Imaging Biomarkers: MRI vs. X-Ray

Frank Roemer, MD
Boston University

Arthritis Foundation June 22, 2021 Osteoarthritis Drug Development: Assessment of Long-term Benefit FDA U.S. FOOD & DRUG ADMINISTRATION

Imaging Biomarkers in OA MRI vs. X-ray

Frank W. Roemer, MD

Adjunct Professor of Radiology, Boston University School of Medicine (BUSM), Boston, MA
Co-Director, Quantitative Imaging Center, Dept. of Radiology, BUSM
Professor of Radiology, Friedrich-Alexander-University Erlangen-Nürnberg & Universitätsklinikum Erlangen, Erlangen, Germany
Associate Editor for Imaging *Osteoarthritis and Cartilage*
Editor-in-Chief *Osteoarthritis Imaging*

FAU FRIEDRICH-ALEXANDER UNIVERSITÄT ERLANGEN-NÜRNBERG MEDIZINISCHE FAKULTÄT
BOSTON UNIVERSITY
QIC
Universitätsklinikum Erlangen
frank.roemer@uk-erlangen.de

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Consultant to Calibr – California Institute of Biomedical Research

OARSI Clinical Trial Recommendations

Osteoarthritis and Cartilage 23 (2015) 698–715

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

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 ‡‡‡‡§§§§ |||||||

Role of Imaging in Clinical DMOAD Trials

"Summary and Conclusion:

The goals of imaging the knee in clinical trials can include subject selection, monitoring disease progression and treatment effect, and/or identifying complications of the disease or the treatment."

AKA:

- Eligibility
- Outcome Measure /Surrogate Endpoint
- Safety Monitoring

Hunter DJ et al. Osteoarthritis and Cartilage 23 (2015) 698-715

Eligibility

Eligibility: Kellgren-Lawrence - Ordinal Grading

„early to moderate disease“

KL 0 KL 1 KL 2 KL 3 KL 4

No ROA ROA

BUT!

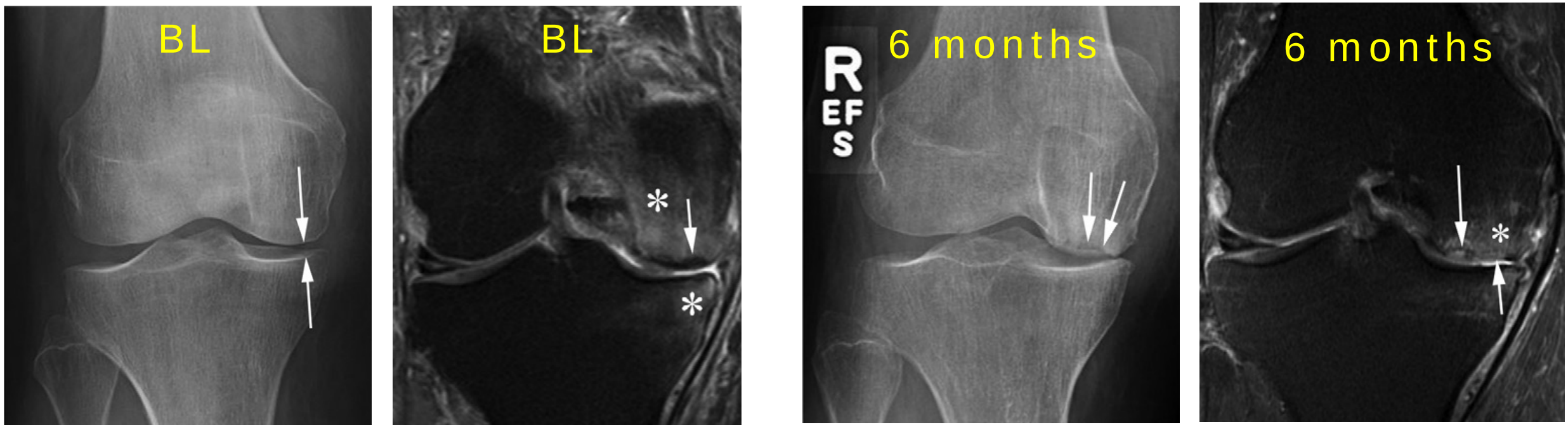
KL2 and 3 knees are very heterogeneous!

- e.g. in MOST Study 21% of KL2 knees have no cartilage damage in the MTFJ (and 41% in the LTFJ)!
- 25% of KL2 show severe wide-spread full-thickness damage medially

=> KL 2 (and 3) is not a homogeneous sample of “early-to-moderate” OA!

- Roemer FW et al. SUBREGIONAL ANATOMICAL PREVALENCE OF CARTILAGE DAMAGE IN KNEES WITH RADIOGRAPHIC DISEASE SEVERITY KELLGREN-LAWRENCE 2 AND 3: THE MOST STUDY OARSI CONNECT 2021; Poster 413
- Roemer FW et al. HETEROGENEITY OF CARTILAGE INVOLVEMENT IN KNEES WITH RADIOGRAPHIC DISEASE SEVERITY KELLGREN-LAWRENCE 2 AND 3: THE MOST STUDY OARSI CONNECT 2021; Poster 401

Eligibility: Exclude adverse findings at BL affecting efficacy !



Baseline SIF medial femur only seen on MRI ! Other findings: e.g.bone marrow infiltration, meniscal root tears, occult fractures etc. NOT modifiable by any DMOAD!

Roemer FW, et al. MRI-based screening for structural definition of eligibility in clinical DMOAD trials: Rapid OsteoArthritis MRI Eligibility Score (ROAMES) . Osteoarthritis Cartilage. 2020 Jan;28(1):71-81

Eligibility: Enrichment

