis Cartilage 2015

Location specific JSW







Neumann G et al
Osteoarthritis Cartilage 2009

Osteoarthritis and Cartilage 19 (2011) 606–610

Osteoarthritis and Cartilage

Summary and recommendations of the OARSI FDA osteoarthritis Assessment of Structural Change Working Group

P.G. Conaghan †‡*, D.J. Hunter §‖, J.F. Maillefert ¶#††, W.M. Reichmann ‡‡§§, E. Losina ‡‡§§

Osteoarthritis and Cartilage 23 (2015) 698–715

Osteoarthritis and Cartilage

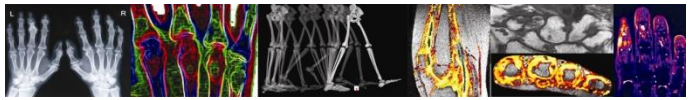
Review

OARSI Clinical Trials Recommendations: Knee imaging in clinical trials in osteoarthritis

D.J. Hunter †‡*, R.D. Altman §, F. Cicuttini ‖, M.D. Crema ¶#, J. Duryea ††, F. Eckstein ‡‡§§, A. Guermazi ¶, R. Kijowski ‖‖, T.M. Link ¶¶, J. Martel-Pelletier ##, C.G. Miller †††, T.J. Mosher ‡‡‡ §§§, R.E. Ochoa-Albíztegui ‖‖‖, J.-P. Pelletier ##, C. Peterfy ¶¶¶, J.-P. Raynauld ##, F.W. Roemer ¶###, S.M. Totterman ††††, G.E. Gold ‡‡‡‡ §§§§ ‖‖‖‖‖

OARSI OA Knee Trial Recommendations: X-rays

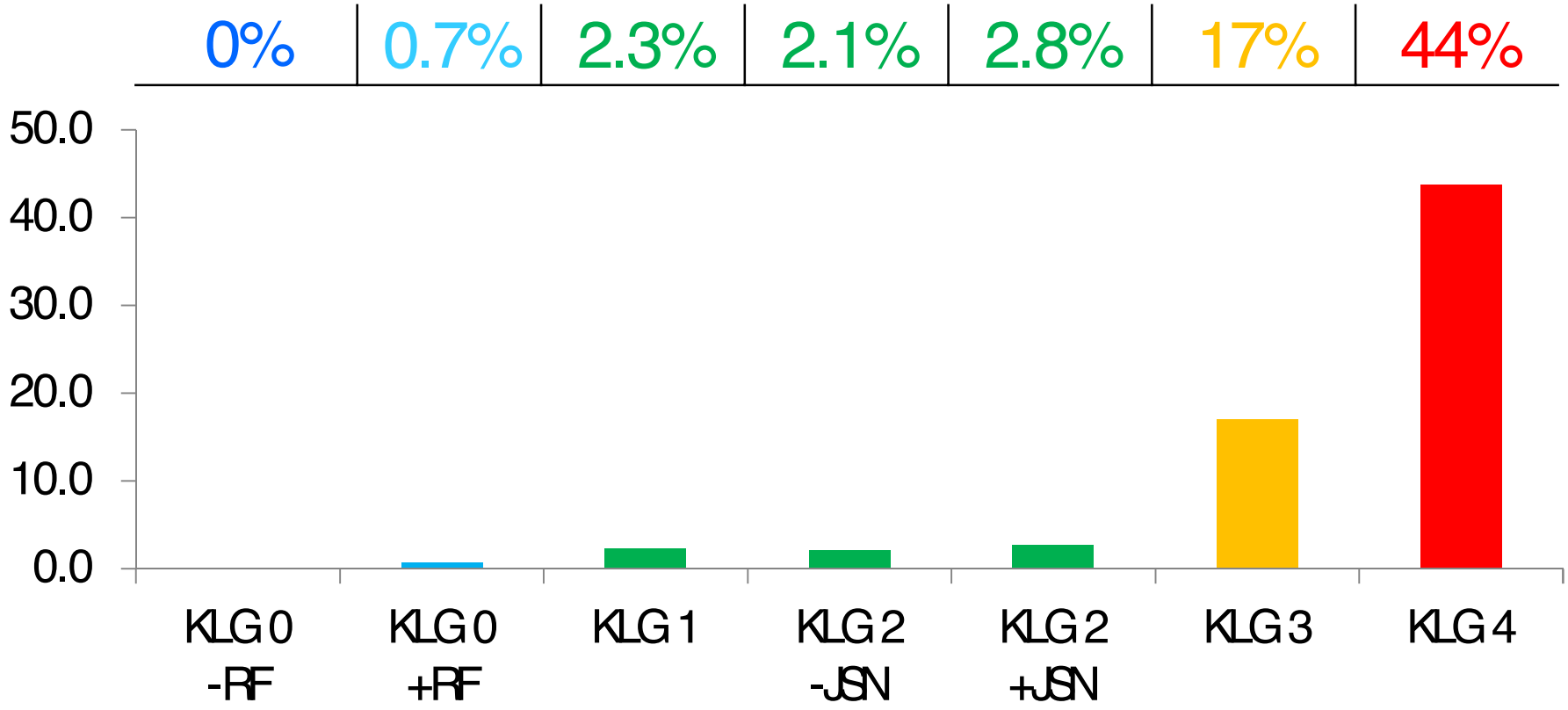
- The use of fluoroscopic positioning and semi-flexed views improves responsiveness, although … access to fluoroscopic facilities is restricted
- Studies will generally need to be at least 12 and more likely 24 months duration
- The IMD of the tibial plateau should not change between visits, and ideally should be no more than 1.5 mm
- It is advisable to “enrich” a knee OA study population to increase the rate of JSW loss
- Automated [quantitative] methods for assessing parameters of JSW offer promise of improved.. responsiveness

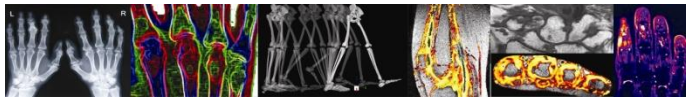


Hunter DJ et al
Osteoarthritis Cartilage 2015

Incident Knee Replacement by X-ray Status

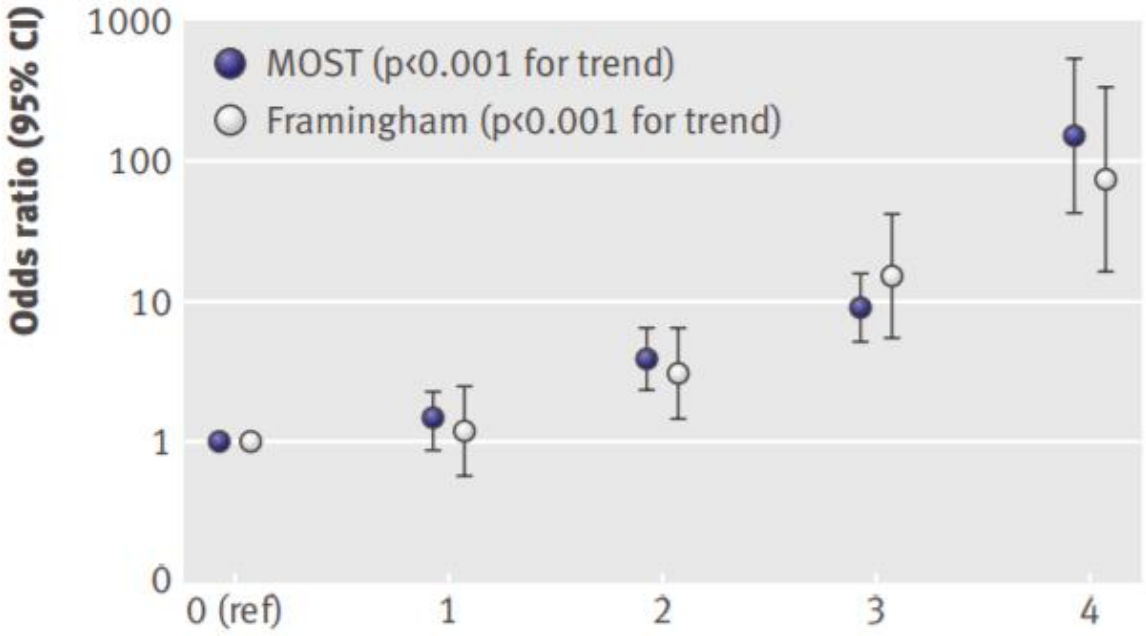
- 8201 OAI knees, 9 yr follow up, 436 with KR





Eckstein F. OARSI 2019
[Oral presentation]

Pain predicted by X-ray KL grade



MOST (n=696)					
Case	210	96	95	177	108
Control	300	162	96	119	19
Framingham (n=336)					
Case	162	28	51	61	34
Control	205	40	54	32	5

- MOST and Framingham
- Within-person knee-matched design, eliminating between-person differences
- Strong relationship between KL grade and severity of pain

Neogi T et al.
BMJ 2009

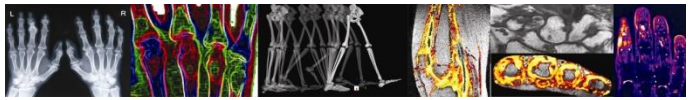
OA Imaging Biomarkers: X-rays

Strengths:

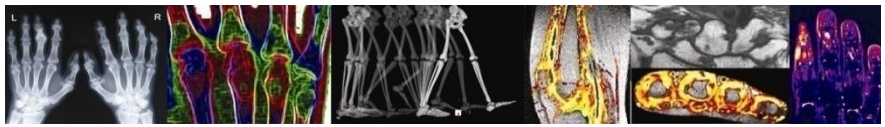
- Cheap, feasible
- Measure a broad OA construct involving JSW (surrogate for cartilage) and osteophytes
- Provided our understanding of OA epidemiology

Weaknesses:

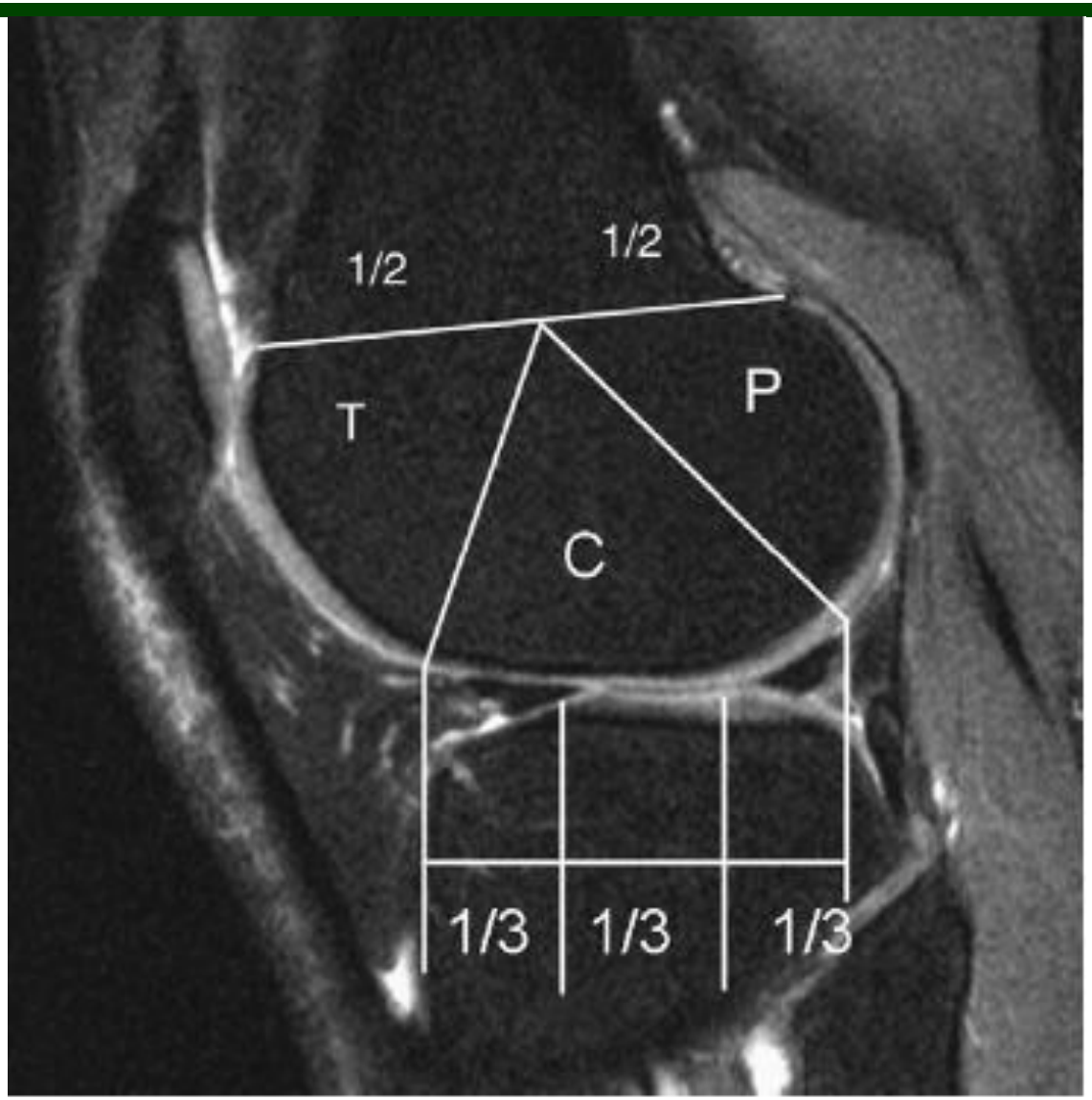
- JSW is a very ‘noisy’ measure; osteophytes disappear if knee rotates slightly
- Needs large, long duration trials
- Poor relationship to symptoms at individual level



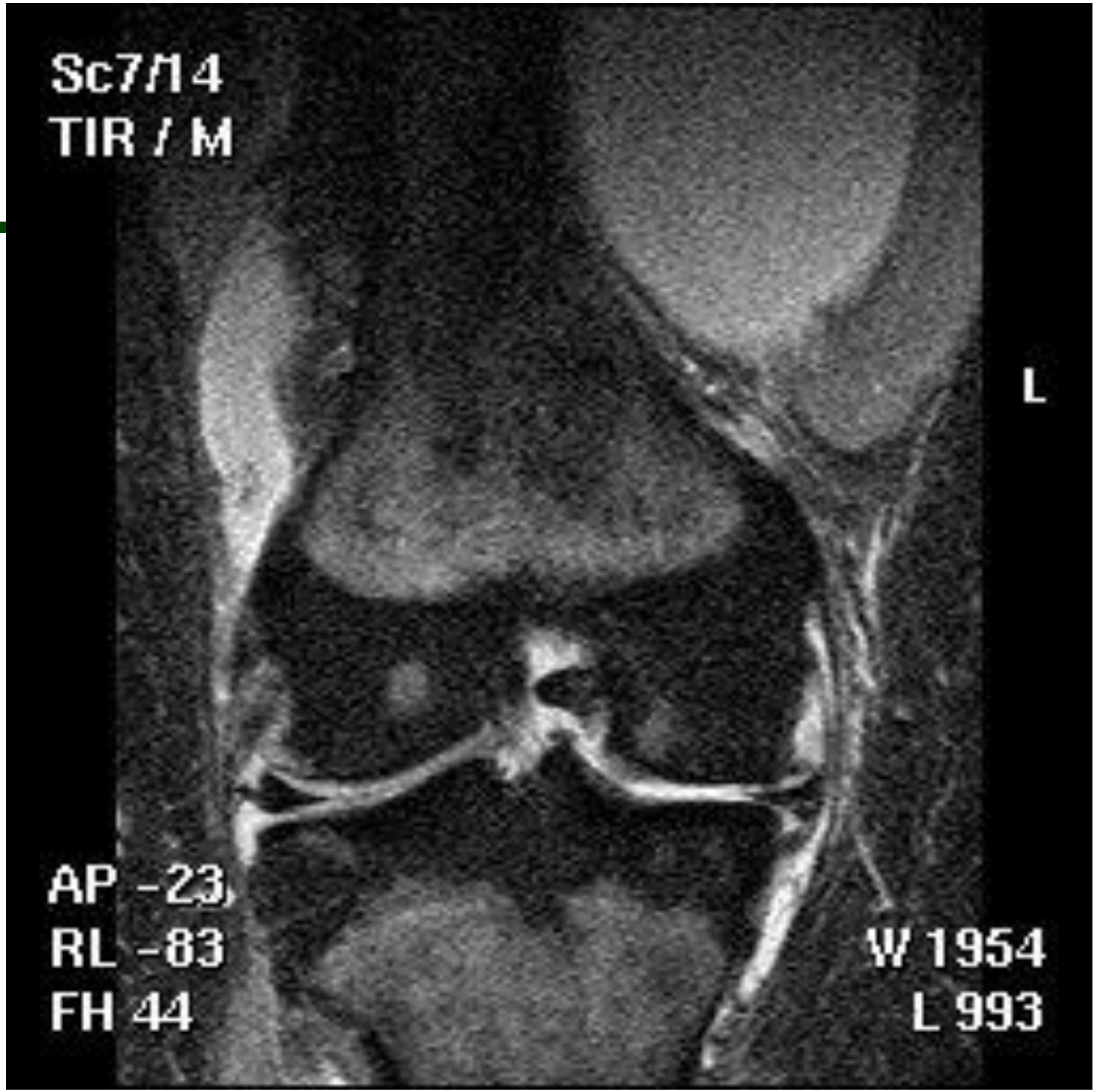
How has MRI helped?



Direct visualisation of tissues



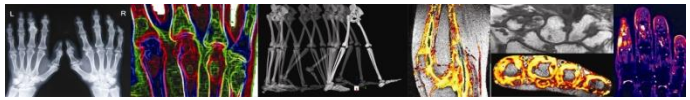
Hunter et al.
Osteoarthritis Cartilage
2011


Sc7/14
TIR / M
L
AP -23
RL -83
FH 44
W 1954
L 993

Demonstrated insensitivity of Xray

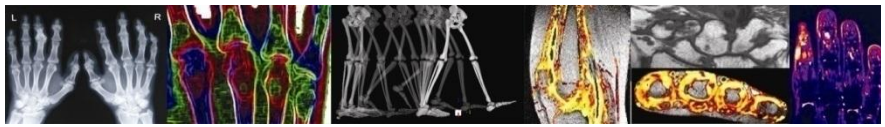
- Community-based study of 710 people >50yo
- No radiographic evidence of knee OA (weight-bearing, flexed PA view)
- 1.5T MRI, read using WORMS

MRI features	Overall (n=710)
Any abnormality	631 (89)
Osteophytes	524 (74)
Cartilage damage	492 (69)
Bone marrow lesions	371 (52)
Synovitis	259 (37)
Attrition	228 (32)
Subchondral cysts	179 (25)
Meniscal lesions	167 (24)
Ligamentous lesions	66 (9)



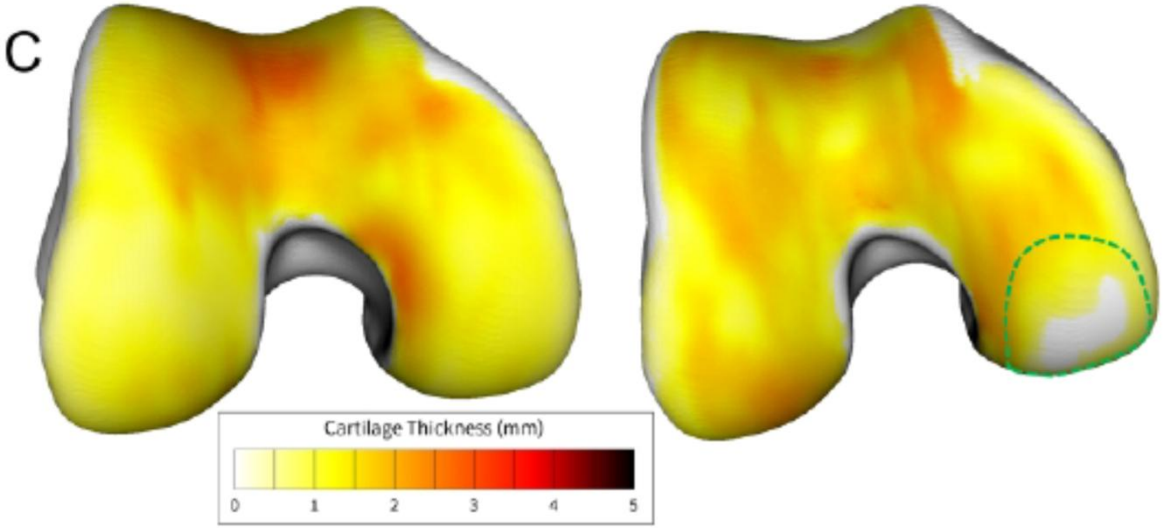
Guermazi A et al,
BMJ 2012;345:e5339

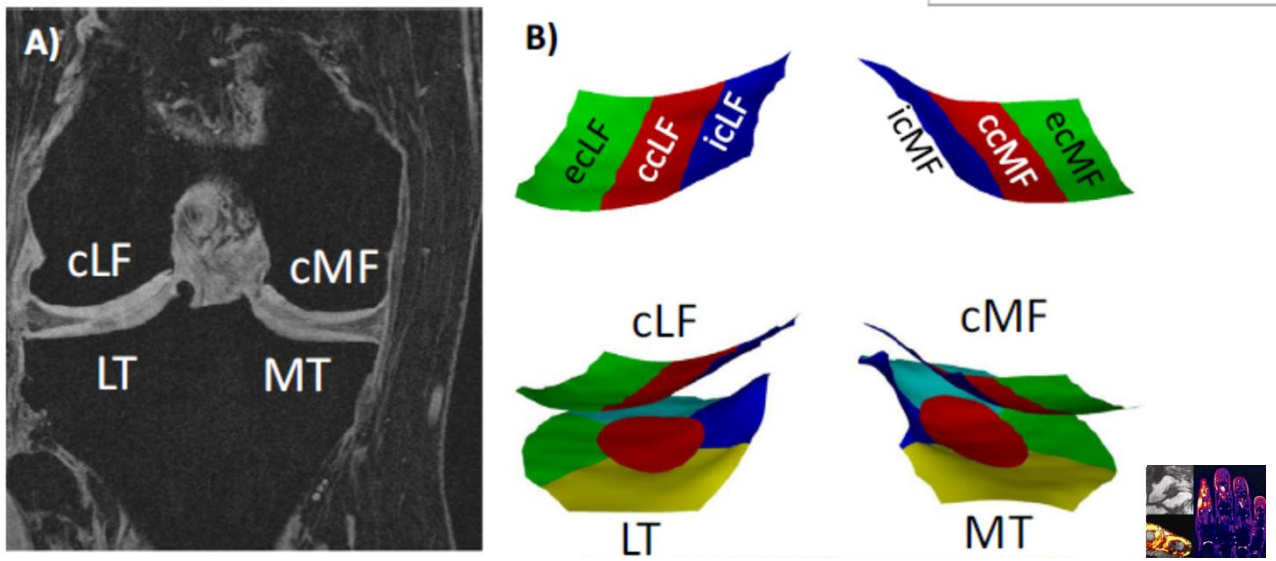
Structure: MRI cartilage



OA MRI: Cartilage Morphology

- Measuring a single construct
- Very good construct validity and reliability



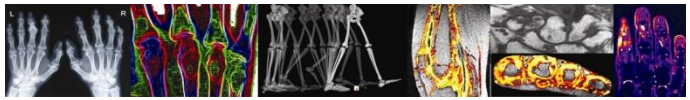


Eckstein & Peterfy.
Semin Arthritis Rheum 2016
Bowes M et al.
J Rheumatol 2019 [epub]

Predictive validity for TJR

Table 3. Odds of knee replacement according to MRI features of osteoarthritis

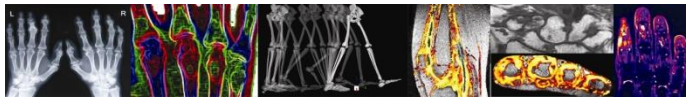
Component	Feature	Odds ratio (95% CI)
Cartilage		
	Tibial cartilage loss >8% vs.	7.1 (1.4–36.5)
	tibial cartilage volume >3%	
	Higher cartilage defect scores (8–15) vs.	6.0 (1.6–22.3)
	Lower cartilage defect scores (2–7)	
	Medial cartilage volume loss	18.7 (2.4–145.7)
	Maximum grade for area extent of cartilage damage in the whole knee	4.00 (2.23–7.18)
	Maximum grade for full thickness cartilage damage in the whole knee	3.45 (2.15–5.55)



Demehri S et al
Curr Opin Rheum 2015
(also Pelletier JP et al
Ann Rheum Dis 2013)

Quantitative MRI Measures of Cartilage (cMFTC) Predict Knee Replacement

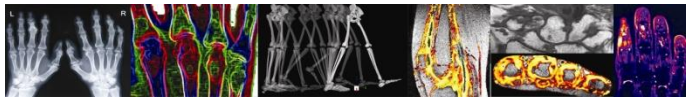
- Nested case-control study of OAI: 127 [113 pts] knees replaced between BL and Y4
- 1 control knee matched for BL KLG, gender, age
- Longitudinal change in cMFTC between T-1 and T0 significantly greater in KR cases: median -0.115 µm vs controls: median -0.060 µm (p=0.006); ccAUC=0.59
- Longitudinal differences differed by KLG, p=0.002;
  KLG 2 cases: median -0.145 µm vs controls: +0.035 µm
  KLG 3 cases: median -0.170 µm vs controls: -0.120 µm



Eckstein F et al.
Ann Rheum Dis 2013

OARSI OA Knee Trial Recommendations: MRI

- For MRI cartilage morphometry in knee OA, there is some evidence for construct and predictive validity, with good evidence for reliability and responsiveness
- Using MRI it is possible to accurately and feasibly measure change in cartilage morphometry over 12 months for knee OA
- It is possible to “enrich” a study population with MRI outcomes in order to increase the rate of cartilage loss, for example, by including higher KL grade…
- In terms of correlations with concurrent symptoms, there is a weak association between progression of cartilage loss and increasing symptoms.
- There is some predictive validity with progression of cartilage loss predicting subsequent total joint replacement
- More information is required on the performance metrics of MRI semi-quantitative and compositional measures of cartilage



Hunter DJ et al
Osteoarthritis Cartilage 2015

Predictive Validity for Symptoms (FNIH)

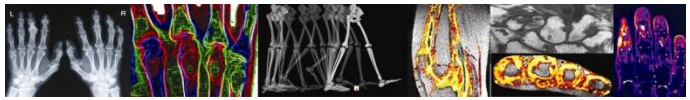
Group comparison[&]		Cartilage thickness change	
		BL→24M	BL→12M
		aOR (95% CI)	aOR (95% CI)
1 vs. 4	Xray + pain vs. control	3.8 (2.7, 5.3) #	1.8 (1.4, 2.3) #
2 vs. 4	Xray vs. control	3.8 (2.7, 5.5) #	2.0 (1.5, 2.6) #
3 vs. 4	Pain vs. conrol	0.9 (0.6, 1.3)	1.2 (0.9, 1.5)
1+2+3 vs. 4	Xray or pain. vs. control	2.5 (1.9, 3.3) #	1.6 (1.3, 2.0) #
1+2 vs. 3+4	Xray vs non-Xray	4.0 (2.9, 5.3) #	1.8 (1.4, 2.1) #
1+3 vs. 2+4	Pain vs. Non-Pain	1.3 (1.1, 1.6) §	1.2 (1.0, 1.4)

*p<0.01;

§p< 0.001;

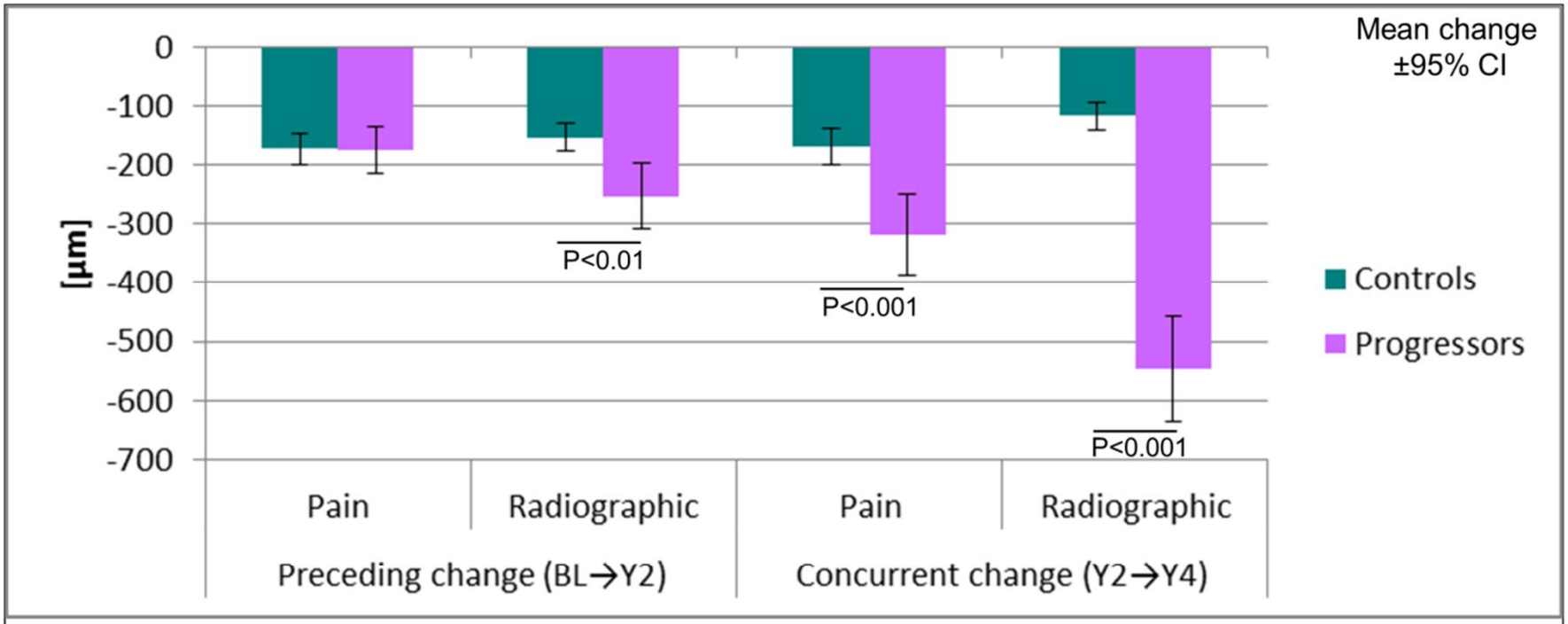
#p< 0.001;

&group 1 = knees with both radiographic (Xray) and pain progression (primary cases); group 2 = knees with radiographic progression but not pain progression; group 3 = knees with pain progression but not radiographic progression; group 4 = knees with neither radiographic nor pain progression (super controls).

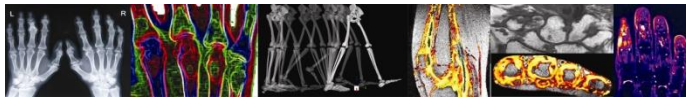


Eckstein F et al.
Arthritis Rheumatol 2015

Predictive Validity for Symptoms



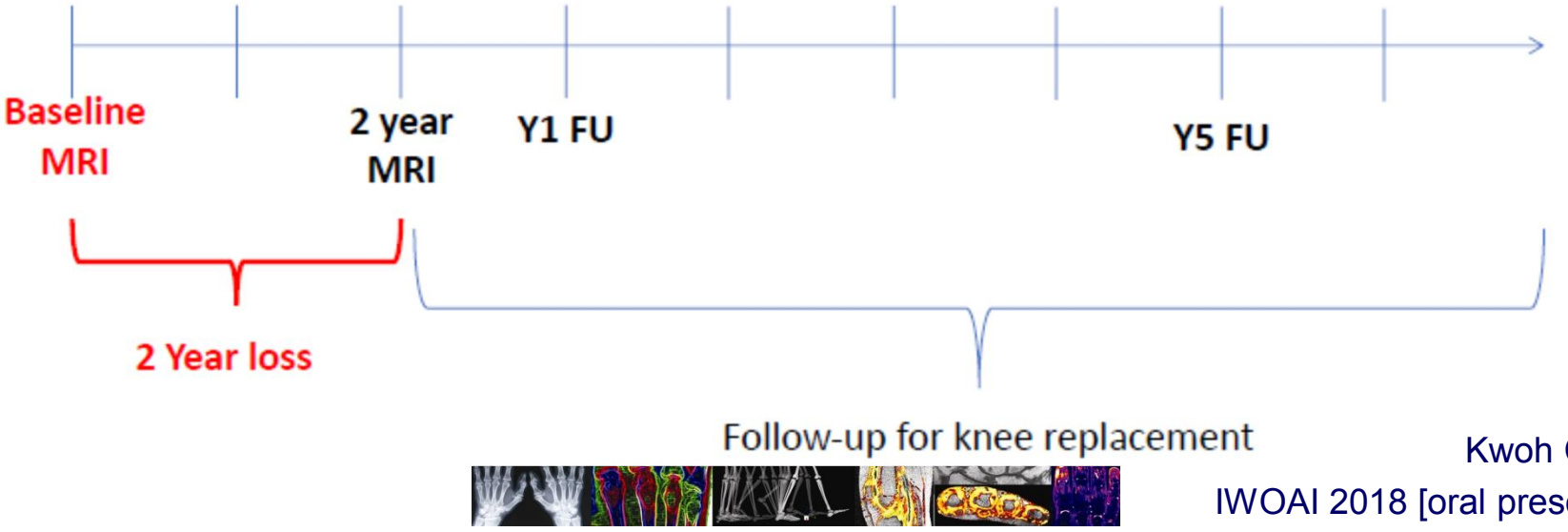
: Preceding and concurrent cartilage thickness change in the cMFTC of knees with or without pain progression and knees with or without radiographic progression in the period Y2→Y4.



Wirth W et al.
Osteoarthritis Cartil 2017

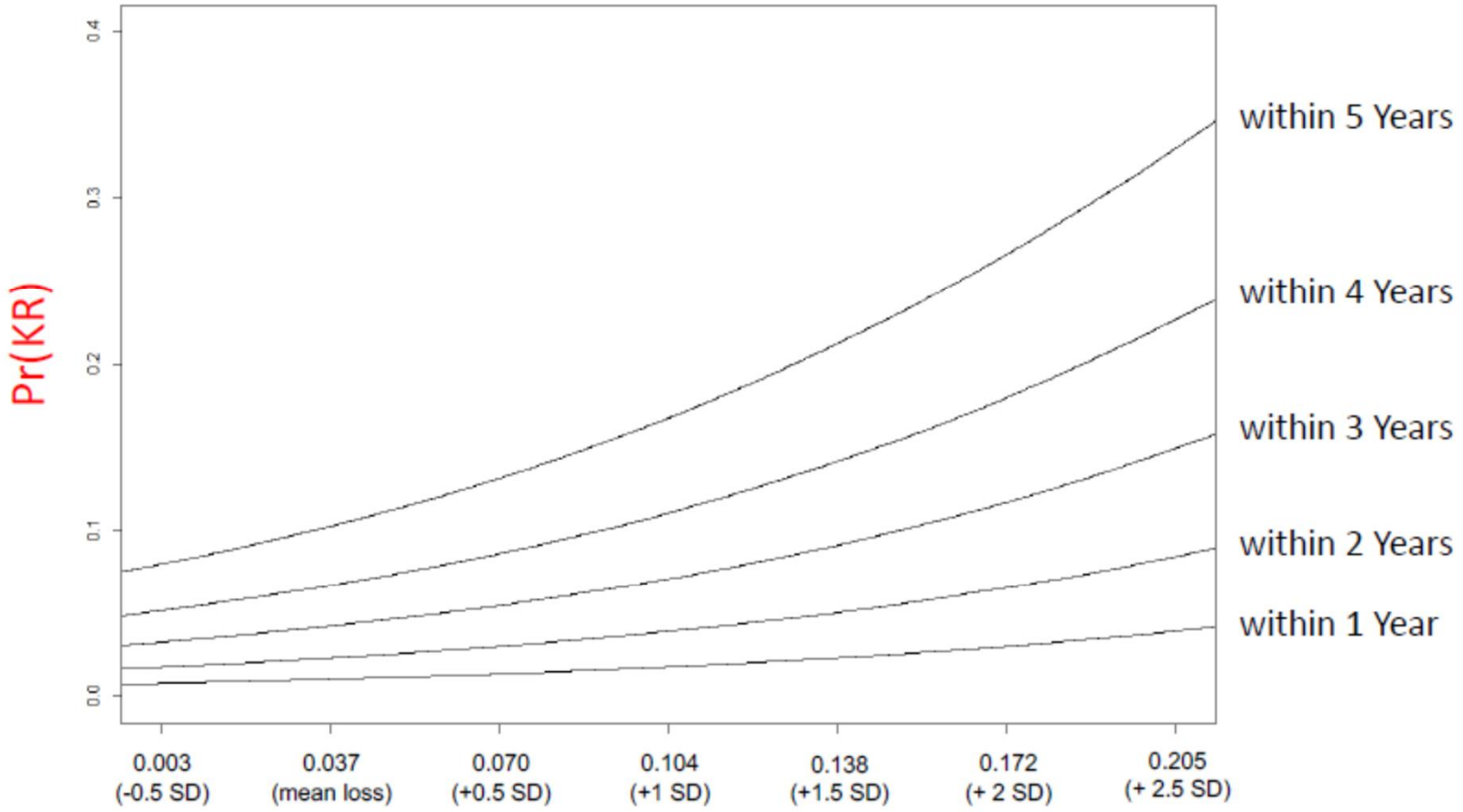
MRI Cartilage: Predictive Probability for KR

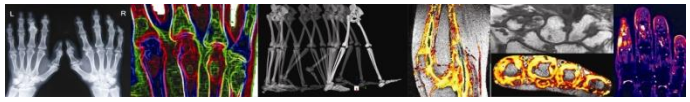
- OAI knees with symptomatic OA at baseline
  - Definite osteophyte (OARSI atlas grade 1-3; clinical center screening reading
  - Frequent knee symptoms at baseline
- MRI readings at baseline and Y2; knee replacement outcomes after the 2-year imaging window



Kwoh CK et al.
IWOAI 2018 [oral presentation]

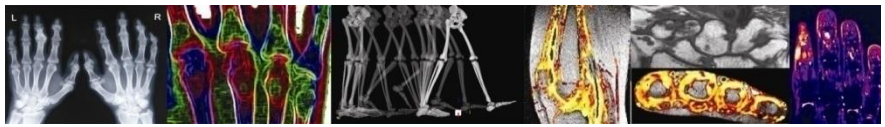
MRI Cartilage: Predictive Probability for KR



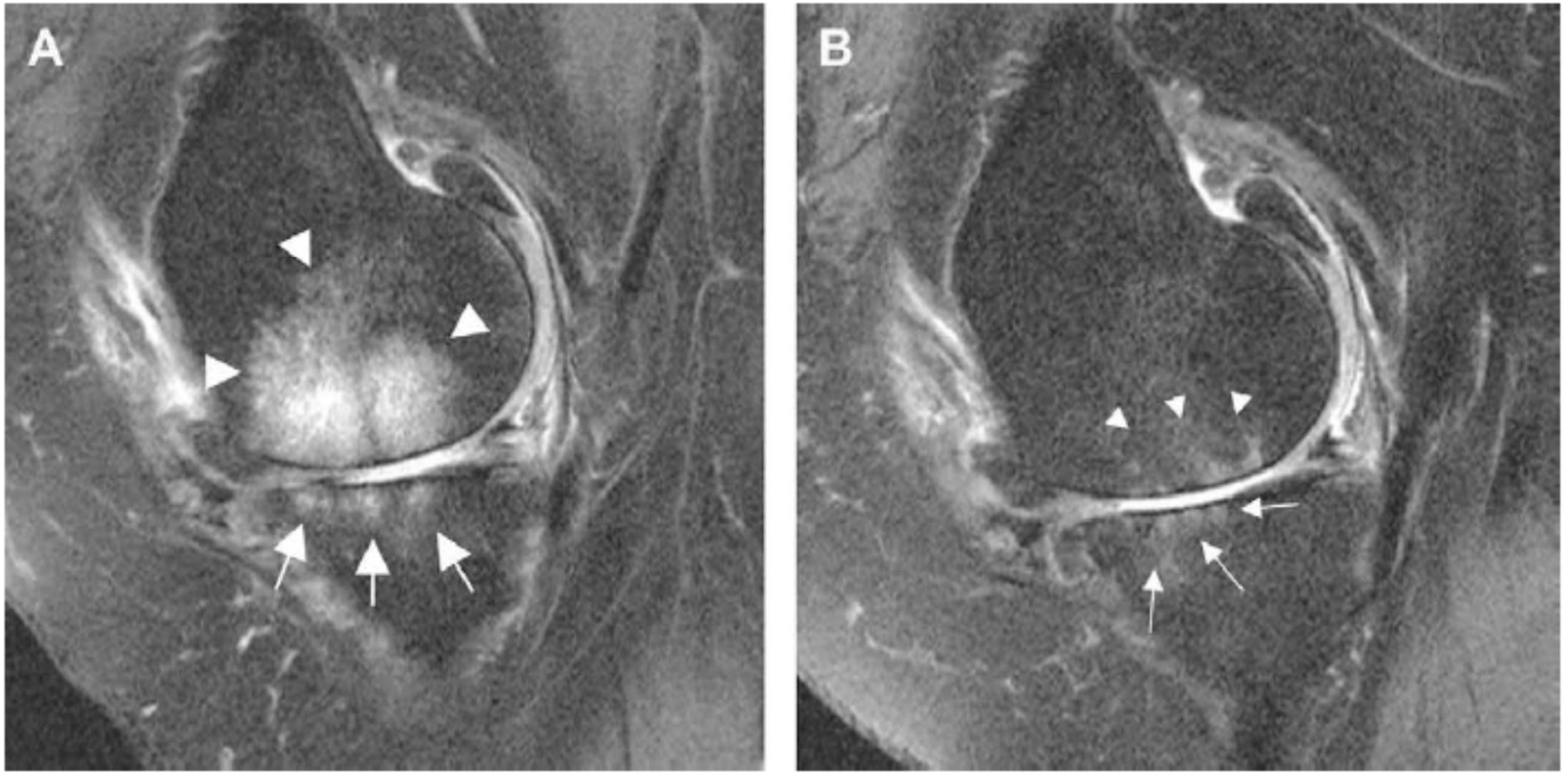


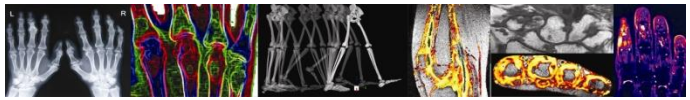
Kwoh CK et al.
IWOAI 2018 [oral presentation]

Structure: MRI bone



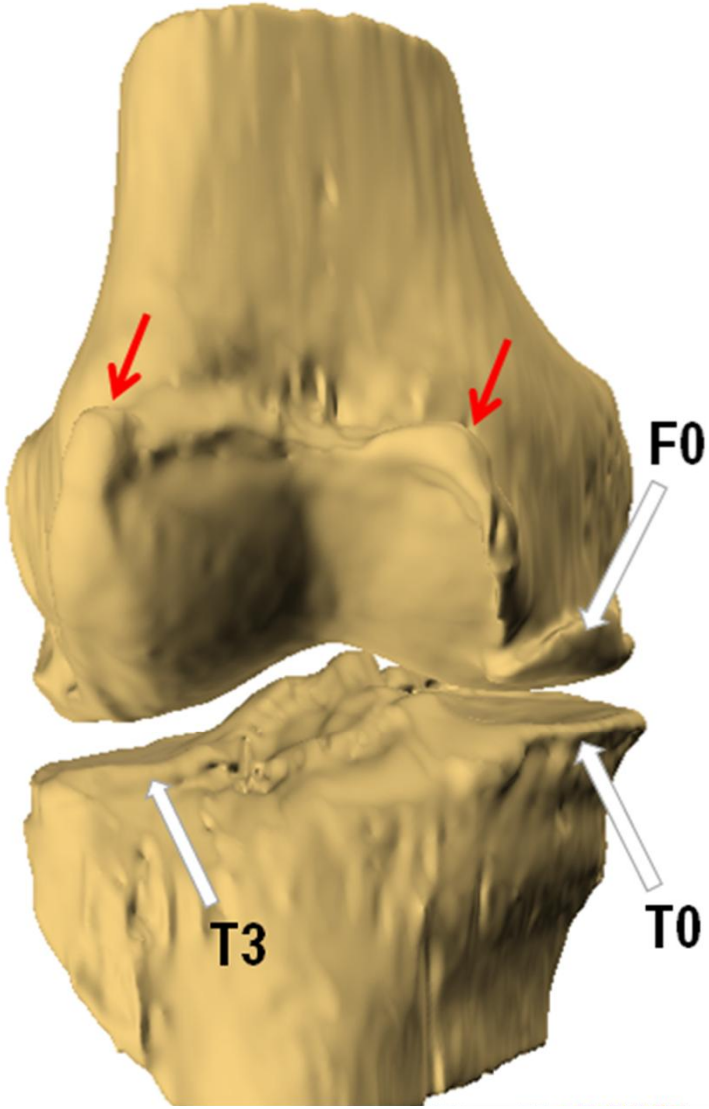
MRI Bone: Bone Marrow Lesions

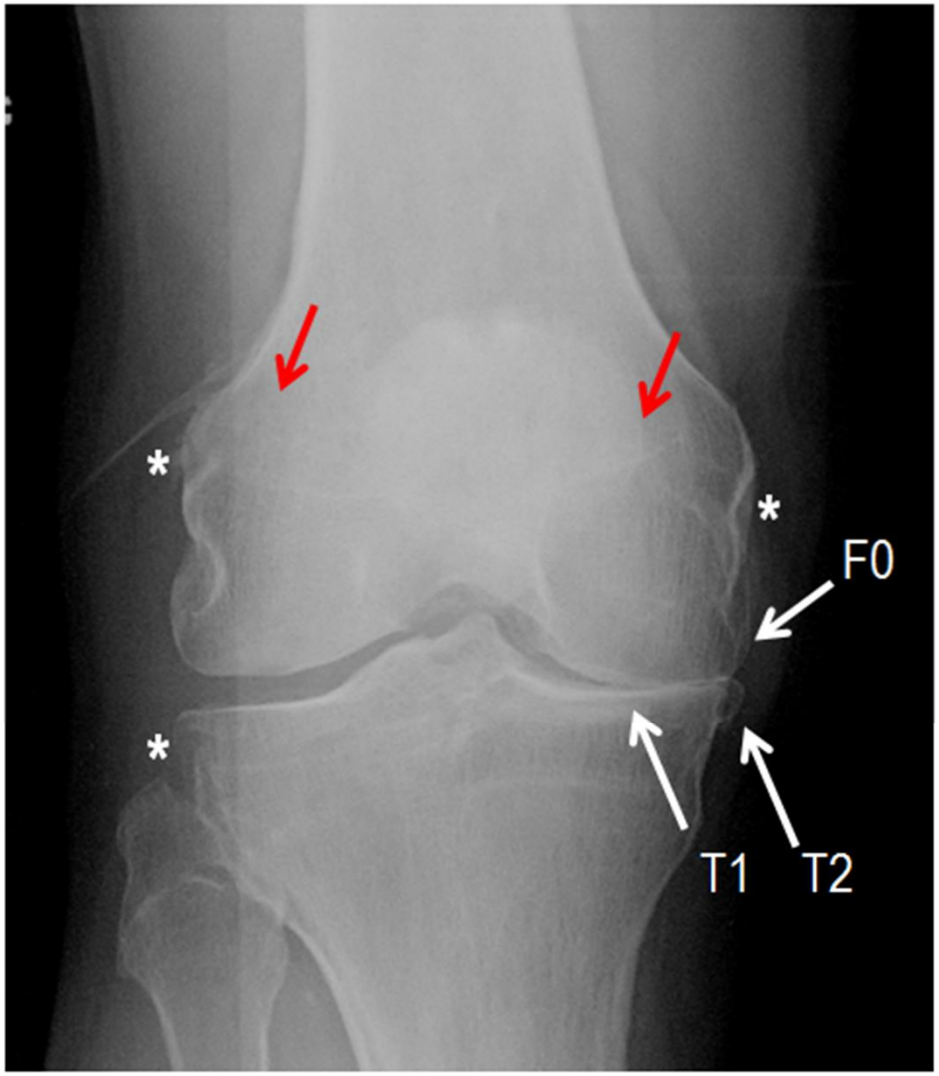




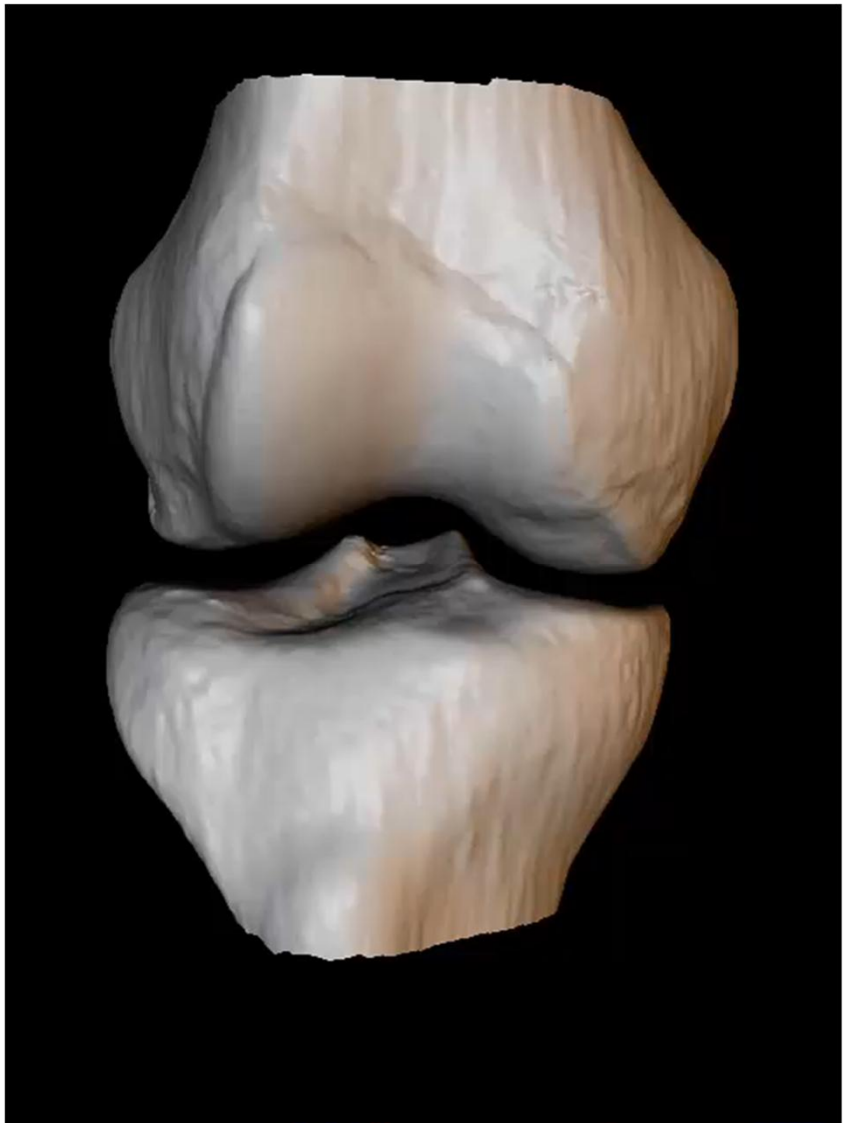
Roemer F et al.
Osteoarthritis Cartilage 2009

Understanding 3D bone shape





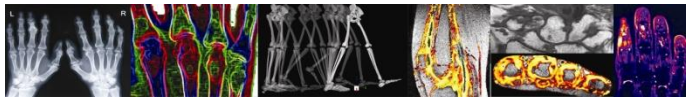
Understanding 3D bone shape: machine learning



Courtesy Imorphics

3D bone shape: predictive validity

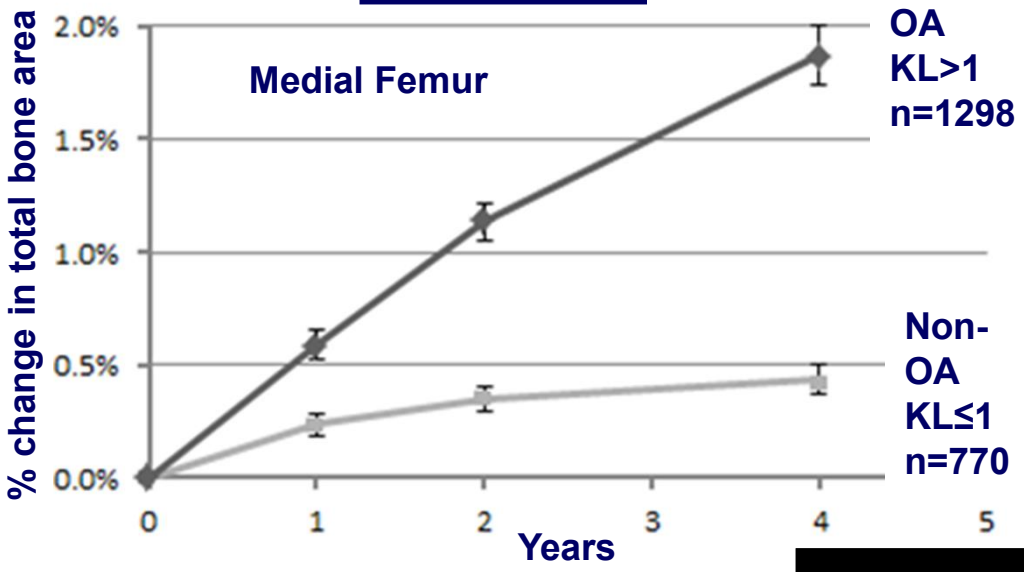
3-D bone shape vector	Relationship of baseline 3-D bone shape to incident radiographic OA in the whole sample: Incident radiographic knee OA, irrespective of time of OA onset — Adjusted OR (95% CI)†	*P*‡	Incident radiographic knee OA, occurring 24–48 months later — Adjusted OR (95% CI)†	*P*‡
Whole joint (femur, tibia, and patella)				
Highest tertile	2.5 (1.5–4.1)	0.0005	3.0 (1.5–6.0)	0.003
Middle tertile	1.8 (1.1–2.9)		2.6 (1.3–5.1)	
Lowest tertile (reference)	1.0		1.0	
Per SD unit change toward mean OA shape	1.5 (1.2–1.8)	0.0003	1.6 (1.2–2.1)	0.001
Tibiofemoral joint (femur and tibia)				
Highest tertile	1.8 (1.1–2.9)	0.03	2.4 (1.2–4.7)	0.01
Middle tertile	1.6 (1.0–2.6)		2.3 (1.2–4.5)	
Lowest tertile (reference)	1.0		1.0	
Per SD unit change toward mean OA shape	1.3 (1.1–1.6)	0.003	1.5 (1.2–2.0)	0.002



Neogi T et al
Arthritis Rheum 2013

Quantitative MRI bone area

Specific



Responsive

Measure	1 year SRM	2 year SRM
Radiograph mJSW	0.186	0.311
MRI cartilage thickness	0.317	0.401
qMRI 3D bone shape	0.500	0.644

Bowes et al,
Ann Rheum Dis 2015

Bone Shape predicts Knee Replacement

	Univariable (unadjusted)				Multivariable*		
Imaging variable	OR	95% CI	p value	AIC	OR	95% CI	AIC
Femur vector	1.79	1.54, 2.09	<0.001	309.51	1.21	1.01,1.45	228.33
Tibia vector	1.64	1.42, 1.90	<0.001	334.86	1.02	0.84,1.24	232.66
Patella vector	1.40	1.26, 1.56	<0.001	346.33	1.09	0.95,1.26	231.24
KL grade (ref=KL zero)					*Adjusted for KL		
1	2.42	0.75, 7.82	0.14				
2	9.08	3.36,24.49	<0.001				
3	31.55	11.23,88.63	<0.001				
4	72.77	22.62,234.07	<0.001	230.70			

Barr AJ et al.
Ann Rheum Dis 2015

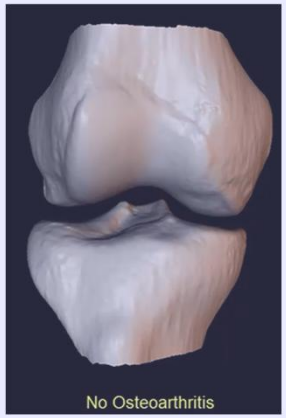
3D Bone vs Structure and Symptom Progression

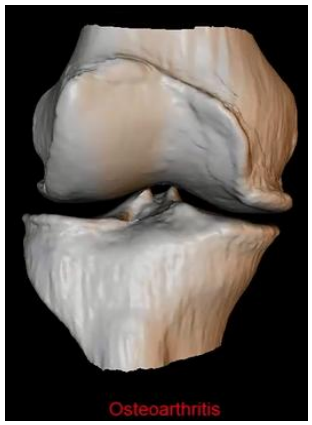
	Any progression OR (95% CI) per 1 SD increase in change	Radiographic progression OR (95% CI) per 1 SD increase in change	Pain progression OR (95% CI) per 1 SD increase in change
Medial			
Femur	2.13 (1.68 to 2.71)	2.62 (2.07 to 3.34)	1.30 (1.08 to 1.56)
Tibia	1.63 (1.33 to 1.99)	1.84 (1.51 to 2.24)	1.17 (0.99 to 1.39)
Patella	1.39 (1.15 to 1.68)	1.45 (1.21 to 1.75)	1.25 (1.05 to 1.48)
Lateral			
Femur	1.25 (1.04 to 1.50)	1.29 (1.08 to 1.55)	1.17 (0.98 to 1.40)
Tibia	1.51 (1.24 to 1.83)	1.73 (1.43 to 2.10)	1.22 (1.03 to 1.45)
Patella	1.45 (1.19 to 1.76)	1.52 (1.26 to 1.84)	1.29 (1.08 to 1.54)
Notch	1.51 (1.24 to 1.83)	1.57 (1.31 to 1.89)	1.16 (0.98 to 1.37)
Lateral			
Trochlea	1.35 (1.12 to 1.63)	1.53 (1.27 to 1.84)	1.21 (1.02 to 1.44)
Medial			
Trochlea	1.71 (1.38 to 2.12)	2.02 (1.63 to 2.49)	1.26 (1.06 to 1.50)
Shape (vector)			
Femur	1.86 (1.48 to 2.33)	2.56 (2.03 to 3.24)	1.16 (0.97 to 1.39)
Tibia	1.42 (1.18 to 1.72)	1.83 (1.51 to 2.22)	1.16 (0.98 to 1.37)
Patella	1.33 (1.10 to 1.62)	1.26 (1.05 to 1.50)	1.23 (1.03 to 1.47)

Hunter DJ et al.
Ann Rheum Dis 2015

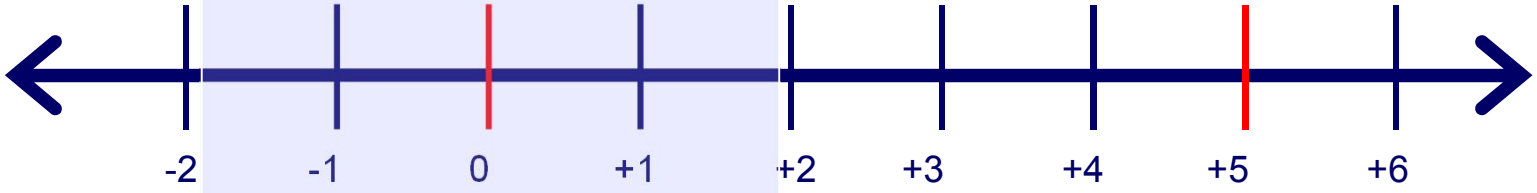
3D bone shape: B score

Less structural severity

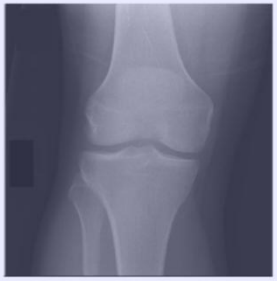




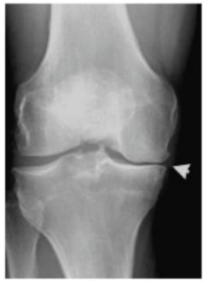
Greater structural severity



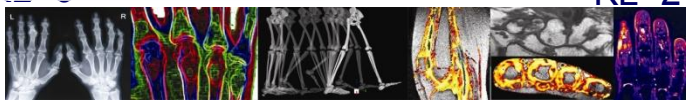
Blue box shows healthy range – 95% CL of KL 0 knees



KL=0

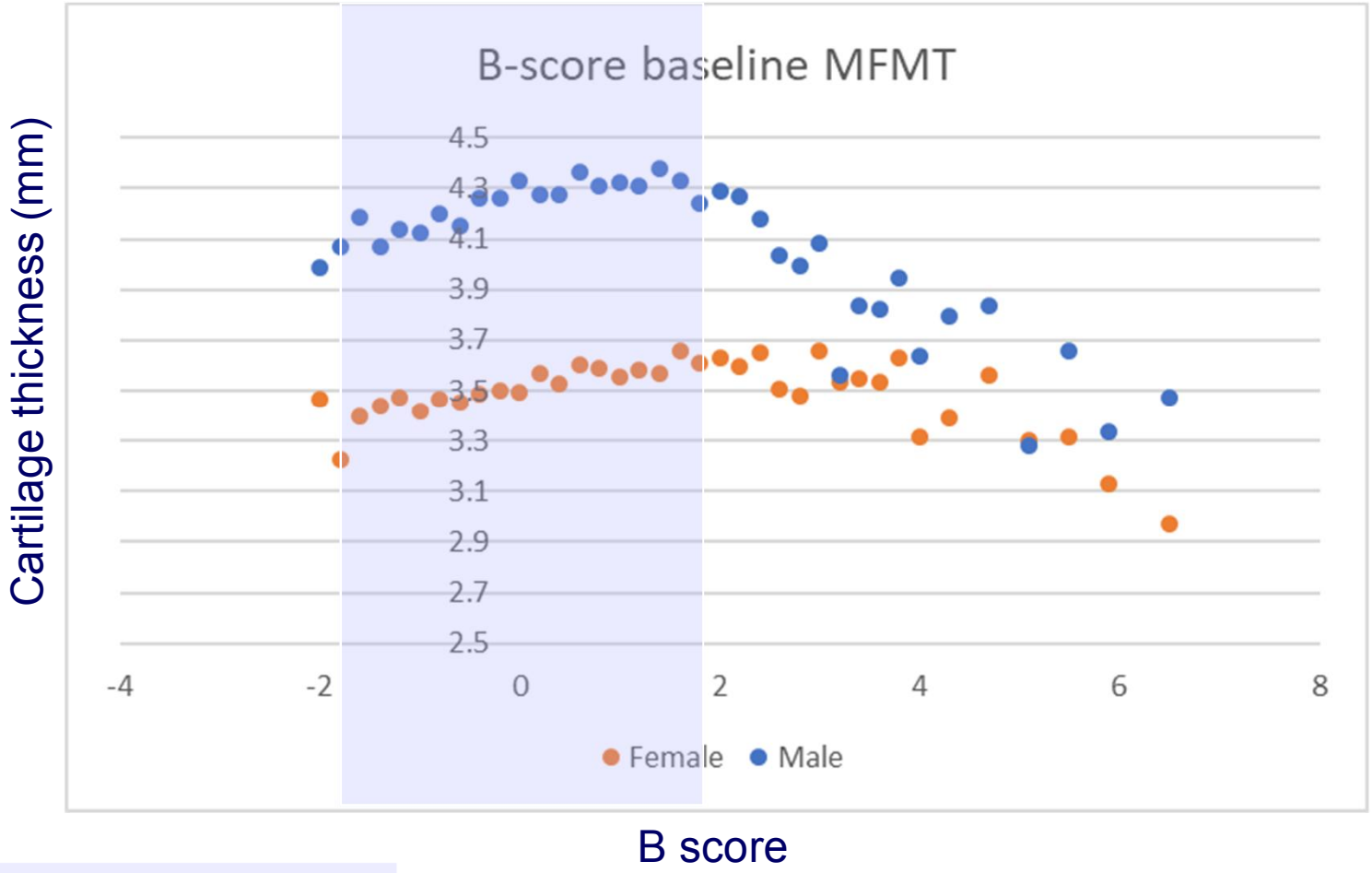


KL=2-3

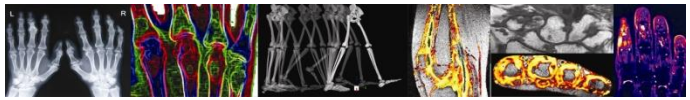


Neogi A&R 2013;65(8):2048–58

Relationship of cartilage to bone: whole OAI (9433 knees)



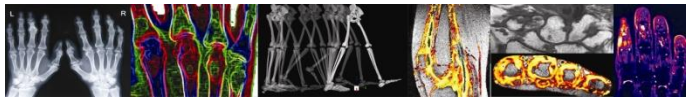
Blue box shows healthy range – 95% CL of KL 0 knees



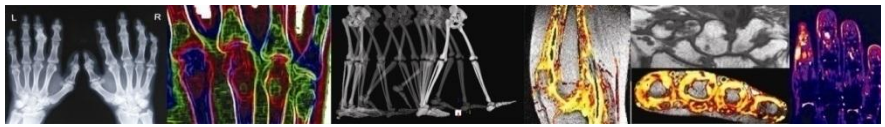
Bowes MA et al
In preparation

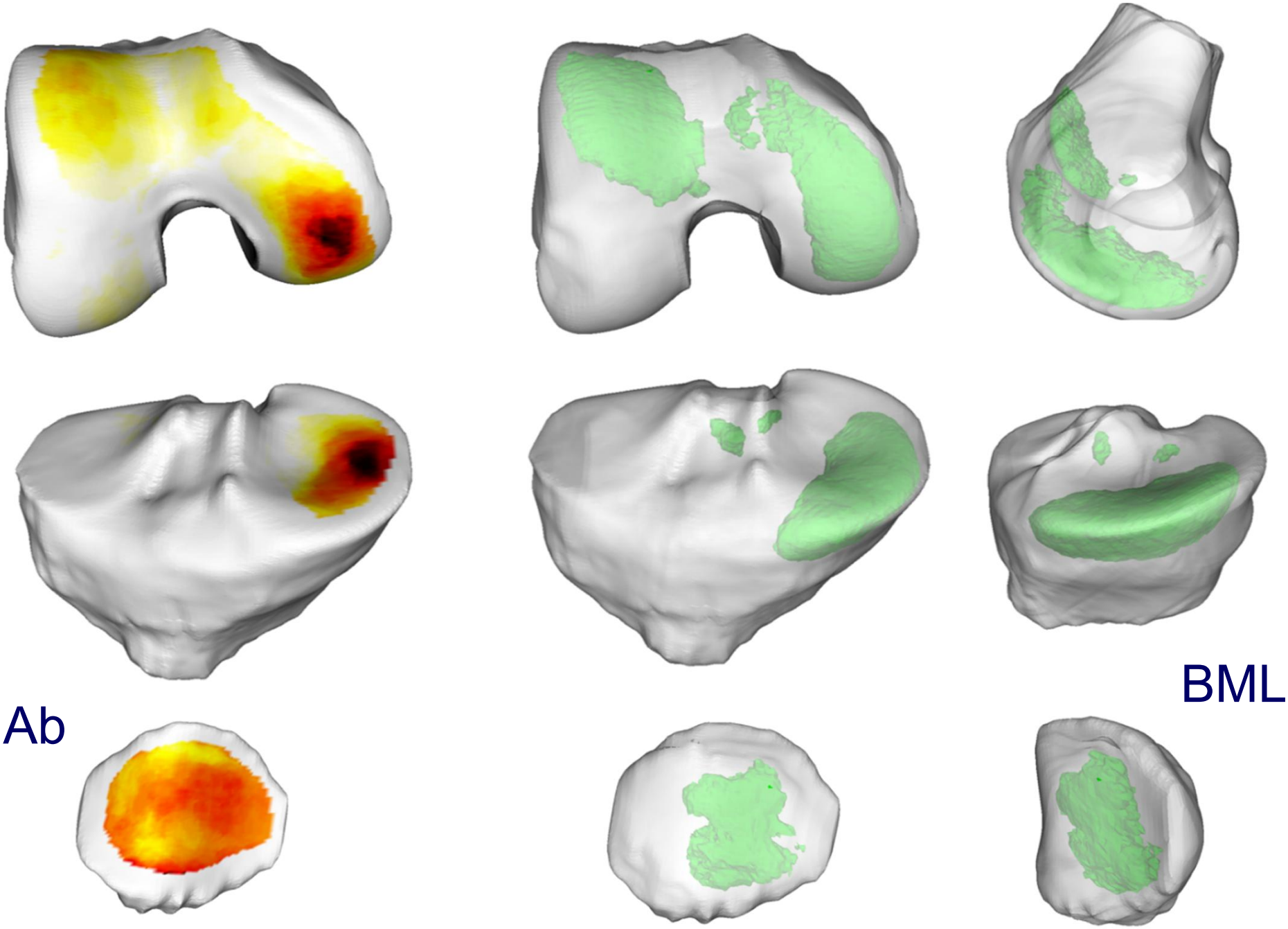
OA Imaging Biomarkers: MRI B score

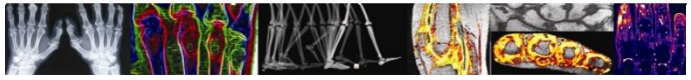
- Reader independent
- Extremely reliable
- Scalar instrument, provides a better ruler for assessing OA structure (40 pts vs 5 for KL grade)
- From a single time point, predicts radiographic progression and patient symptoms



In this multi-tissue disease, which imaging structure should we choose?

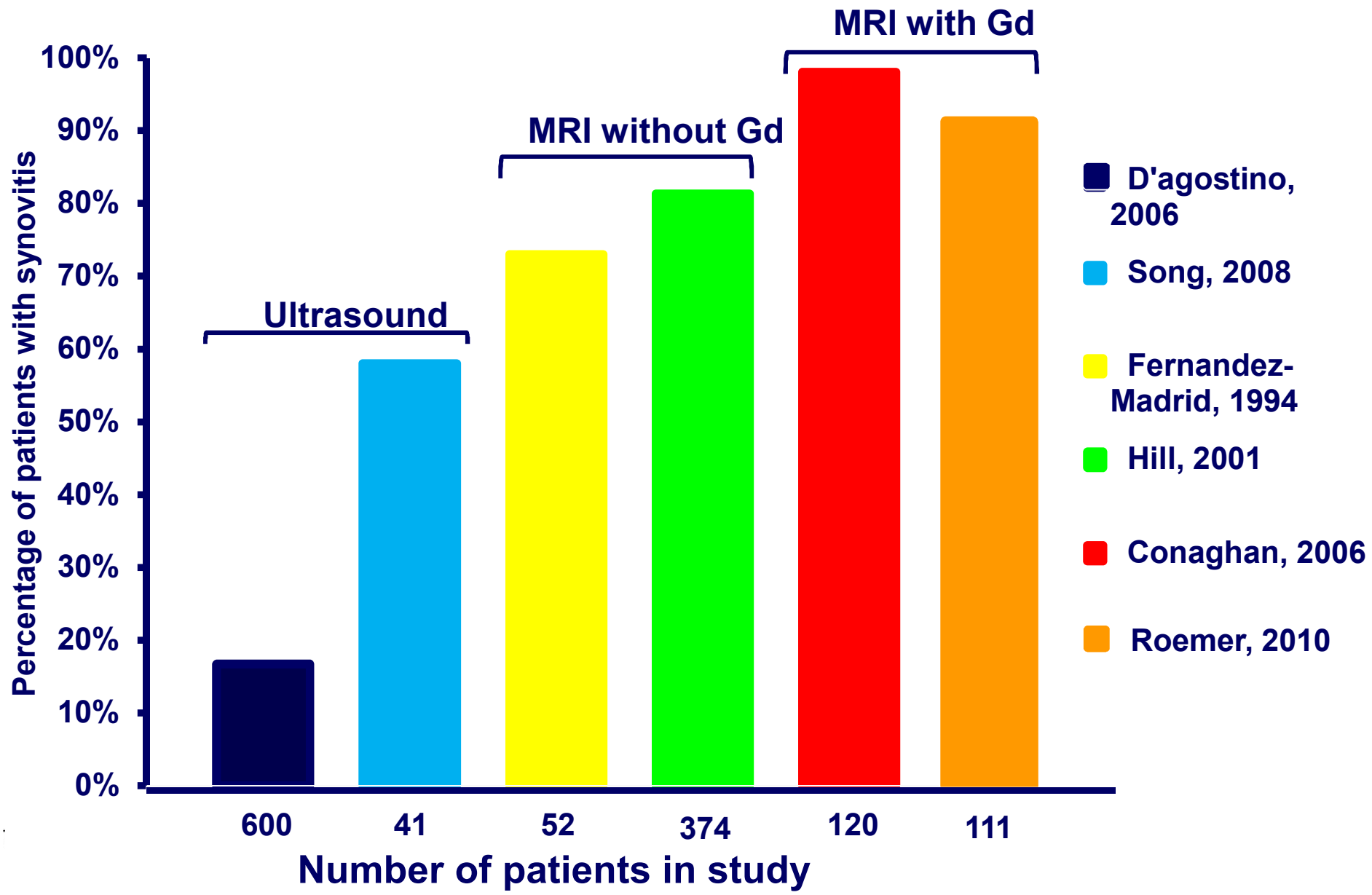




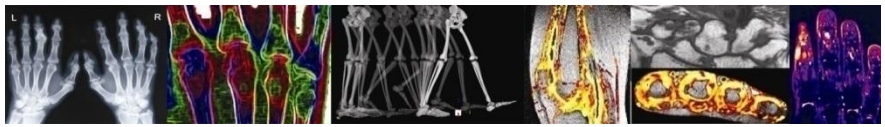


Bowes et al, Ann Rheum Dis 2016

Synovial Hypertrophy in OA Knee

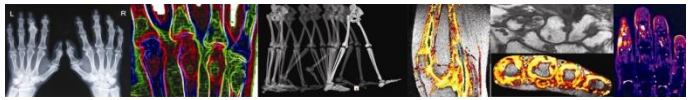


What are the implications of better structural measurement?

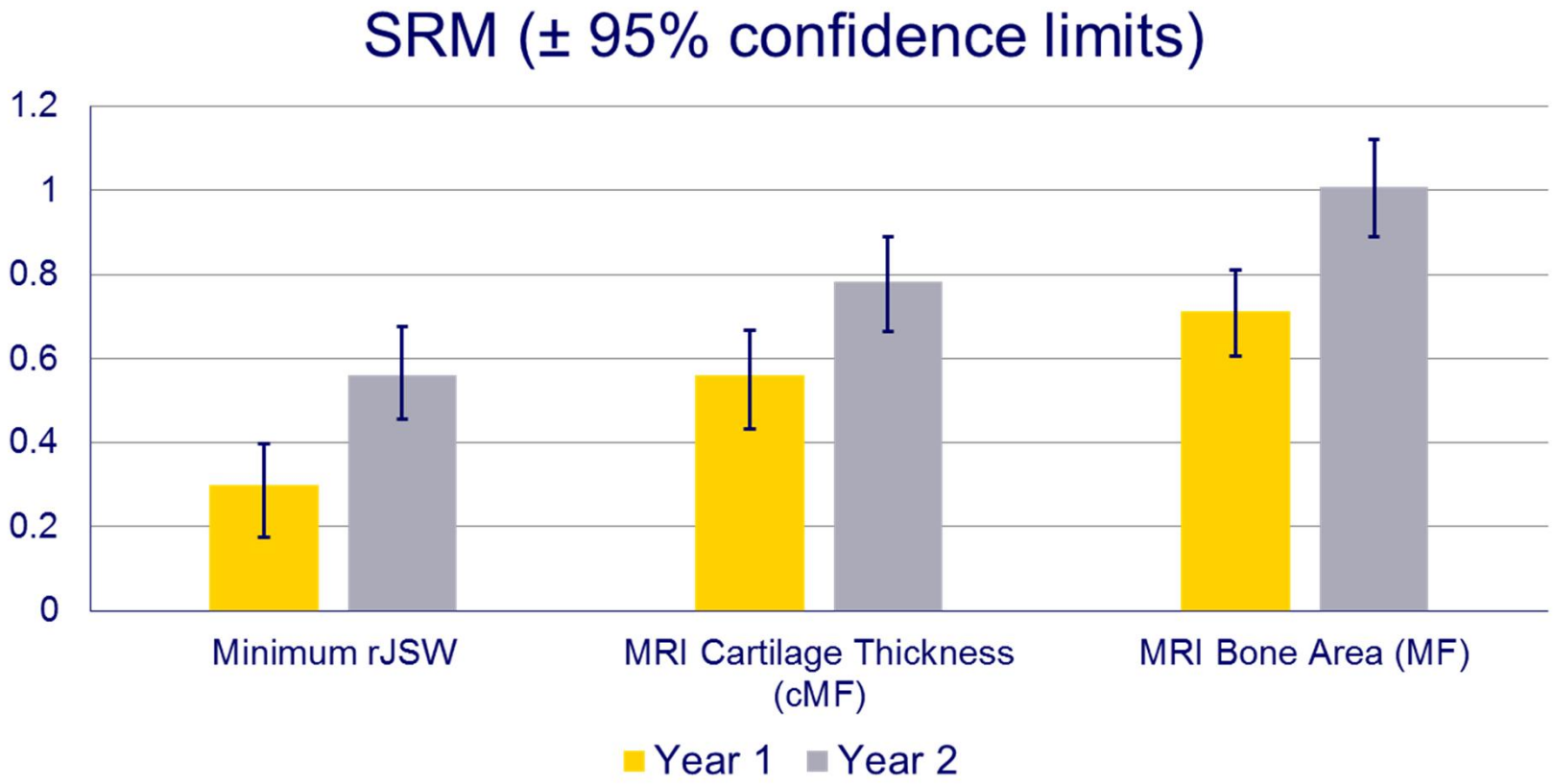


Can we enrich?

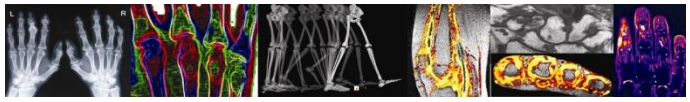
- Traditionally KL2-3 is a common inclusion, attempting to find real OA
- KL grading quite noisy



Improving Responsiveness of Imaging Biomarkers by JSW Criteria

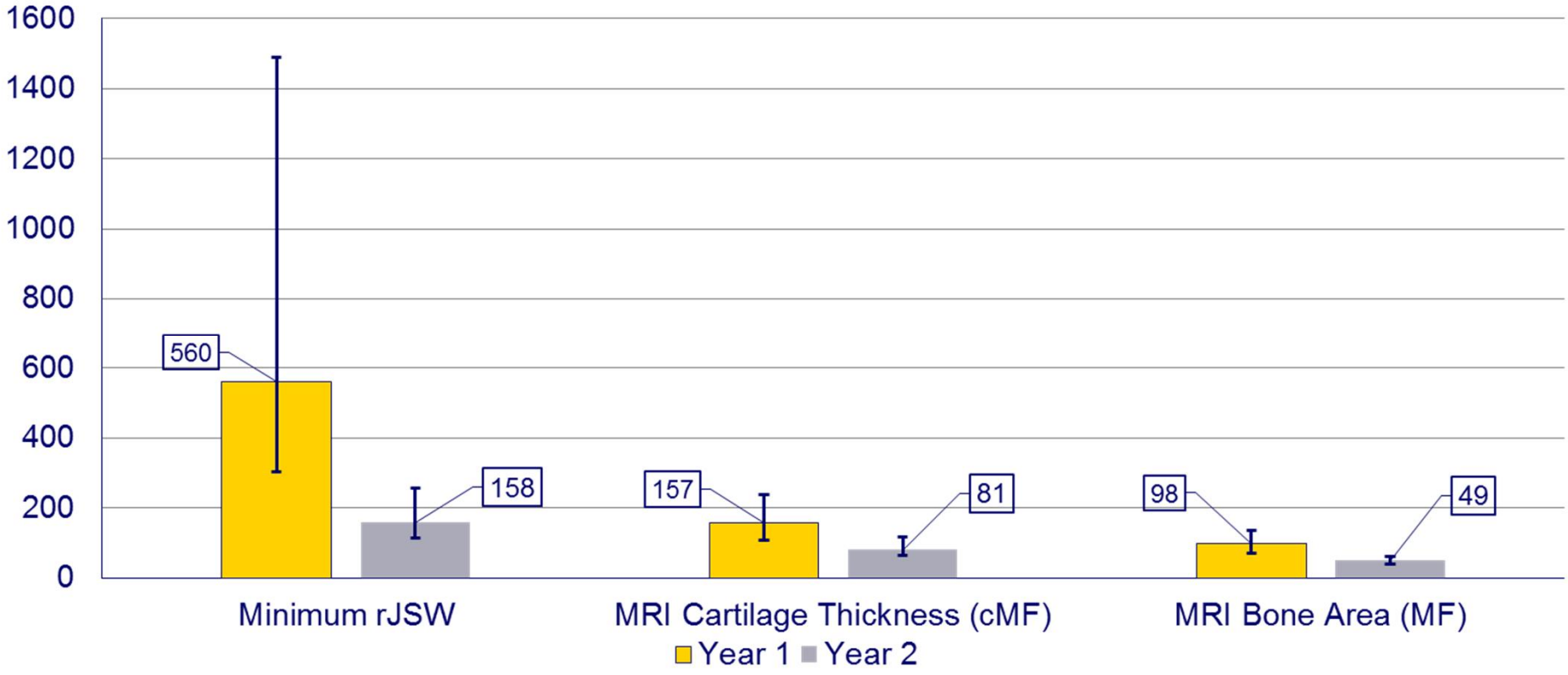


- Responsiveness of knees selected for rJSW 2-4mm and WOMAC pain ≥3 (n=331, from OAI)

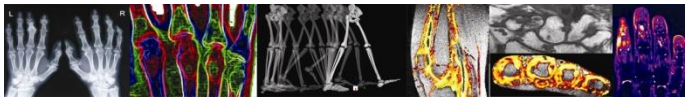


Bowes M et al
Ann Rheum Dis [suppl] 2017

Improving Study Numbers



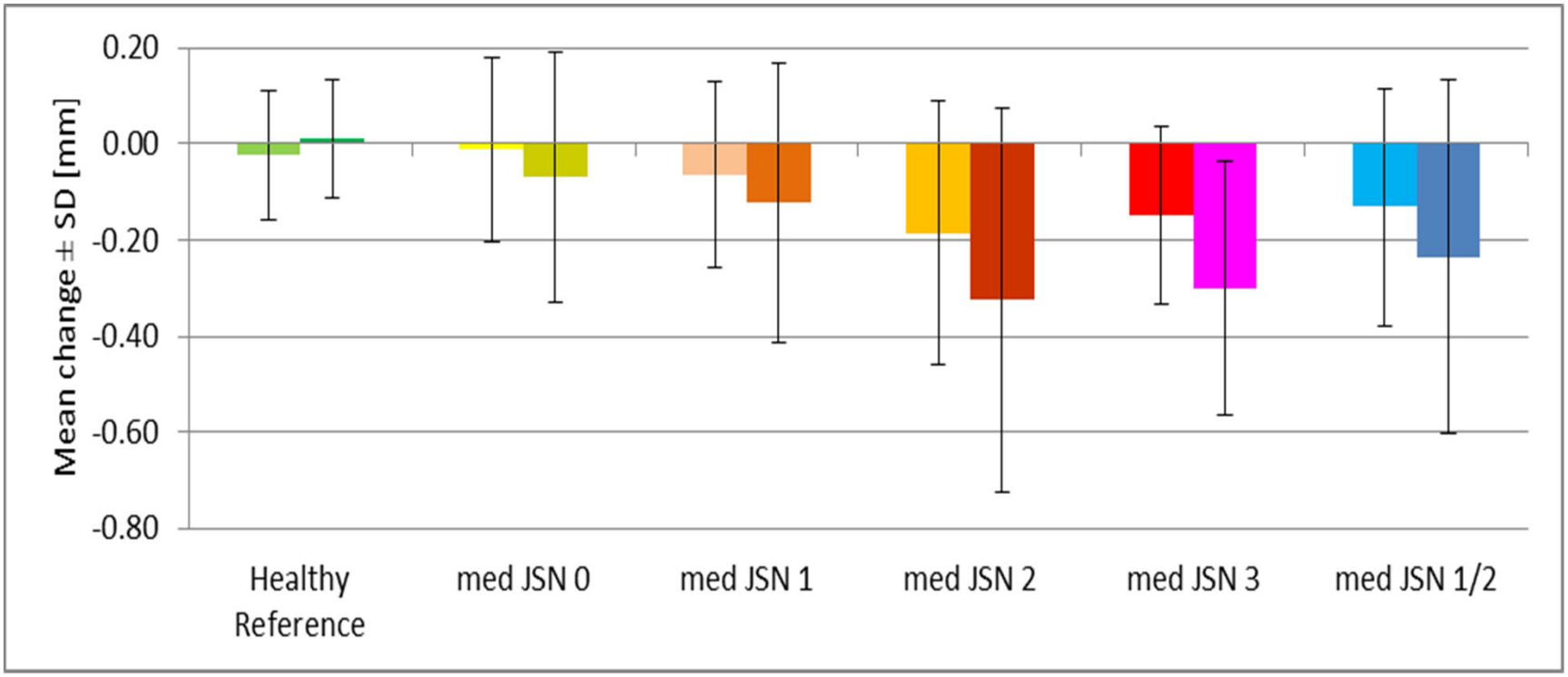
- Patient Numbers Per Arm to detect 50% change, 80% power, α = 0.05

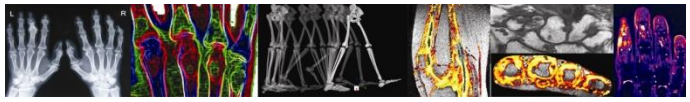


Bowes M et al
Ann Rheum Dis [suppl] 2017

Improving Responsiveness of Imaging Biomarkers by JSW Criteria

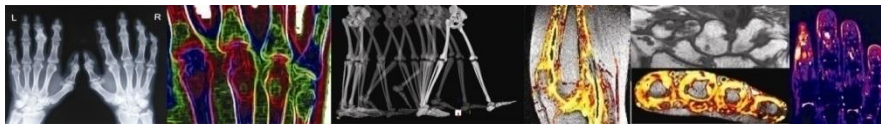
SRM 1y	-0.19	-0.07	-0.33	-0.68	-0.80	-0.53
SRM 2y	0.09	-0.27	-0.43	-0.81	-1.14	**-0.64**



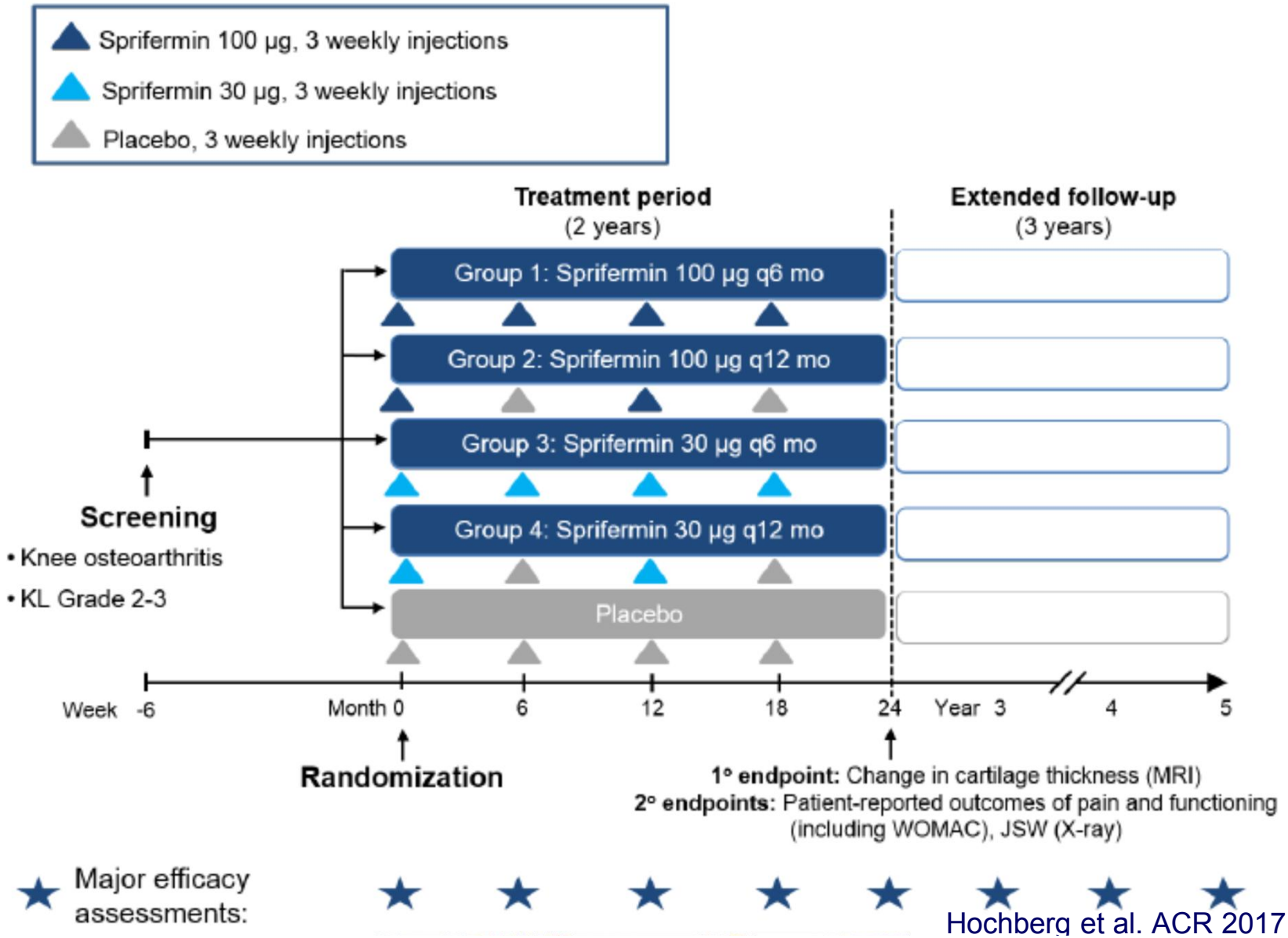


Eckstein F. OARSI 2019
[Oral presentation]

Is it possible to modify OA structure?

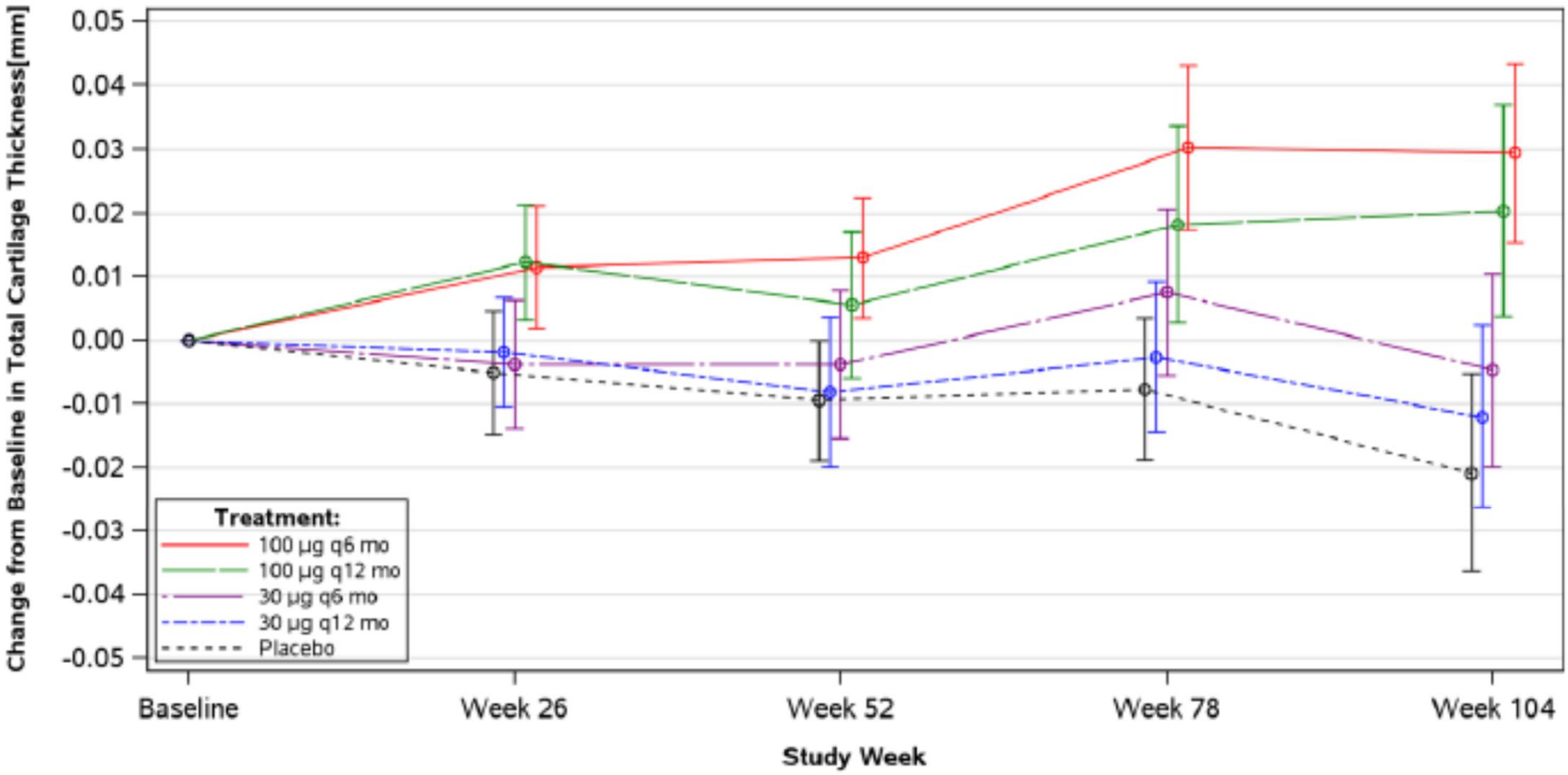


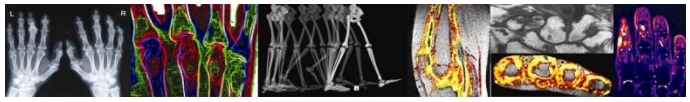
Sprifermin 5 yr PhII trial: FORWARD



Hochberg et al. ACR 2017

Sprifermin 5 yr PhII trial: FORWARD

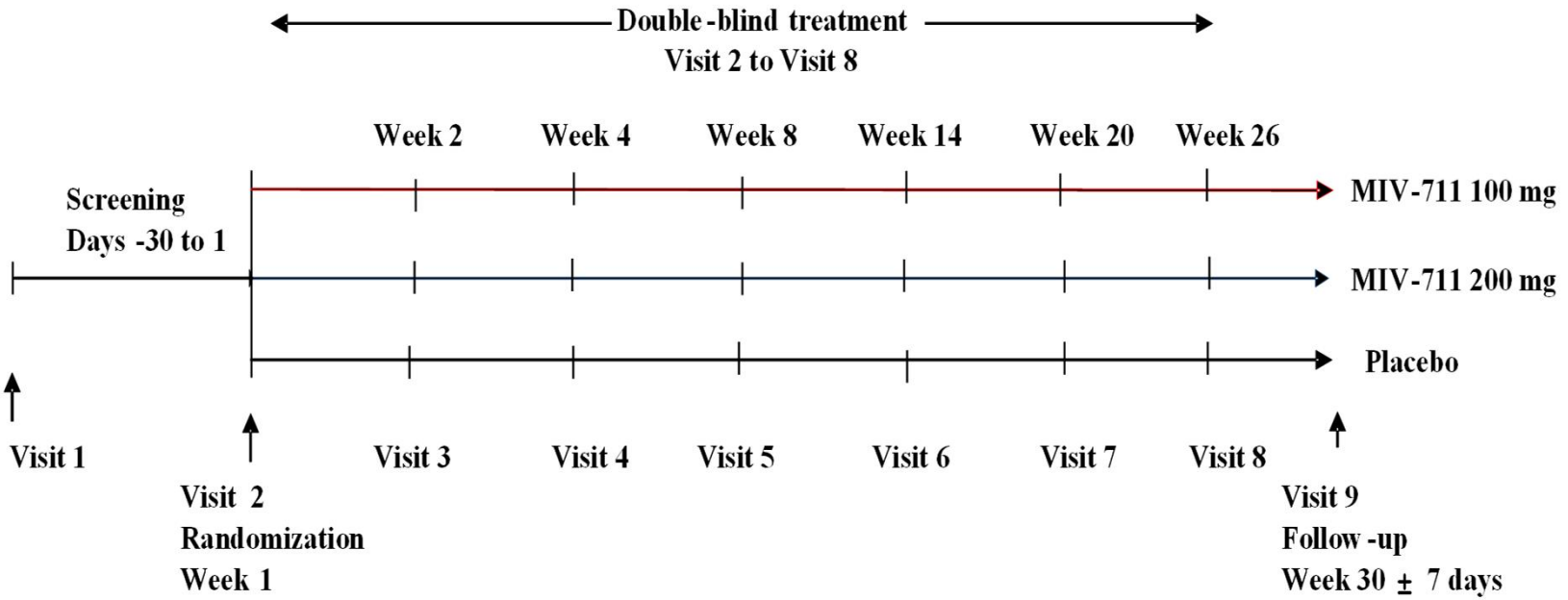


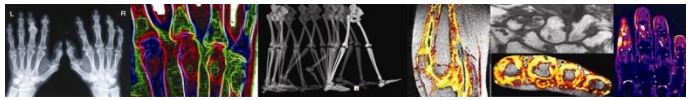


Hochberg et al. ACR 2017

New Cathepsin K inhibitor (MIV-711): Study design

- Knee pain ≥4, <10 on NRS, K-L grade 2 or 3
- All patients remained on current stable analgesia

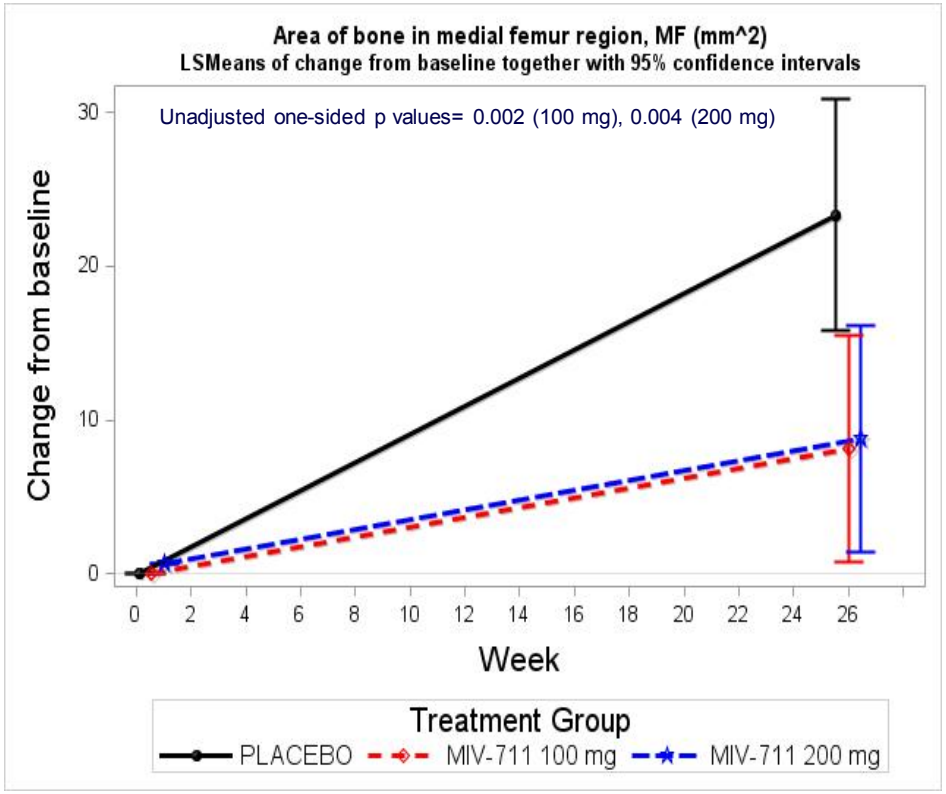




Conaghan et al. ACR 2017

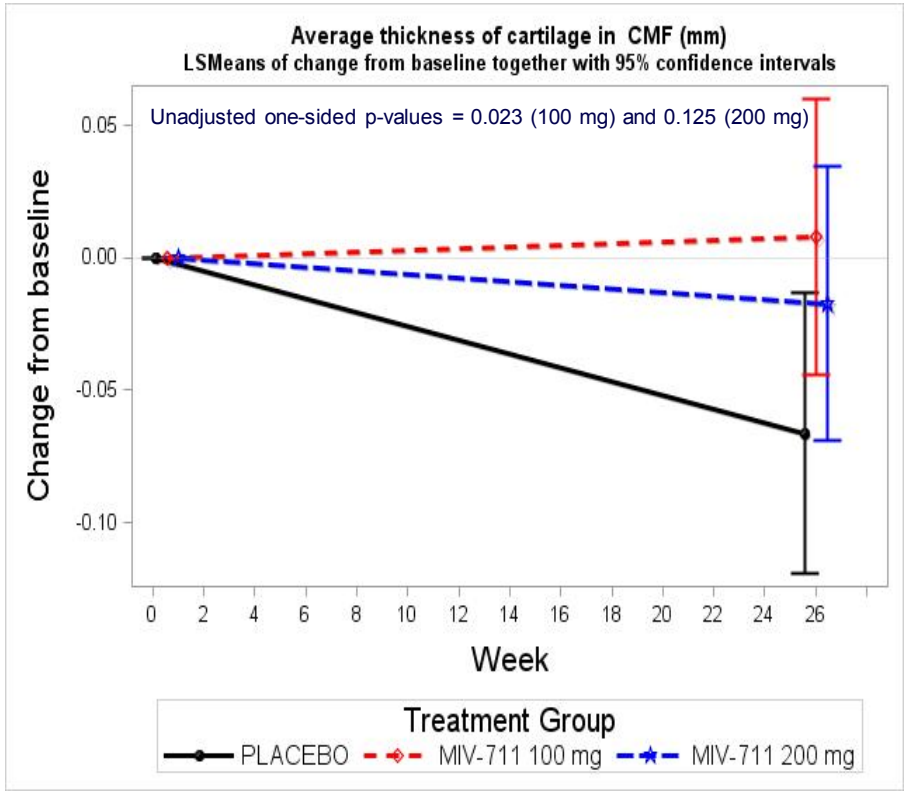
Results: MRI measures

Area of bone in MF

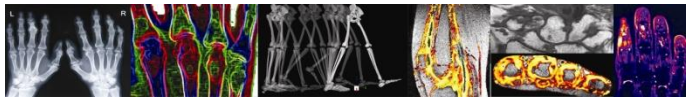


Reduction in bone area increase for both doses

Average cartilage thickness in CMF



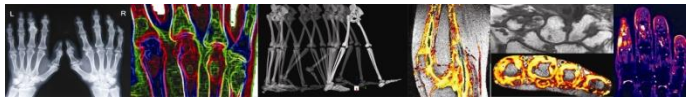
Trend for reduced cartilage thickness loss for both doses



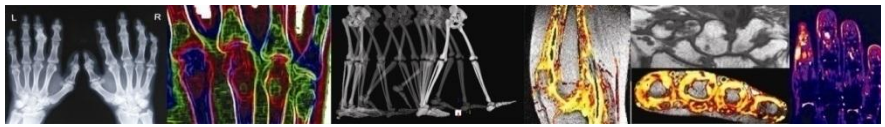
Conaghan et al. ACR 2017

Lessons from RCTs

- Our 2 best MRI biomarkers can show change
- Change is measurable over a reasonable time period
- Symptomatic benefit likely occurs in a different time frame

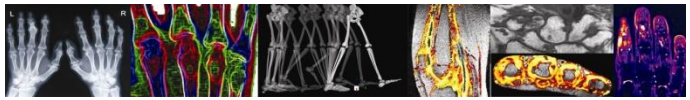


How do we we move forward?



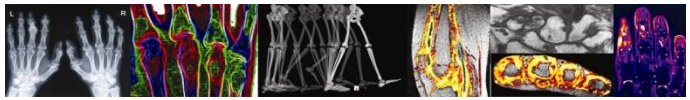
OA is more like osteoporosis…

- …than rheumatoid arthritis
- In RA, concept of DMARD came first from modification of symptoms (inflammation) and reducing consequent damage
- In OA, we see many, many years of accumulation of silent tissue pathologies before any symptoms



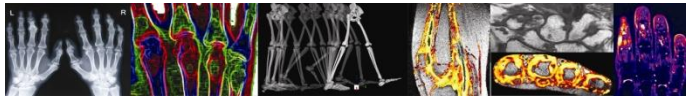
But OA is unique and different from osteoporosis…

- We can detect change in bone and cartilage from people in their 20s (not post-menopausal)
- People also have symptoms for many years before requiring total joint replacement (osteoporosis is asymptomatic till fracture)
- This means long-term trials waiting to see benefits in terms of joint replacement are unfair to patients (leaving them in pain) and unfeasible (so we can't do analogous fracture endpoint trials)



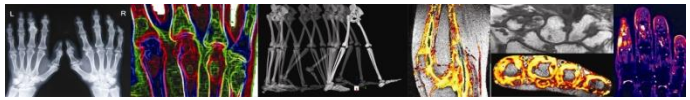
The conundrum

- OA is multi-tissue disease but cartilage and bone do reflect the disease process
- We have very good validated MRI quantitative tools for cartilage and bone that allow feasible clinical trials
- However clinical outcomes resulting from structural improvements (only) will likely be many years away



Acknowledgements

- Mike Bowes
- Alan Brett
- Felix Eckstein
- Virginia Kraus
- Lee Simon



CURRENT STATUS OF SOLUBLE BIOMARKERS FOR OA

Virginia Byers Kraus, MD, PhD

5.16.19

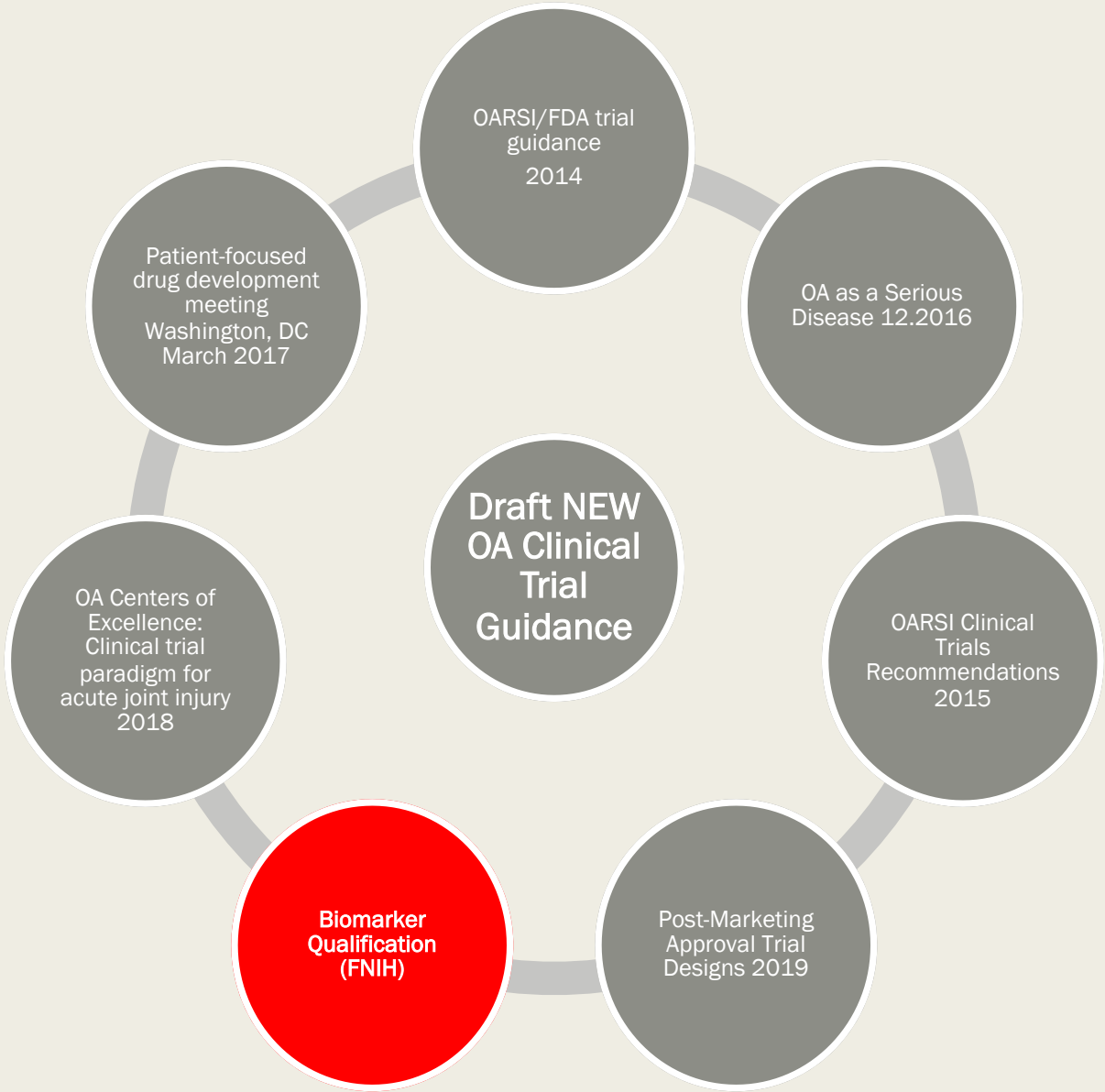
Rationale for biomarkers in OA as endpoints of disease modification (accelerated and traditional approval)

- More likely to be disease related;
- More appropriate for Disease Modifying OA Drug (DMOAD) development;
- Creates a potential path for treating early OA -- BEFORE illness -- when disease more likely modifiable;
- Reports on overall burden of disease (holistic endpoint for generalized disease);
- Potentially avoids unintended consequences of primary emphasis on PROs:
  - ✓ Pain — opioid crisis
  - ✓ Pain — Nerve Growth Factor inhibitor induced rapidly progressive osteoarthritis
- Improves chances of drug program success;
- Creates a path for developing personalized medicine strategies for OA.

Overview

- Summary FNIH OA Biomarkers Consortium status
- Highlight link of type II collagen degradation and synthesis biomarkers to clinically relevant outcomes

Status of Soluble Biomarker Qualification - Synergy of Current Endeavors



FNIH Foundation for the National Institutes of Health

THE biomarkers CONSORTIUM

Phase I: Soluble Biomarker Qualification

- **Biomarkers:** measured in *OAI*
- **Endpoint:** 48M
- **Primary Outcome:** **CLINICALLY RELEVANT (case)** radiographic progression (0.7 mm joint space narrowing) + Pain progression (increase WOMAC pain score of ≥9 out of 100 units)
- **Predictors of CASE status:** Baseline biomarkers & Change OR time-integrated concentrations over 12M or 24M

JE Collins, t al. 2016. Semi-quantitative imaging biomarkers of knee osteoarthritis. Arthritis Rheumatol Oct;68(10):2422-31. doi: 10.1002/art.39731 doi: 10.1002/art.39731 PMID:27111771 PMC5599158

FW Roemer, et al. 2016. Semi-quantitative imaging biomarkers of knee osteoarthritis progression in the FNIH biomarkers consortium cohort. BMC Musculoskeletal Disorders Nov 10;17(1):466. PMC5105263

V Kraus et al. 2017. Predictive validity of biochemical biomarkers in knee osteoarthritis. Annals Rheumatic Diseases. Jan;76(1):186-195 doi: 10.1136/annrheumdis-2016-209252, PMID:27296323, PMC5851287

V Kraus et al. 2017. Establishment of reference intervals for osteoarthritis-related soluble biomarkers. Annals Rheumatic Diseases. Jan;76(1):179-185. PMID:27343253 [PMC journal in progress]

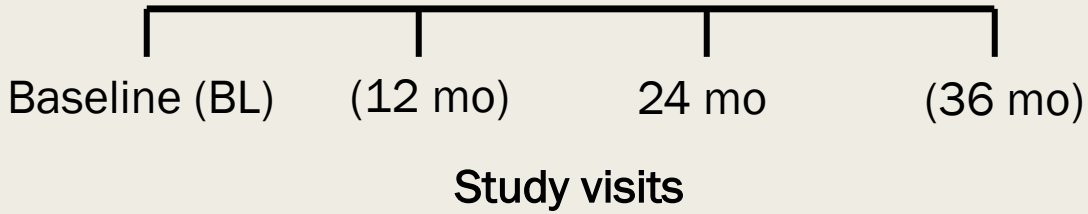
V Kraus et al. 2018. Predictive validity of radiographic trabecular bone texture in knee OA. Arthritis Rheum Jan;70(1):80-87. PMID: 29024470, NIHMS911846, PMC5745253

FNIH Foundation for the National Institutes of Health

THE biomarkers CONSORTIUM

Phase II: Soluble Biomarker Qualification

- **Biomarkers:** measured in *placebo* arms of clinical trials
- **Endpoint:** 24M (12M when 24M unavailable; 36M ancillary when available)
- **Primary Outcome:** Radiographic progression (0.7 mm joint space narrowing)
- **Secondary Outcomes:** Radiographic progression (0.5 mm joint space narrowing); Pain Progression; Radiographic+Pain Progression



Trials & number (n) placebo treated participants with data available for trabecular bone texture (TBT) biomarker analyses:

Calcitonin (NCT00486434, NCT00704847)	n=809 [Novartis]
VIDEO (vitamin D) (ISRCTN94818153)	n=237
Cindunistat (iNOS inhibitor) (NCT00565812)	n=27 [Pfizer]
Sprifermin I (FGF-18) (NCT01033994)	n=48 [Merck Serono]
Sprifermin II (FGF-18) (NCT01033994)	n=108 [Merck Serono]
TissueGene-C (TGF-beta1) (NCT02072070)	n=81 [Invossa/KOLON Life Science]
SEKOIA (Strontium Ranelate) (ISRCTN41323372)	n=120 (Servier]

FNIH Foundation for the National Institutes of Health

THE biomarkers CONSORTIUM

Status of Soluble Biomarker Qualification

Primary COU:

Prognostic baseline biomarkers - MRI, biochemical and radiographic trabecular bone texture (TBT) - to enrich enrollment/identification of osteoarthritis patients that are likely to experience long term radiographic progression in the absence of treatment.

Secondary or allied COUs:

Prognostic short-term change in MRI or time-integrated concentrations (TICs) in biochemical and TBT biomarkers (baseline to 12 months) to provide a method of identification of osteoarthritis patients that are likely to experience long-term radiographic progression in the absence of treatment.

LOI for biochemical markers targeted for June 2019 submission to FDA

Status of Soluble Biomarker Qualification

Biochemical: 9 biochemical markers in urine (u) or serum (s) -- uCTXII sPIIANP and uC2C-HUSA (are derived from COL2A1); sNTXI, uNTXI, sCTXI, uCTXIalpha, uCTXIbeta (are derived from COL1A1); and sHyaluronan (PDB name 3HYA). uCreatinine (uCr) for normalizing urine biomarkers

Biomarker Domain	Available Sample Size	OA Progression Rate	Predicted Odds of progression	Estimated Power
Biochemical (n=1126)	1000	11%	1.4	88%

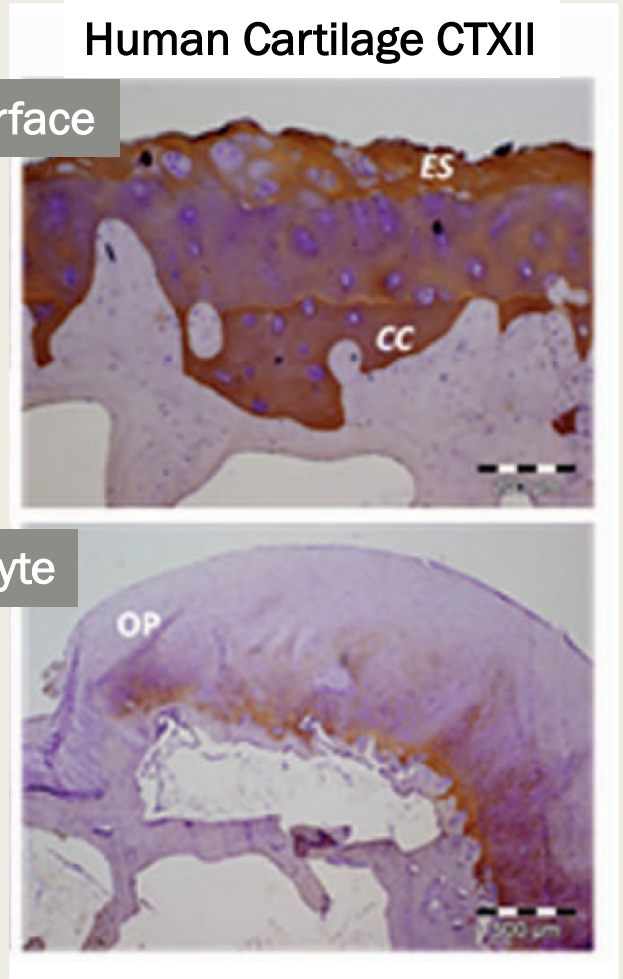
FNIH Foundation for the National Institutes of Health

THE biomarkers CONSORTIUM

Biomarkers of Collagen Degradation and Synthesis

HIGH Degradation

Type II Collagen Degradation: uCTXII



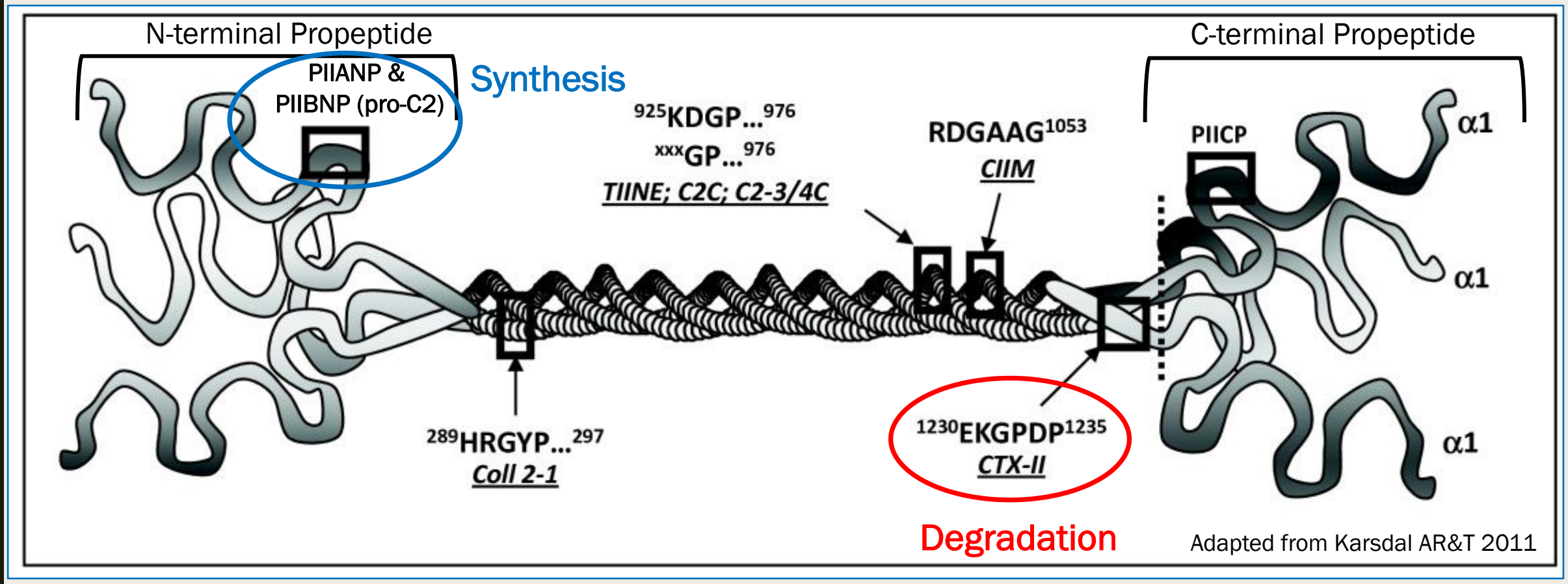
Huebner, Karsdal, Kraus et al. A&R 2014

Joint tissue Degeneration
& OA Progression

Synthesis LOW

Type II Collagen Synthesis: sPIIANP (pro-C2)

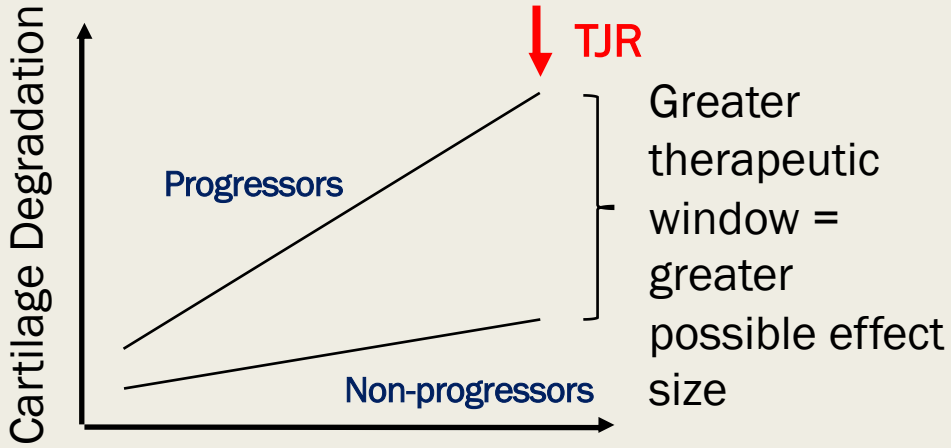
Key Biomarkers of Type II Collagen Degradation & Synthesis



TYPE II COLLAGEN

High baseline uCTX-II predicts ‘clinically relevant progression’

Pain+Radiographic Worsening over 4 years



Predictive validity of biochemical biomarkers in knee osteoarthritis: data from the FNIH OA Biomarkers Consortium. Kraus VB, Collins JE, Hargrove D, et al ARD 2017, 76:186-195.

N=600

Biomarker	Baseline concentration Mean (SD) median z score Comparators	Cases	OR (95% CI) p Value
Serum C1, 2C	−0.03 (0.98) −0.09	0.06 (1.04) −0.02	1.09 (0.91 to 1.30) 0.3510
Serum C2C	−0.02 (0.94) −0.16	0.04 (1.11) −0.12	1.05 (0.88 to 1.26) 0.5772
Serum Coll2-1 NO2	0.00 (1.03) −0.18	−0.00 (0.94) −0.13	1.00 (0.83 to 1.21) 0.9601
Serum CPII	0.00 (1.02) −0.15	−0.00 (0.95) −0.13	0.98 (0.81 to 1.18) 0.8017
Serum CS846	−0.01 (0.96) −0.21	0.03 (1.09) −0.23	1.06 (0.89 to 1.25) 0.5286
Serum CTXI	−0.05 (1.01) −0.28	0.10 (0.96) −0.04	1.18 (0.99 to 1.41) 0.0583
Serum COMP	0.02 (1.02) −0.13	−0.05 (0.95) −0.24	0.89 (0.74 to 1.07) 0.2254
Serum HA	−0.04 (1.03) −0.32	0.07 (0.93) −0.22	1.07 (0.89 to 1.29) 0.4466
Serum MMP3	−0.02 (1.00) −0.22	0.03 (1.00) −0.24	0.99 (0.81 to 1.22) 0.9416
Serum NTXI	−0.05 (0.99) −0.22	0.10 (1.01) −0.01	1.18 (0.99 to 1.41) 0.0591
Serum PIINP	0.04 (0.99) −0.03	−0.09 (1.03) −0.16	0.88 (0.74 to 1.06) 0.1729
Urine Coll2-1 NO2 creatinine adjusted	−0.02 (1.02) −0.27	0.03 (0.96) −0.20	1.05 (0.88 to 1.24) 0.6075
Urine C1, 2C creatinine adjusted	0.03 (1.02) −0.14	−0.06 (0.96) −0.30	0.91 (0.76 to 1.09) 0.3166
Urine C2C-HUSA creatinine adjusted	−0.04 (0.95) −0.20	0.09 (1.09) −0.08	1.12 (0.94 to 1.34) 0.2030
Urine CTXII creatinine adjusted	−0.07 (0.96) −0.35	0.15 (1.06) −0.09	**1.29 (1.08 to 1.55) 0.0049**
Urine NTXI creatinine adjusted	−0.04 (1.03) −0.24	0.09 (0.94) −0.07	1.17 (0.98 to 1.39) 0.0842
Urine CTXIα creatinine adjusted	−0.05 (0.99) −0.26	0.11 (1.01) −0.10	**1.20 (1.01 to 1.43) 0.0364**
Urine CTXIβ creatinine adjusted	−0.03 (1.01) −0.27	0.06 (0.97) −0.12	1.14 (0.96 to 1.36) 0.1408

Type II collagen degradation [IDS (AC-10F1)]

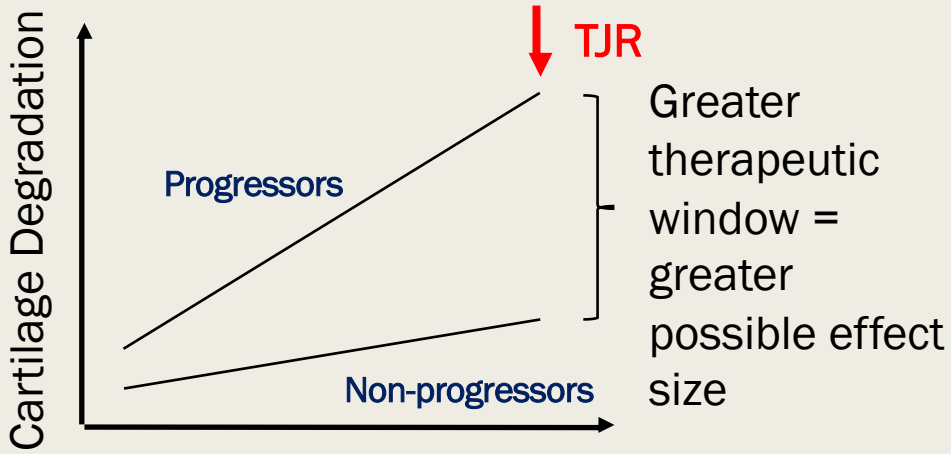
CVs 5.21%

FNIH Foundation for the National Institutes of Health

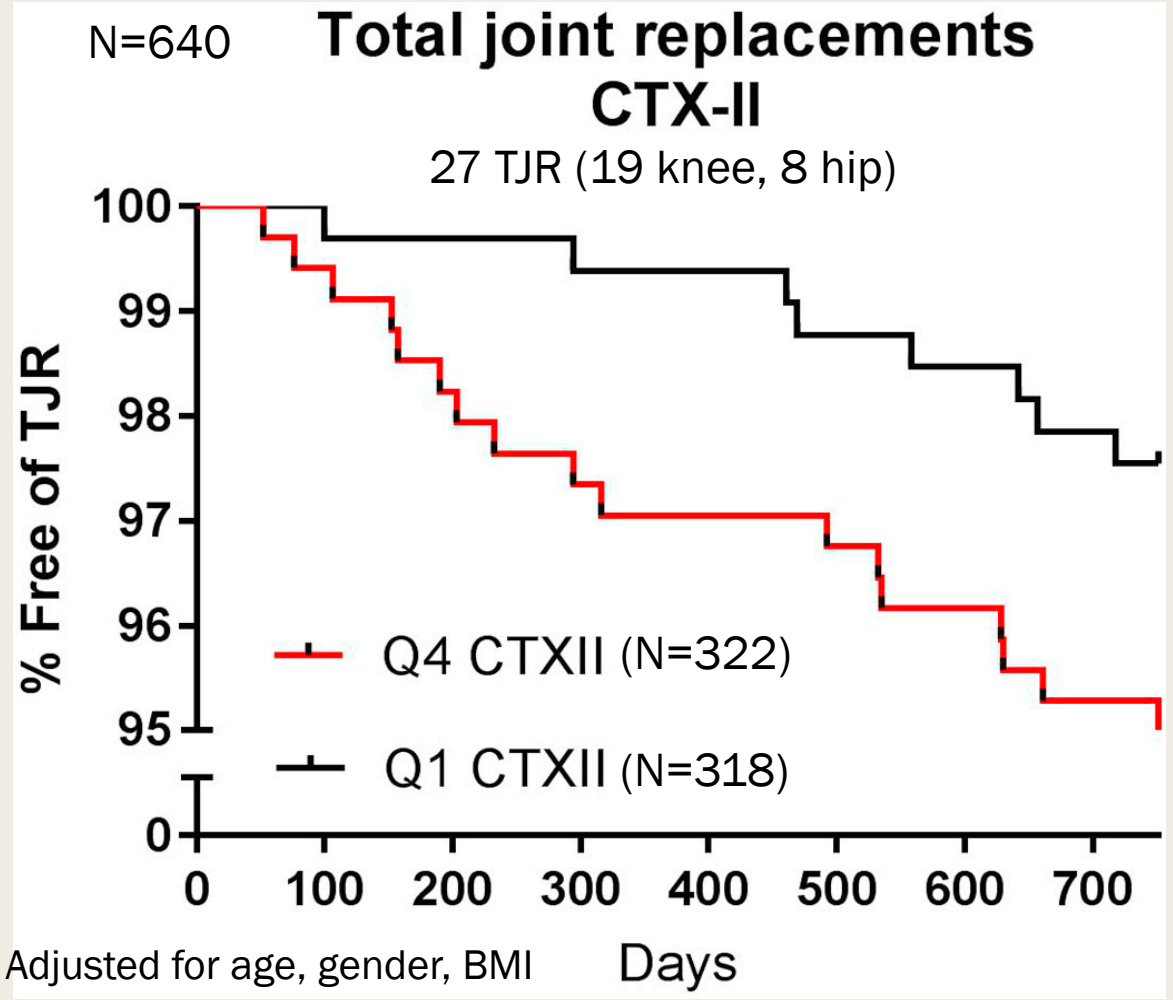
THE biomarkers CONSORTIUM

High baseline uCTX-II predicts total joint replacements (TJR) in OA trial participants over 2 years

High baseline CTXII:
3 X higher risk of TJR (knee or hip)
9 X higher risk of TKR (knee)



Post hoc analysis of two clinical trials investigating oral salmon calcitonin in OA, CSMC021C2301 (NCT00486434) and CSMC021C2302 (NCT00704847)

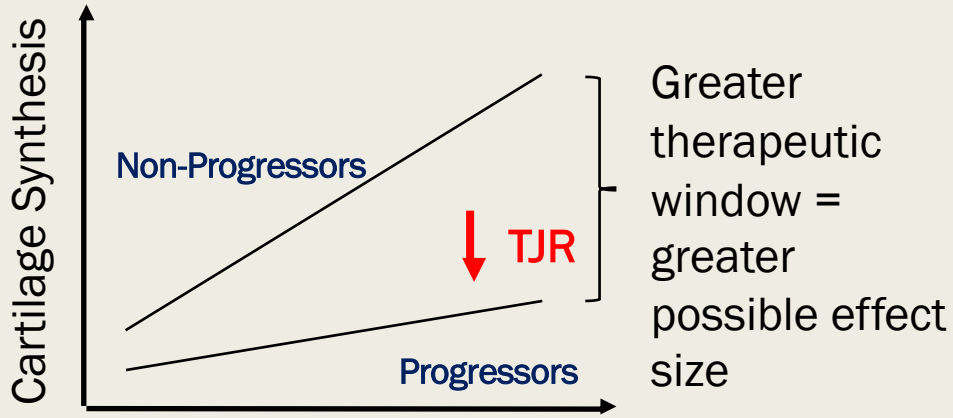


Biomarkers of bone and cartilage turnover CTX-I and CTX-II predict total joint replacements in osteoarthritis

J.J. Bjerre-Bastos, A.-C. Bay-Jensen, M.A. Karsdal, I. Byrjalsen, J.R. Andersen, B.J. Riis, C. Christiansen, A.R. Bihlet

Osteoarthritis and Cartilage 2019 27, S31-S32DOI: (10.1016/j.joca.2019.02.046)

Low 12 month Time-Integrated-Concentration of PIIANP predicts ‘clinically relevant progression’ Pain+Radiographic Worsening



Predictive validity of biochemical biomarkers in knee osteoarthritis: data from the FNIH OA Biomarkers Consortium. Kraus VB[1], Collins JE[2], Hargrove D, et al ARD 2017, 76

N=600

Biomarker	12 M TIC Mean (SD) median z score Comparators	Cases	OR (95% CI) p Value
Serum C1, 2C	−0.01 (1.00) −0.04	0.02 (1.00) −0.04	1.02 (0.85 to 1.22) 0.8354
Serum C2C	−0.01 (0.98) −0.12	0.02 (1.05) −0.09	1.00 (0.83 to 1.20) 0.9940
Serum Coll2-1 NO2	0.01 (1.02) −0.19	−0.01 (0.96) −0.18	0.98 (0.80 to 1.19) 0.8195
Serum CPII	0.01 (1.00) −0.11	−0.02 (1.00) −0.18	0.95 (0.78 to 1.16) 0.6212
Serum CS846	−0.01 (0.95) −0.19	0.03 (1.11) −0.26	1.06 (0.89 to 1.26) 0.5024
Serum CTXI	−0.07 (0.98) −0.24	0.16 (1.04) 0.02	**1.29 (1.08 to 1.54) 0.0057**
Serum COMP	0.02 (1.02) −0.10	−0.05 (0.95) −0.26	0.90 (0.74 to 1.09) 0.2687
Serum HA	−0.06 (1.00) −0.35	0.12 (1.00) −0.14	1.18 (0.98 to 1.44) 0.0877
Serum MMP3	−0.03 (0.99) −0.22	0.07 (1.03) −0.15	1.06 (0.86 to 1.31) 0.5978
Serum NTXI	−0.07 (0.97) −0.21	0.16 (1.05) 0.00	**1.28 (1.07 to 1.53) 0.0084**
Serum PIIANP	0.06 (0.98) 0.09	−0.13 (1.04) −0.18	**0.83 (0.69 to 1.00) 0.0490**
Urine Coll2-1 NO2 creatinine adjust	−0.03 (1.01) −0.29	0.06 (0.98) −0.12	1.10 (0.92 to 1.31) 0.2878
Urine C1, 2C creatinine adjusted	0.01 (1.02) −0.11	−0.03 (0.96) −0.09	0.97 (0.80 to 1.16) 0.7105
Urine C2C-HUSA creatinine adjusted	−0.05 (0.98) −0.25	0.11 (1.04) −0.05	1.16 (0.96 to 1.39) 0.1231
Urine CTXII creatinine adjusted	−0.08 (0.98) −0.30	0.19 (1.02) 0.03	**1.35 (1.12 to 1.62) 0.0015**
Urine NTXI creatinine adjusted	−0.06 (1.00) −0.18	0.12 (0.98) −0.11	**1.24 (1.03 to 1.49) 0.0199**
Urine CTXIα creatinine adjusted	−0.07 (0.98) −0.27	0.15 (1.03) −0.02	**1.28 (1.07 to 1.53) 0.0065**
Urine CTXIβ creatinine adjusted	−0.06 (0.97) −0.27	0.13 (1.06) −0.11	**1.27 (1.06 to 1.52) 0.0099**

Type II collagen synthesis [Merck Group/Millipore (EZPIIANP-53K)]
CV 12.3%

FNIH Foundation for the National Institutes of Health

THE biomarkers CONSORTIUM

Low baseline sPIIANP with MRI features predicts 'clinically relevant progression' -- Pain+Radiographic Worsening over 4 years

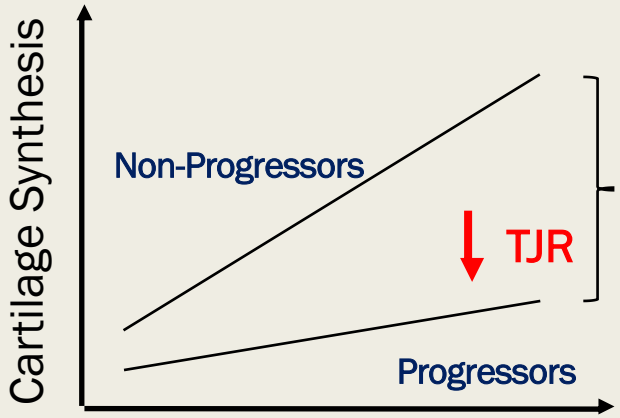
Model	A*	B	C	D
Selection Method	Stepwise, SBC Imaging + Biochem	Stepwise, AIC Imaging only	Stepwise, AIC Imaging + Biochem	Stepwise, AIC BICL + Biochem (exclude cMFTC.THCtAB)
Model Characteristics				
AUC (unadjusted)	0.679	0.682	0.696	0.692
AUC (adjusted)	0.707	0.715	0.737	0.720
AUC (adusted, 10 fold cross val)	0.670	0.677	0.697	0.678
IDI (vs covariates only model)	0.0825	0.0896	0.1090	0.0927
NRI (vs covariates only model)	0.5229	0.5847	0.5753	0.5613
% cases correctly reclassified	34%	34%	28%	30%
% controls correctly reclassified	19%	24%	29%	26%
Biomarkers Included				
BICL	Locations with osteophyte	Locations with osteophyte	Locations with osteophyte	Locations with osteophyte
Chondrometrics	Cart thickness: ccMF.ThCtABMFTC	Cart thickness: ccMF.ThCtABMFTC	Cart thickness: ccMF.ThCtABMFTC cMF.ThCtABMFTC eMF.ThCtABMFTC	Cart thickness: ccMF.ThCtABMFTC ecMF.ThCtABMFTC
BiomediQ	Med meniscus volume	Med meniscus volume	Med meniscus volume	Med meniscus volume
Imorphics		Patella Vector of 3D shape	Patella Vector of 3D shape	Patella Vector of 3D shape
BIOCHEM			Serum PIIANP	Serum PIIANP

* The same set of biomarkers are chosen in the SBC imaging only analysis, and the p-value based selection (N=600) [Hunter & Kraus et al, unpub)

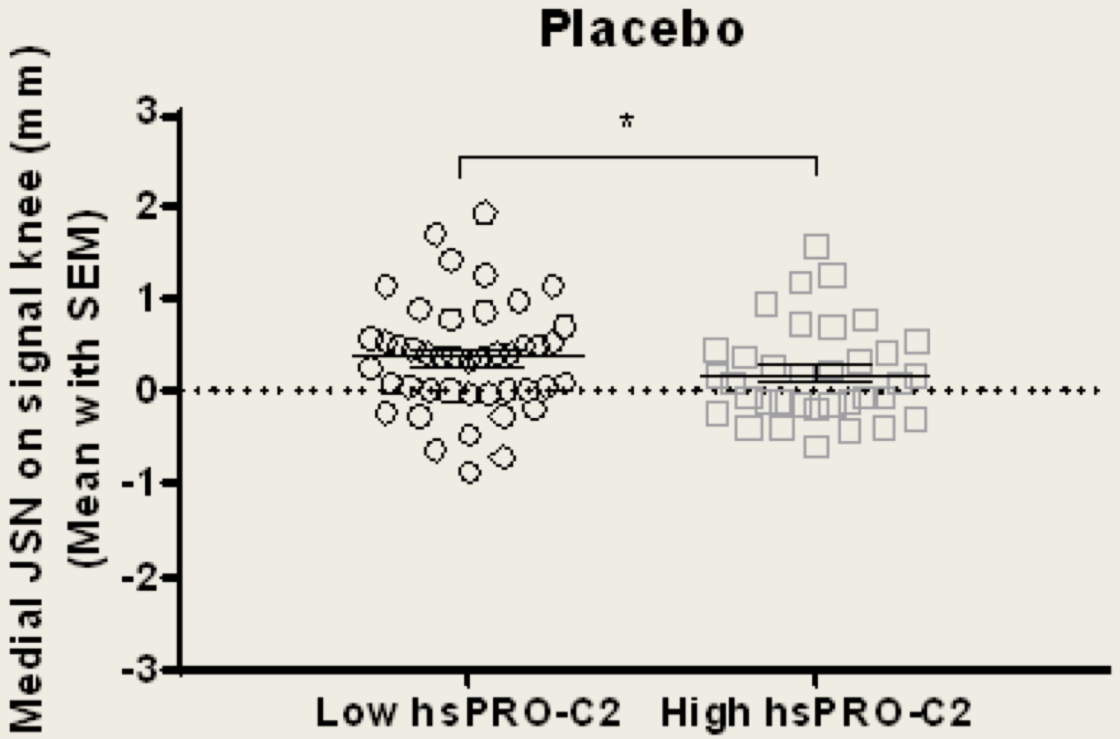
FNIH Foundation for the National Institutes of Health

THE biomarkers CONSORTIUM

Low Baseline PIIBNP (Pro-C2) predicts radiographic progression



Greater therapeutic window = greater possible effect size



≤Median (n=44)

>Median (n=35)

Student's t-test. Adjusted for BMI, sex, age, and baseline JSW

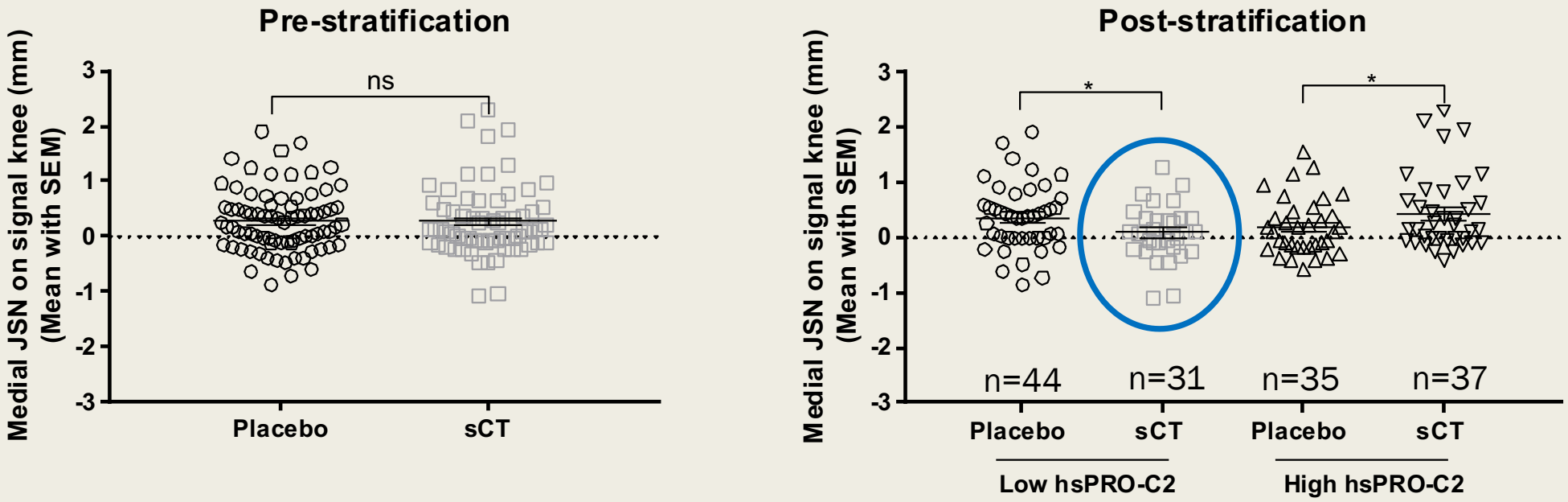
CSMC021-2301 Sub-study of oral salmon calcitonin trial NCT00486434

Yunyun Roy Luo1,2, Niamh Higgins2, Yi He2, Inger Byrjalsen2, Jeppe Andersen2, Asger Bihlet2, Morten Karsdal1, Anne C. Bay-Jensen1

1University of Copenhagen, Denmark

2Nordic Bioscience A/S, Denmark

Low baseline PIIBNP (Pro-C2) predicts greater response to Oral Salmon Calcitonin



Student's t-test. Adjusted for BMI, sex, age, and baseline JSW

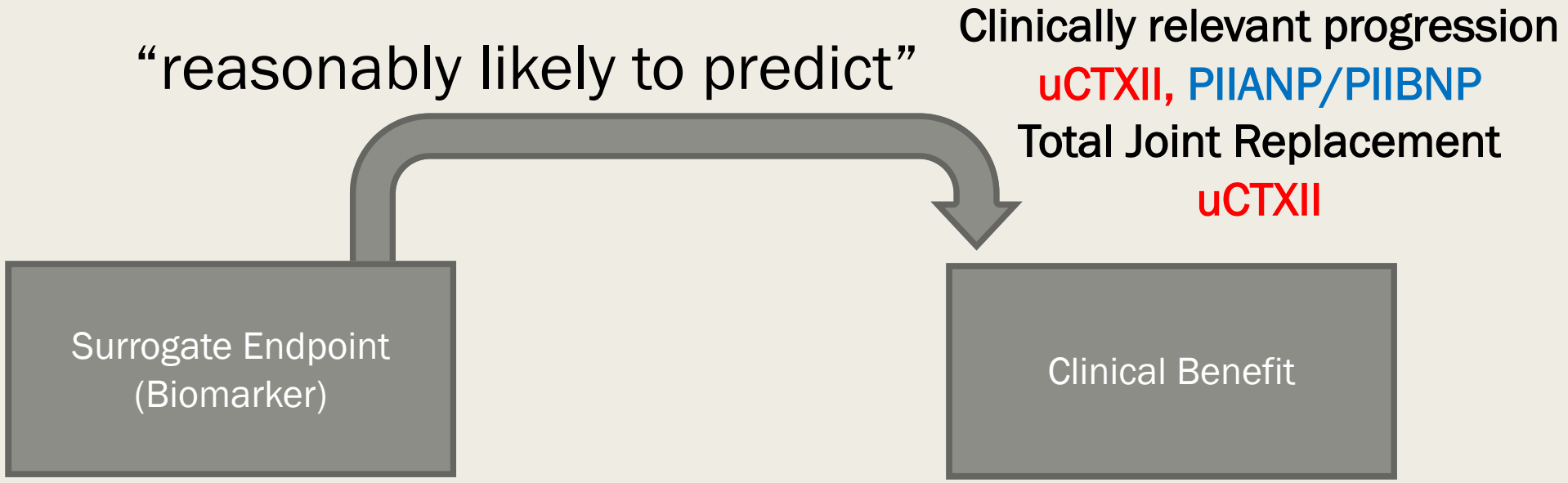
CSMC021-2301 Sub-study of oral salmon calcitonin trial NCT00486434

Yunyun Roy Luo1,2, Niamh Higgins2, Yi He2, Inger Byrjalsen2, Jeppe Andersen2, Asger Bihlet2, Morten Karsdal1, Anne C. Bay-Jensen1

1University of Copenhagen, Denmark

2Nordic Bioscience A/S, Denmark

Linking biomarkers to clinically relevant outcomes



<u>To qualify for accelerated approval</u>: A drug that treats a serious condition AND generally provides a meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit on……irreversible morbidity or mortality (IMM) or other clinical benefit (i.e., an intermediate clinical endpoint)

Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014)

Remaining Challenges

- 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.

QUESTIONS?

Applying Biomarkers for Accelerated Approval of OA Structure Modifying Drugs

OARSI Meeting
Washington DC
May 16, 2019

Nikolay P. Nikolov, M.D.
Associate Director for Rheumatology
Division of Pulmonary, Allergy, and Rheumatology Products
U.S. Food and Drug Administration

Disclosure

- This presentation is not intended to convey official US FDA policy, and no official support or endorsement by the US FDA is provided or should be inferred
- The materials presented are available in the public domain
- I do not have any financial interest or conflict of interest with any pharmaceutical company

Outline

- Background
- Benefit-Risk Framework
- Definitions
- Considerations on Biomarkers and Accelerated Approval
- Structural Endpoints in OA: Challenges and Opportunities
- Summary

Background

- Significant public health issue, affecting over 30 million people in the US[1]
- Causes significant pain and disability
- Can be a serious disease[2]
- Current treatment options limited to symptomatic therapies and have toxicities
- Unmet need for therapies that would impact the natural history of OA

[1] Castaneda MG, et al., Arthritis Care and Res (Hoboken), 2016 May; 68(5):574-80

[2] https://www.oarsi.org/sites/default/files/docs/2016/oarsi_white_paper_oa_serious_disease_121416_1.pdf

Benefit-Risk Assessment

Basis for FDA's regulatory decision-making

- Benefit = Clinical Benefit = an improvement in how a patient
  - Feels → *Feel*
  - Functions → *Function*
  - Survives → *Survival (Joint survival)*

  Endpoints in trials of OA treatments need to demonstrate the clinical benefit directly or at least be interpretable with respect to the clinical benefit to be expected
- Risk: every therapeutic carries some degree of risk and in this framework every product is expected to show some benefit that outweighs the risk of the therapy

Outcome Measures

- Efficacy assessment
  - Clinical endpoint
    - Measures how a patient feels, functions, or survives
  - Surrogate endpoint
    - A measure expected to predict clinical benefit or harm
  - Biomarker
    - Objective measure of normal biologic process, pathogenic process, or pharmacologic response to an intervention
- Safety assessment
  - Descriptive and empiric
  - Guided by drug class, prior experience, events of interest, etc.

BEST: Biomarkers, EndpointS, and other Tools

- A glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care
- Created by the NIH-FDA Biomarker Working Group
- BEST harmonizes terms and definitions and addresses nuances of usage and interpretation among various stakeholders

http://www.ncbi.nlm.nih.gov/books/NBK326791/

Definitions

- **<u>Clinical Outcome:</u>** An outcome that describes or **reflects how an individual feels, functions or survives**
  - Historically, clinical outcomes have served as **direct measures of clinical benefit**
- **<u>Biomarker:</u>** A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. *Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers*
  - **A biomarker is not an assessment of how an individual feels, functions, or survives**

Definitions

- **<u>Surrogate Endpoint:</u>** An endpoint that is used in clinical trials as **a substitute for a direct measure of clinical benefit.** A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather **is expected to predict that clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence**

  From a U.S. regulatory standpoint, surrogate endpoints and potential surrogate endpoints can be characterized by the level of clinical validation: **validated surrogate endpoint, reasonably likely surrogate endpoint, candidate surrogate endpoint**

Section 507(e)(9) of the FD&C Act

"[t]he term 'surrogate endpoint' means a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is **not itself a direct measurement of clinical benefit**, and—

- ''(A) is **known to predict clinical benefit** and could be used to support **traditional approval** of a drug or biological product; or
- ''(B) is **reasonably likely to predict clinical benefit** and could be used to support the **accelerated approval** of a drug or biological product in accordance with section 506(c).''

*Section 3011 of the 21st Century Cures Act established section 507 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

Accelerated Approval Considerations

- Product must be for a serious or life-threatening disease or condition
- FDA is to take "…into account the **severity, rarity, or prevalence of the condition** and the **availability or lack of alternative treatments**" when determining whether to grant approval under this program
- For drugs granted accelerated approval, **postmarketing confirmatory trials are generally required to verify and describe the anticipated effect** on irreversible morbidity or mortality or other clinical benefit
- Approval of a drug may be withdrawn, if trials fail to verify clinical benefit or do not demonstrate sufficient clinical benefit to justify the risks associated with the drug

Guidance for Industry: Expedited Programs for Serious Conditions, issued May 2014:
https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf

Surrogate Endpoints: Examples

- **Traditional Approval**
  - Serum uric acid (Gout)
  - Blood pressure (HTN)
  - Electrolytes (Na, K)
  - Hemoglobin A1c (DM)
  - LDL cholesterol
  - Viral load (HIV)
- **Accelerated Approval**
  - PFS, ORR (solid tumors)
  - Ig responses (Vaccines)
  - Skeletal muscle dystrophin (DMD)
  - Sputum conversion to negative (TB)
  - Viral load (HIV)

Table of Surrogate Endpoints:
https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

Evidentiary Criteria for Surrogate Endpoints

What the law says: Discusses, in general terms, the evidence needed to support a "reasonably likely surrogate" but not a validated surrogate endpoint

What FDA guidance documents say:

- FDA has issued a guidance document that contains fairly granular guidance on evidence that should be considered when evaluating a "reasonably likely surrogate" supporting accelerated approval
- At present, no FDA guidance document contains a detailed discussion of the evidence needed to establish a "validated surrogate endpoint" supporting traditional approval, however FDA has stated that the standard is high

Guidance for Industry: Expedited Programs for Serious Conditions, issued May 2014:
https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf

Assessment of Candidate Surrogate Endpoints

- **Biologic plausibility**: whether surrogate is on pathophysiologic pathway leading to clinical outcome of interest (causal? necessary intermediate?)
- **Strength and consistency of epidemiologic data supporting relationship** between surrogate and clinical outcome of interest
- **Whether treatment effects on surrogate have been shown to predict treatment effects on clinical outcome of interest** (with drugs in the same/related pharmacologic class? with drugs from distinct pharmacologic classes/ regardless of the mechanism of the intervention?)

Guidance for Industry: Expedited Programs for Serious Conditions, issued May 2014:
https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf

Complex Relationships: *Disease – BM – Clin Outcome*

Disease processes are complex and drugs have effects beyond those that are intended, thus…

- **Identifying the right surrogate endpoints** that can reliably or reasonably likely predict a treatment's effect on a clinical outcome, and
- **Defining the magnitude of change** in the surrogate endpoint that would reliably predict a meaningful changes in the clinical outcome of interest

…can be a challenge

Complex Relationships: *Disease – BM – Clin Outcome*

- When biomarkers/surrogate endpoints are used, there is always some **residual uncertainty** about the nature of a treatment's benefit
  - Biomarkers may fail to predict clinical benefit, i.e. the assumption of the strength (or presence) of relationship to clinical endpoint is not valid
- Notable examples of biomarkers that performed well in identifying patients at risk for poor outcomes/progression but **failed** to predict a treatment's effect on those outcomes:
  - HDL-C and CV outcomes
  - NSVT and death

Complex Relationships: *Disease – BM – Clin Outcome*

- **Correlation between a biomarker and a clinical endpoint is not sufficient** to demonstrate that an effect on the proposed surrogate endpoint will reliably predict an effect on the clinical outcomes of interest
- **Ideally**, this demonstration would be based on empirical evidence from randomized, controlled comparisons from clinical trials and/or on a comprehensive understanding of the disease process and drug mechanism of action

 After Fleming TR and Powers JH, 2012, Statistics in Medicine, 31.25: 2973–2984

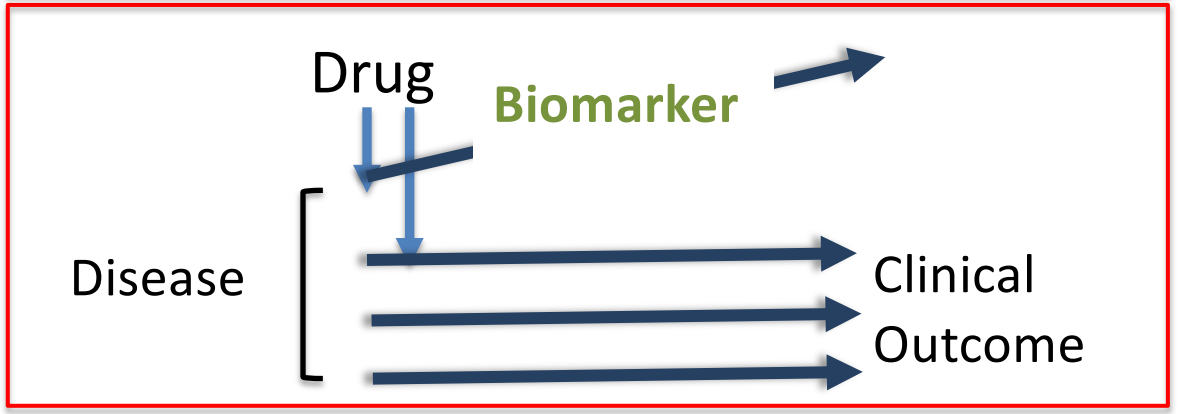
Complex Relationships: *Disease – BM – Clin Outcome*

- Surrogate on **causal pathway** modulated by drug
- Biomarkers may reflect and predict changes in the clinical outcome

Complex Relationships: *Disease – BM – Clin Outcome*

- Surrogate on **causal pathway** modulated by drug
- Biomarkers may reflect and predict changes in the clinical outcome

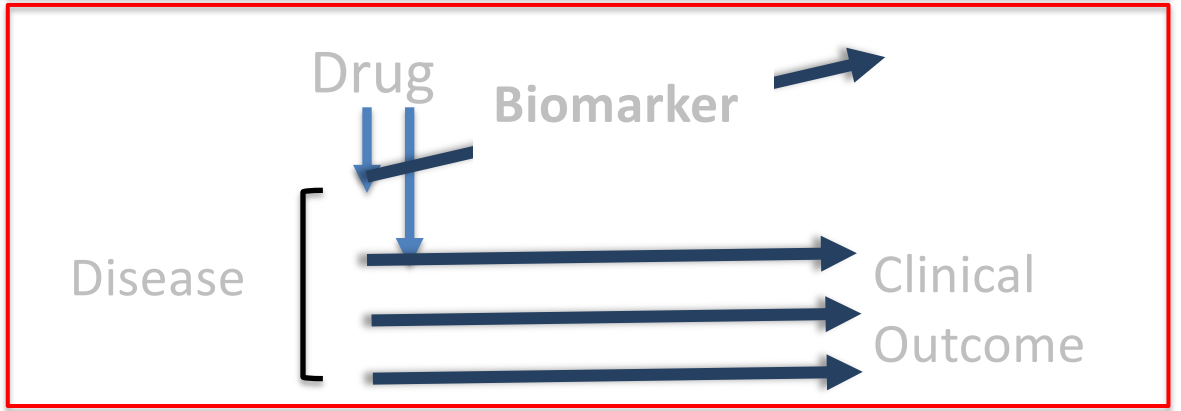
- Surrogate ***not* on pathway** of drug MOA so may only indirectly correlate with outcome
- **Multiple disease MOAs** may lead to clinical outcome and drug may impact only one



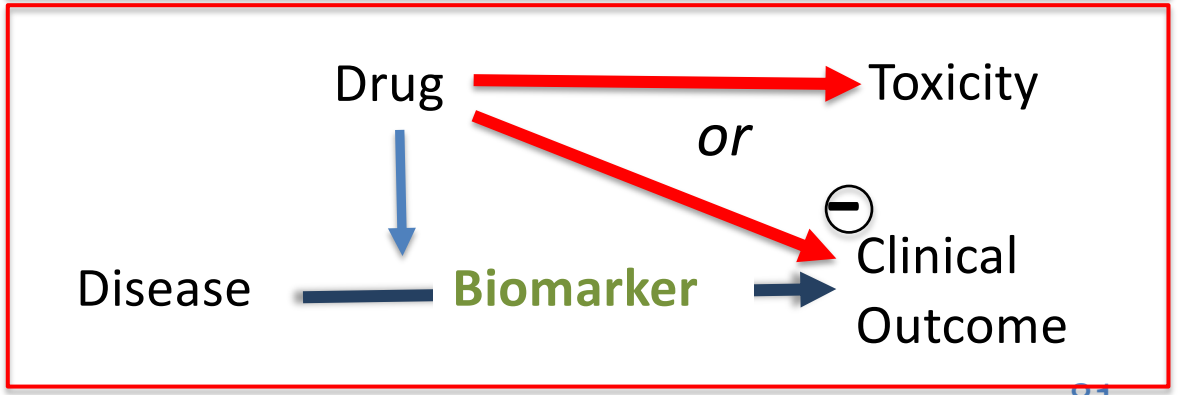
Complex Relationships: *Disease – BM – Clin Outcome*

- Surrogate on **causal pathway** modulated by drug
- Biomarkers may reflect and predict changes in the clinical outcome

- Surrogate ***not* on pathway** of drug MOA so may only indirectly correlate with outcome
- **Multiple disease MOAs** may lead to clinical outcome and drug may impact only one



- May lead to **other toxicities** so that BM does not adequately predict benefit / risk balance
- Drug may induce **adverse effects on desired clinical outcome** through a pathway *not reflected* by BM (so net benefit of drug not reflected by change in BM)



Confirmatory Trial Considerations

- Conducting post-marketing studies to verify the benefit of drugs approved under accelerated approval can be challenging
  - Drug availability after accelerated approval may interfere with the ability to recruit and keep patients assigned to placebo from crossing over to active treatment, especially for long-term clinical trials; missing data is also a concern
- This can compromise the validity of such studies and preclude the reliable assessment of a clinical outcome for drugs approved under accelerated approval, leaving the residual uncertainties about the true clinical benefit-risk assessment of a marketed product unaddressed

Surrogate Endpoint Considerations

- *"**Because of the substantial risk of adversely affecting the public health,** if a biomarker is falsely accepted as a surrogate endpoint**, robust scientific evidence is needed to justify qualification of a biomarker for use as a surrogate endpoint**. There have been **numerous biomarkers that represented plausible surrogate endpoints** (e.g. reduced rate of ventricular premature beats following a heart attack, cardiac output in congestive heart failure, increased HDL cholesterol in patients with coronary artery disease). **However, when tested in outcome trials, these biomarkers have failed to predict the expected clinical benefit**. It has generally not been clear whether this represented an erroneous expectation of a relationship of the biomarker to the outcome or an unrecognized off-target effect of the drug... "*

Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools, issued January 2014:
https://www.fda.gov/files/drugs/published/Qualification-Process-for-Drug-Development-Tools.pdf

Use of Biomarkers in Drug Development

- **Context of use**: the disease setting and how the biomarker is to be used (e.g., the BEST biomarker type)
- Individual biomarkers can (eventually) serve multiple purposes, for example….
  - **Diagnostic**: cut point for diagnosis established
  - **Prognostic**: predicting likelihood of disease outcomes/complications
  - **Predictive**: predicting likelihood of response to drug
  - **Pharmacodynamic**: measures a biological response
  - **Surrogate endpoint**: response to drug predicts benefit on clinical outcome
- Use may **evolve over time**, as experience and data on course, predictive qualities, relationship to outcomes, responsiveness to treatment expands

Surrogate Endpoints: Examples

- **Traditional Approval**
  - Serum uric acid (Gout)
  - Blood pressure (HTN)
  - Electrolytes (Na, K)
  - Hemoglobin A1c (DM)
  - LDL cholesterol
  - Viral load (HIV)
- **Accelerated Approval**
  - PFS, ORR (solid tumors)
  - Ig responses (Vaccines)
  - Skeletal muscle dystrophin (DMD)
  - Sputum conversion to negative (TB)
  - Viral load (HIV)

Table of Surrogate Endpoints:
https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

U.S. FOOD & DRUG ADMINISTRATION

OA Drug Development

Current Approach of Drug Development for OA

- Drugs approved for OA to date have been approved based on patient-reported outcomes (PROs) assessing two key OA domains
  - Pain → *Feel*
  - Function → *Function*

Patient Reported Outcomes in OA

- Examples of endpoints used in OA drug development
  - Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC pain, function, stiffness)
  - Visual Analogue Scale ratings (VAS function and pain)
  - Patient global
  - Investigator's global
- FDA is open to other PROs guided by input from patients

OA Complex Relationships: *Disease – BM – Clin Outcome*

- OA is a complex and variable disease of more than just one tissue
  - Biomechanical factors, i.e. load, alignment, traumatic factors, meniscal injury, etc.
  - Genetic factors
  - Articular changes
  - Periarticular changes, bone remodeling
  - Tissue-level inflammation
- Discordance between structural changes and clinical symptoms
- No uniform definition of disease progression

Structural Outcomes in OA: *Challenges*

- Interruption of structural damage, preventing progressive loss of function and/or progressive increase in pain would be a substantial clinical benefit
  - Treatment may affect one of multiple pathways
    - What structural endpoint is relevant?
    - What magnitude, duration of effect on structural outcome is required?[1]
    - Do on-target effects outweigh off-target effects?
  - Structural Outcomes → *Biomarker, ? Surrogates*

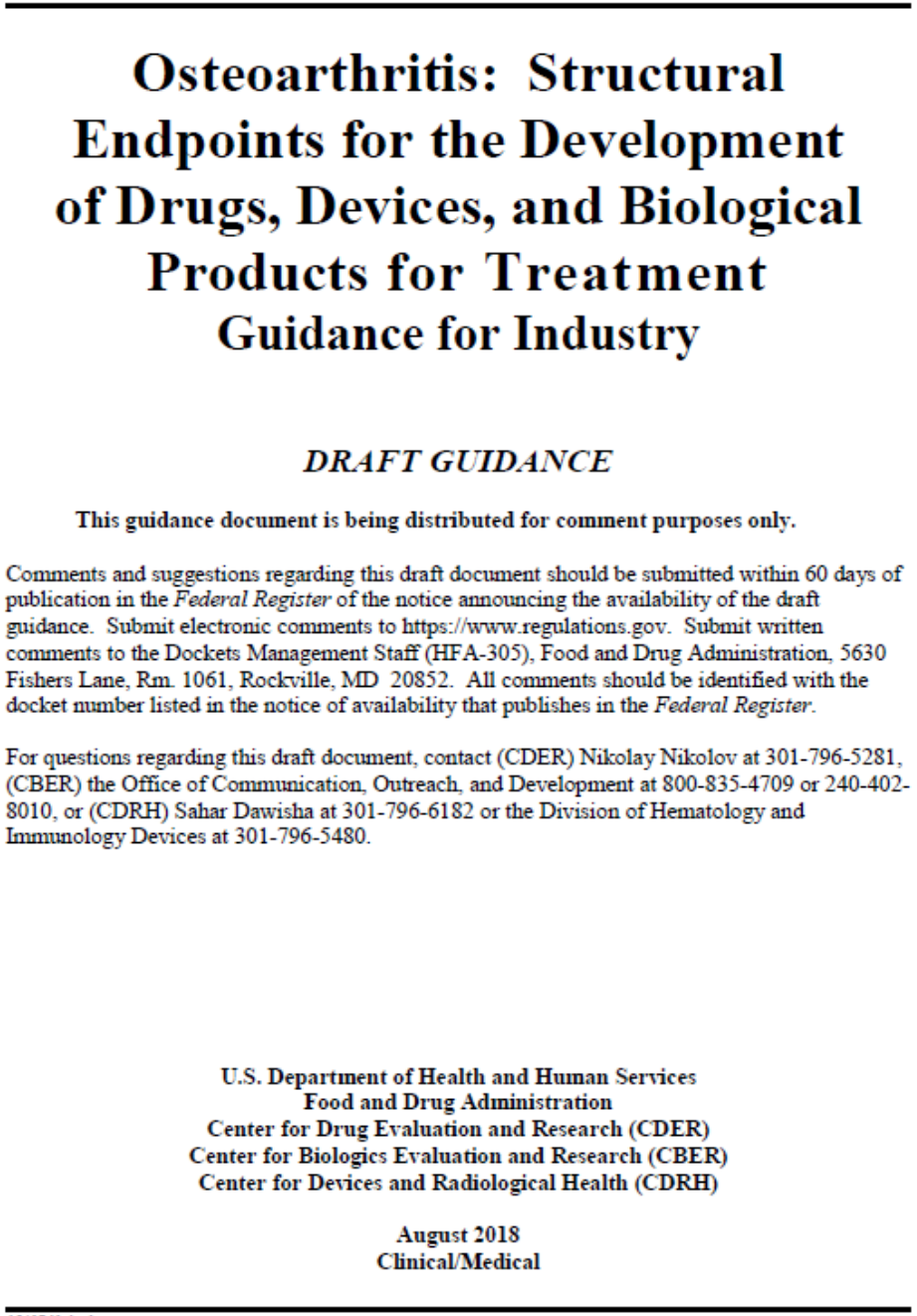
[1]After Fleming TR and Powers JH, 2012, Statistics in Medicine, 31.25: 2973–2984

Structural Outcomes in OA: *Challenges*

- **Endpoints are needed** to reliably assess the ability of a product to alter the pathogenesis and the natural history of OA
- **Knowledge gaps exist** in the ability of treatment effects on common measures of structural progression to reliably predict treatment effects on direct measures of how patients function and feel
- To use structural outcomes in the benefit-risk assessment, we **need to be able to describe the clinical benefit** expected from the structural change

Structural Outcomes in OA: *Challenges*

- Approaches to use of structural outcomes in OA trials will depend on level of evidence and information available to characterize clinical benefit
  - With less information, structural outcomes may still be useful as adjunct or secondary endpoints in drug development
  - To be used as the primary endpoint to support approval, a high level of characterization would be needed about the relationship of the drug-induced changes of the structural outcome to the anticipated clinical benefit



Osteoarthritis: Structural Endpoints for the Development of Drugs, Devices, and Biological Products for Treatment
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Nikolay Nikolov at 301-796-5281, (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010, or (CDRH) Sahar Dawisha at 301-796-6182 or the Division of Hematology and Immunology Devices at 301-796-5480.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

August 2018
Clinical/Medical

15437dftcln.doc
07/18/18

Structural Endpoints in OA: Draft Guidance

Published in August 2018

Structural Outcomes in OA: *Opportunities*

- Engagement of:
  - Patients and their care givers
  - Health care professionals
  - Academics/clinical trialists/researchers
  - Industry
  - Government/regulators/payers

Structural Outcomes in OA: *Opportunities*

- Initial approval based on establishing efficacy on symptomatic endpoints, i.e. pain in OA
  - After the initial approval, investigate the ability of structural outcomes to predict long term clinical benefit

Structural Outcomes in OA: *Opportunities*

- Study designs to assess direct clinical benefit of therapies that inhibit structural damage or target the underlying pathophysiology associated with OA
  - Composite endpoints that capture joint replacement, and "end-stage" joint disease, i.e. the severe, irreversible, intolerable pain or functional impairment
  - Enrichment strategies
    - Models of accelerated OA
    - Trials in subjects prior to knee replacement

Ways to Engage FDA for Review and Advice

IND/NDA/BLA Pathway

Within an individual drug development program

Investigational New Drug (IND) submissions to FDA

Potential to result in *labeling* statements

DDT Qualification Pathway

Outside of an individual drug development program

Development of novel outcome measures (e.g., COA, biomarker) for use in multiple drug development programs addressing unmet measurement needs

Potential to result in *qualification* of outcome measure

Critical Path Innovation Meetings Pathway

Outside of an individual drug development program

Potential for *general CDER advice* on specific methodology or technology (e.g., PRO, wearables) in its early stages of development

Meetings are informal, non-binding discussions

DDT = Drug Development Tool; PRO = Patient-Reported Outcome
NDA = New Drug Application; BLA = Biologics Licensing Application

Summary

- Establishing surrogate endpoints is a challenging, long and resource-intensive process that requires participation of many stakeholders
- Complex relationship exists between pathophysiology, structural damages, and clinical presentation and natural history of OA
- Ultimately, the goal of OA treatments is to provide **clinical benefit to the patient**
  - Goal of clinical trials is to demonstrate this benefit
- FDA recognizes the important public health need in OA and is open to collaborate with all stakeholders to bring safe and effective treatments for OA to market

Key References

- OA Guidance
  - https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071577.pdf
- OA Patient-Focused Drug Development (PFDD)
  - https://www.arthritis.org/Documents/Sections/Science/OA-Voice-of-the-Patient-Report.pdf
- Surrogate Endpoint Resources
  - https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development

APPROVAL OF THERAPEUTICS FOR OSTEOARTHRITIS IN 2019

Lee S. Simon, MD
SDG LLC
Cambridge, MA

Consulting

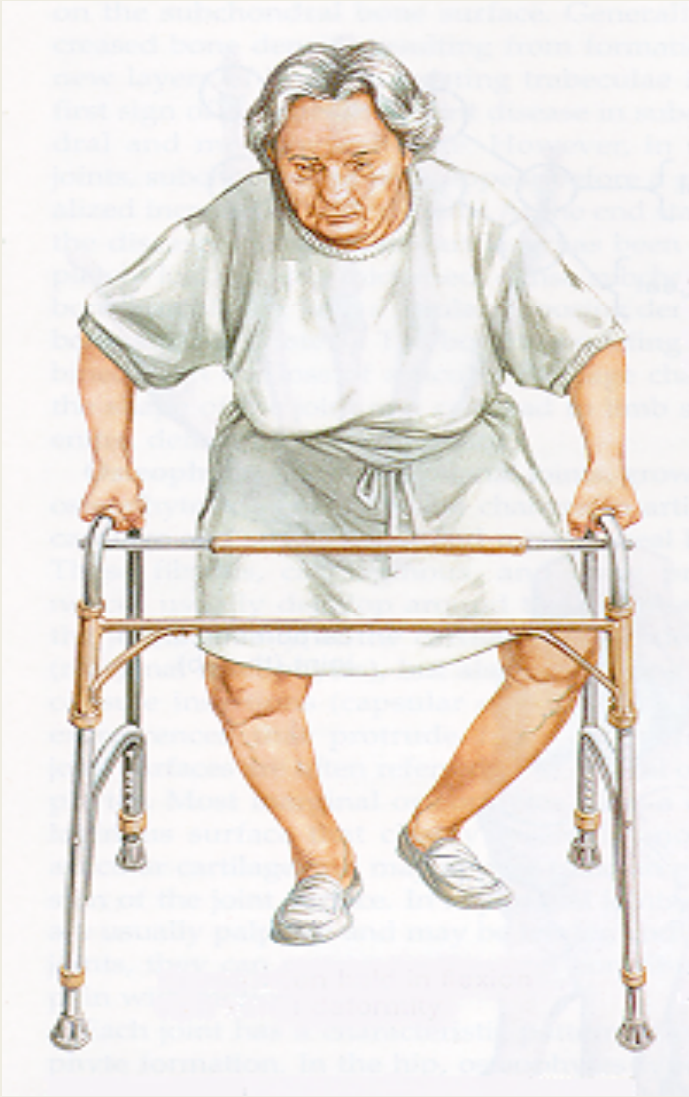
Abbott, Abraxxis, AcelRx, Affinergy, Agenus, Alder, Alimera, Alpha Rx, Altea, Analgesic Solutions, Antares, Anthera, Array, Asahi, Astra Zeneca, Avanir

Bayer, CaloSyn, Cephalon, Cerimon, Daiichi Sankyo, Dara, Dr Reddys, Durect, Elcos Sciences, EMD Serono, Eupraxia, Externa, Fidelity, Flexion, Forest, Genco, Genzyme, Gilead

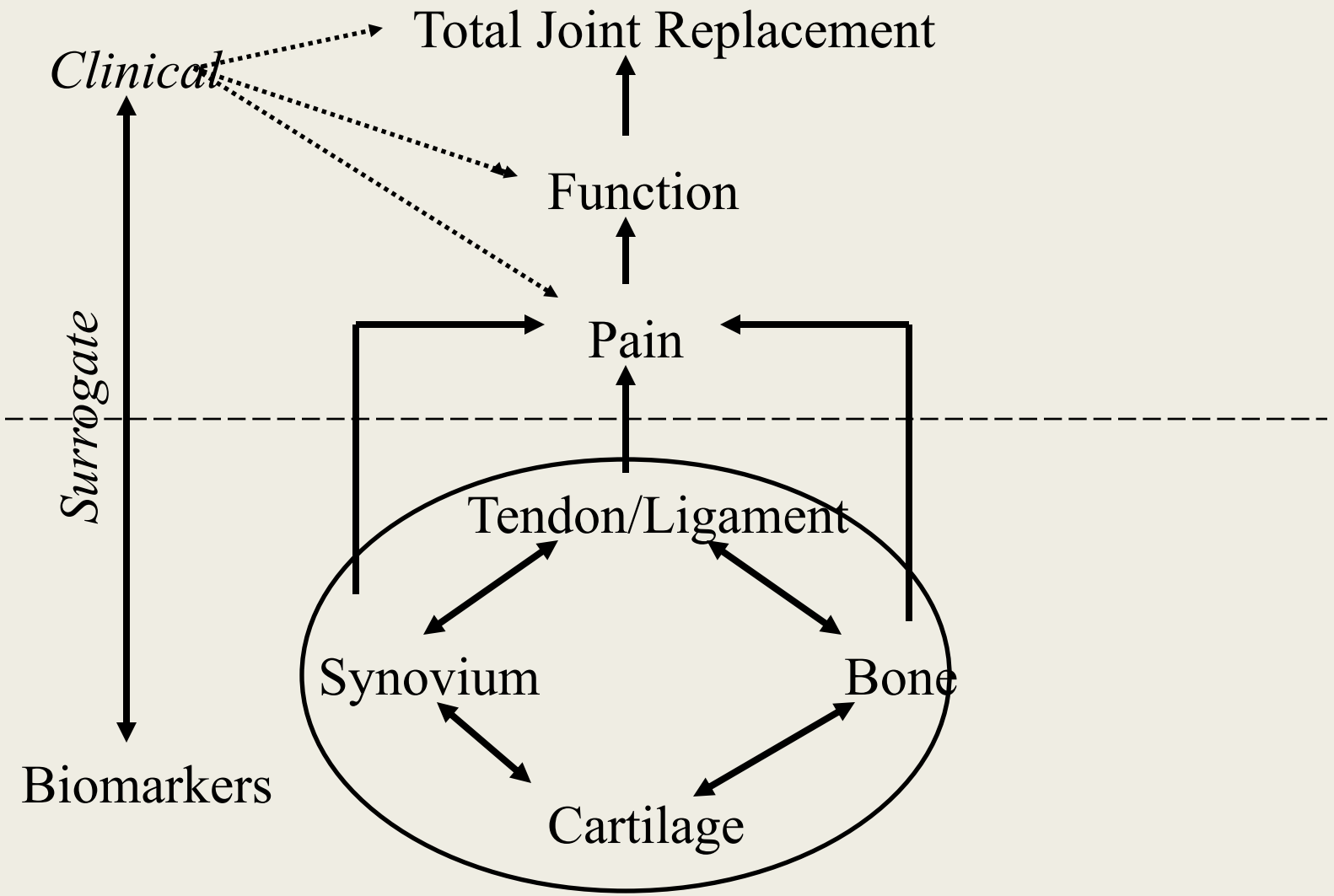
Hisamatsu, Horizon, Idera, Imprimis, Inmedix, Inotek, Jazz, JP Morgan, JRX Biopharm, Kiniksa, Knopp, Kowa, Leerink Swann, Lilly, Luxor, Medac, Metabolex, Neos, Nomura, Novartis, Nuvo Research

Omeros, Paraxel, Pfizer, PLx Pharma, Pozen, Proprius, pSivida, Purdue, Regeneron, Remedy, Rigel, Roche, Samumed, Sandoz, Sanofi, Shire, Takeda, Talagen Tigenix, Vical, Wyeth, XTL, Zydus

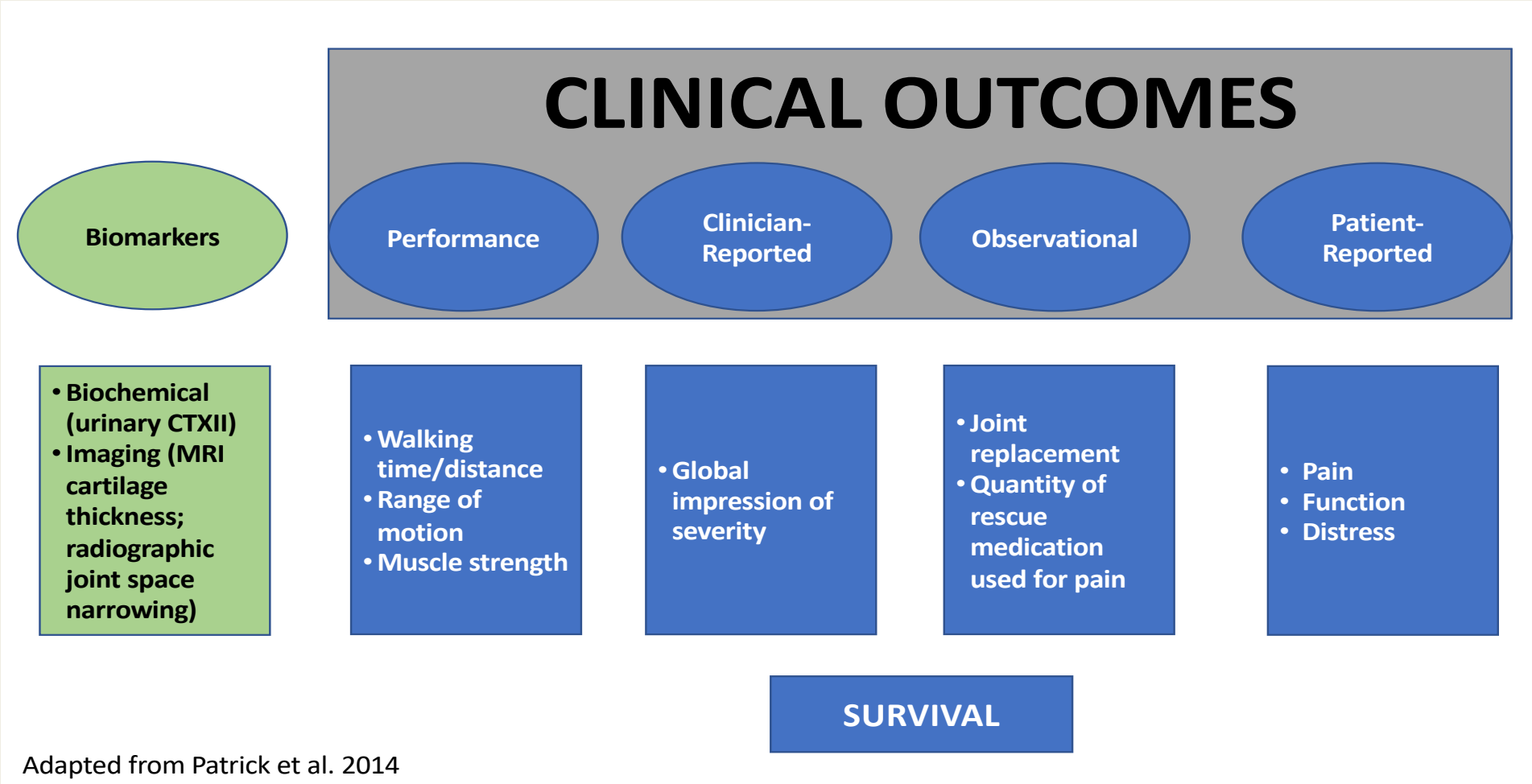
What is the Clinical Benefit from Therapy?



Osteoarthritis: The “Joint Organ”



What Are Potential Measurable Outcomes?



Adapted from Patrick et al. 2014

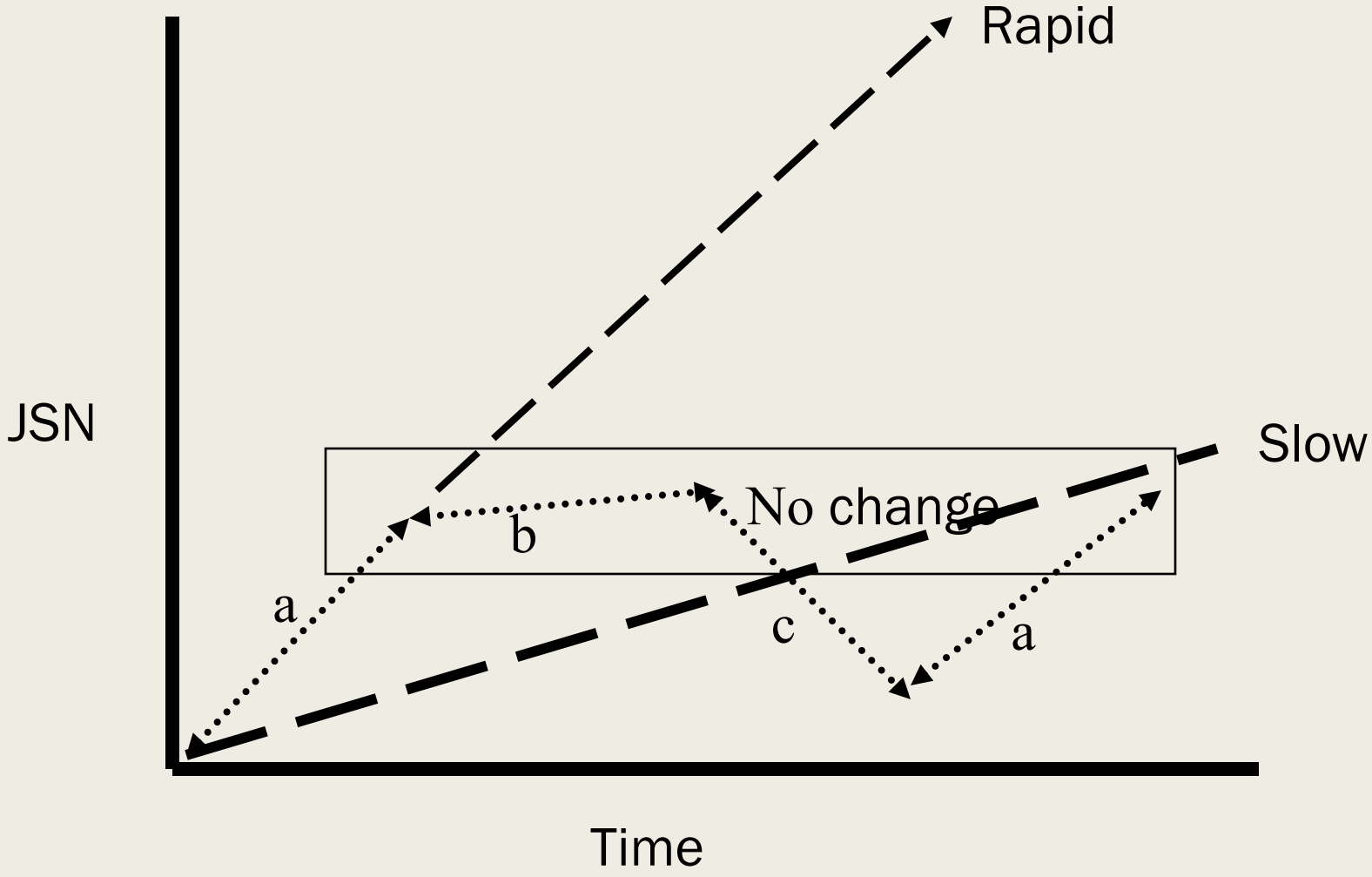
Current OA Drug Development Programs

- To date typical development program
  - *Signs and symptoms*
    - Pain
    - Function
    - Patient global
- What is expected in structural drug development programs
  - *Structural benefit must be linked in some manner with symptomatic benefit (how a patient might feel, function or survive)*
  - *Assess benefit to entire joint*
    - Halt progression of damage
    - Reverse damage

Challenges of OA Drug Development

- OA is multifactorial in cause
- Unpredictable progression
  - *Rapid or slow progression*
- Complex etiopathogenesis
  - *A progressive disease **of the whole joint:***
    - Subchondral bone followed by effects on cartilage, with consequent increase in low grade inflammation
  - *A progressive disease **of cartilage***
    - Subsequently impacting subchondral bone and consequent increase in low grade inflammation
    - Is it a progressive disease of ***abnormal cartilage*** sustaining normal load or ***normal cartilage*** being subjected to abnormal loading
  - *All of the above?*

OA: Joint Space Narrowing Progression



Challenges of OA Drug Development

- There is a recognized discordance between structural changes and signs, symptoms and function
- There remains a lack of standard definitions of disease progression by x-ray, MRI, or other techniques
- There remains an absence of measured endpoints to reliably demonstrate that a product alters OA disease progression

Challenges of OA Drug Development

- These complex and variable pathologic changes lead to significant pain, impaired function and ultimately to long-term disability and in some joint replacement
- It remains unclear what magnitude of change in measured structural endpoints would translate to a clinically meaningful benefit to patients
    - i.e., reliably predict both reduced pain and increased function or prolonged time to end-stage disease or a composite of symptoms and TJR

Considerations for OA Drug Development

- Accepting structural endpoints as valid outcome measures for accelerated approval
- Substantial confidence exists that a change in the proposed structural endpoint will reliably predict an effect on the clinical outcomes
  - Based on empirical evidence from randomized, controlled comparisons from clinical trials
  - Based on a comprehensive understanding of the disease process and product mechanism of action

Goals of a Structure Modifying Development Program

- The ultimate goal of treatment is to impact structural damage, specifically targeting the underlying pathophysiology associated with OA resulting in avoidance or significant delay of the complications of joint failure
  - *The need for joint replacement?*
- Decrease the worsening of function and pain
  - *Either of these might be important clinically relevant outcomes*

An Example of a Structure Modifying Trial

- Risedronate in the treatment of OA
- 23,000 patients screened with 2,300 recruited into trial for 2 years
- Signs and symptoms and fluoroscopically positioned specialized x-ray with central reading
- Post hoc small number of patients who were determined to be rapid progressors evidenced structural modification, but not able to be identified at start of trial and not linked to symptom benefit

Bingham CO III, 2006; Arthritis Rheum 54: 3494-3507

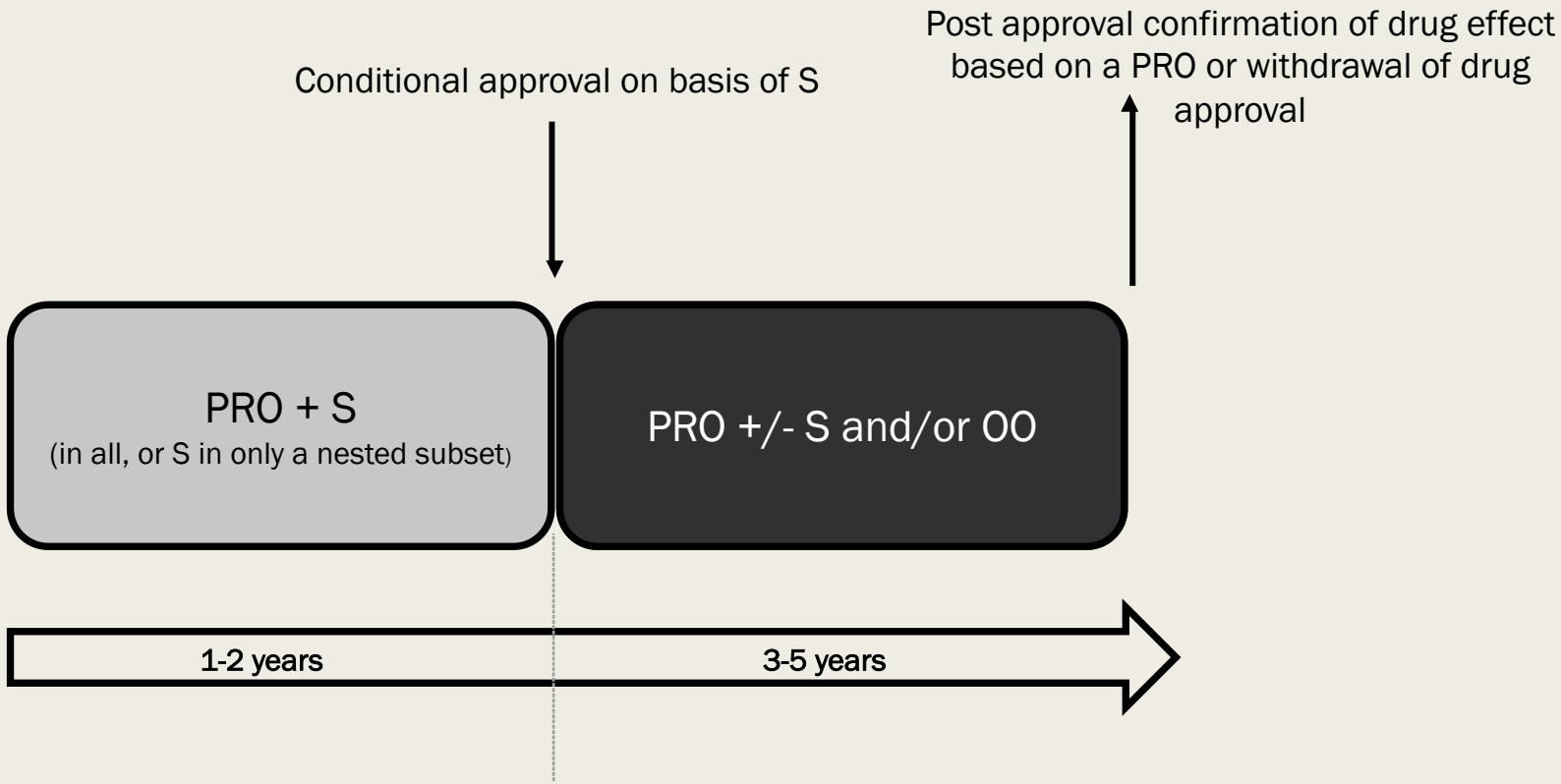
What Did We Learn from the Risedronate Trial or Other Similar Experiences?

- The trial was large and long
- It was an expensive experiment
- Some patients were measurably progressive in damage during the window of the clinical trial
- Other patients did not progress at all
- Examining the enrollment information there was no data to inform which patients would progress and which would not

What Did We Learn from the Risedronate Trial or Other Similar Experiences? (cont.)

- Some patients did benefit in terms of symptoms, but was that measured benefit associated with structural x-ray measured benefit?
- Could a single trial be powered to demonstrate both a symptomatic benefit as well as a structural benefit?
- Could structural benefit once measured be associated with a delayed clinical benefit?

Achieving Evidence for Structural Benefit Linked to Clinical Benefit



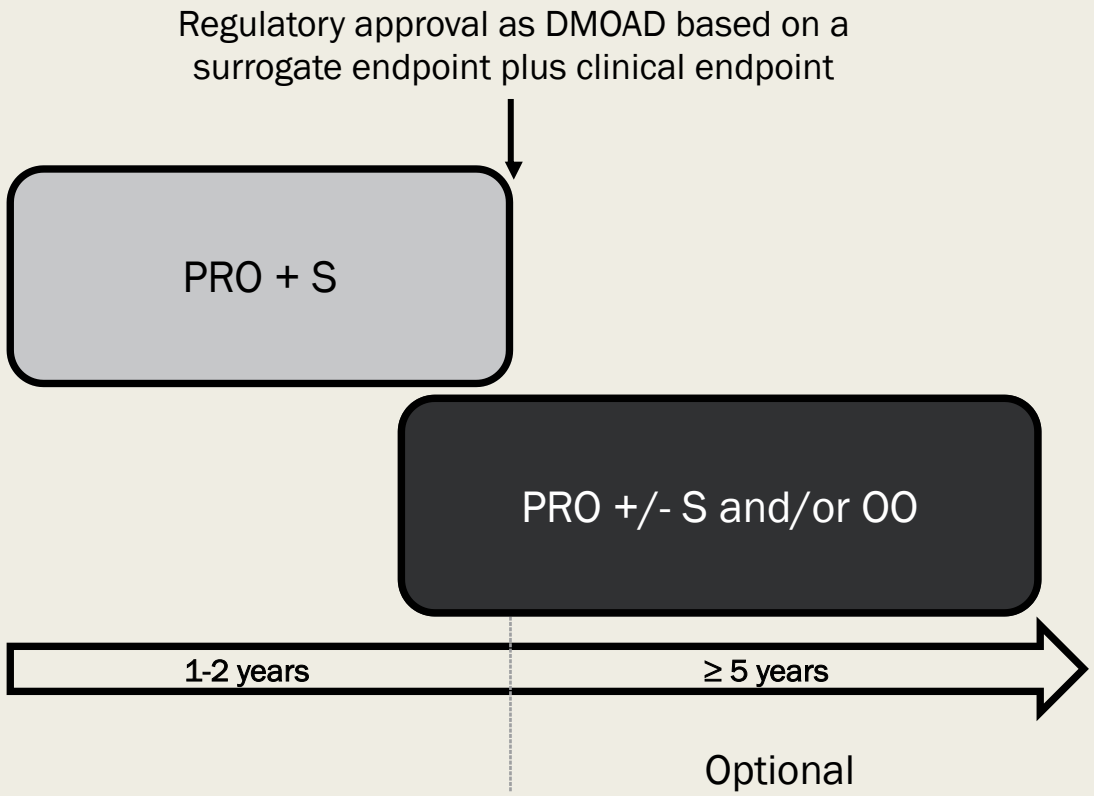
Abbreviations:

PRO: (meaningful) patient reported outcome (how a patient feels, functions, survives)

S: surrogate (biomarker)

OO: observational outcome (e.g. joint replacement)

Achieving Evidence for Structural Benefit Linked to Clinical Benefit

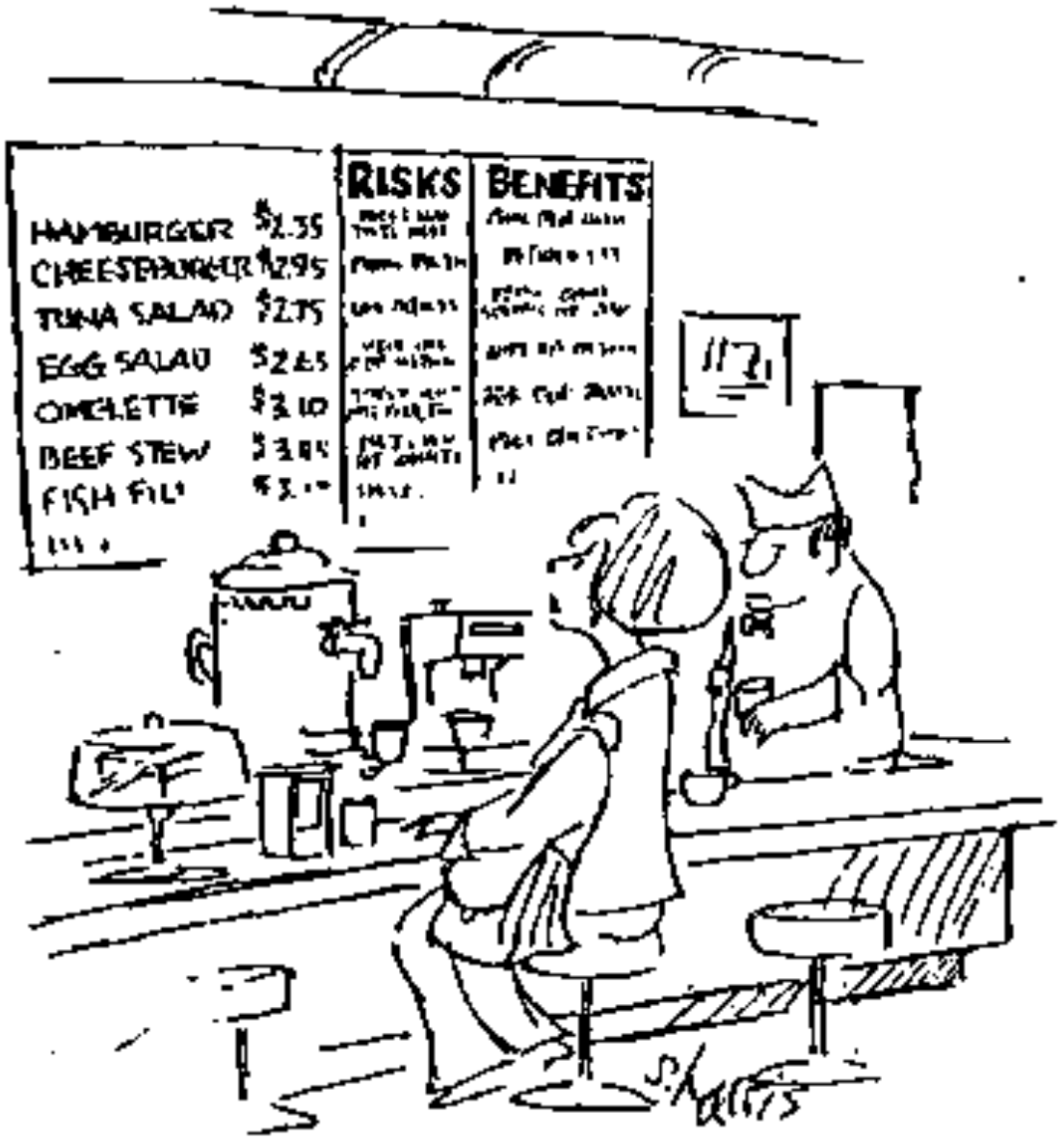


Abbreviations:
PRO: (meaningful) patient reported outcome (how a patient feels, functions, survives)
S: surrogate (biomarker)
OO: observational outcome (e.g. joint replacement)

*Study Population contains **SOME** or **NONE** of the Original Trial subjects as a nested cohort

Conclusions

- OA has significant patient impact with pain, loss of function, consequent increased disability along with significant risk of increased mortality, in some patients
- OA affects a large population
- Developing drugs to alter the complex structures involved in the joint will be difficult
  - *Target cartilage?*
    - Decrease loss?
    - Stimulate new cartilage growth?
  - *Target subchondral bone? And show what?*
  - *Both? And do changes link to how a patient feels, functions or survives?*



Drawing by S. Harris. Reprinted with permission of The New Yorker Magazine, Inc.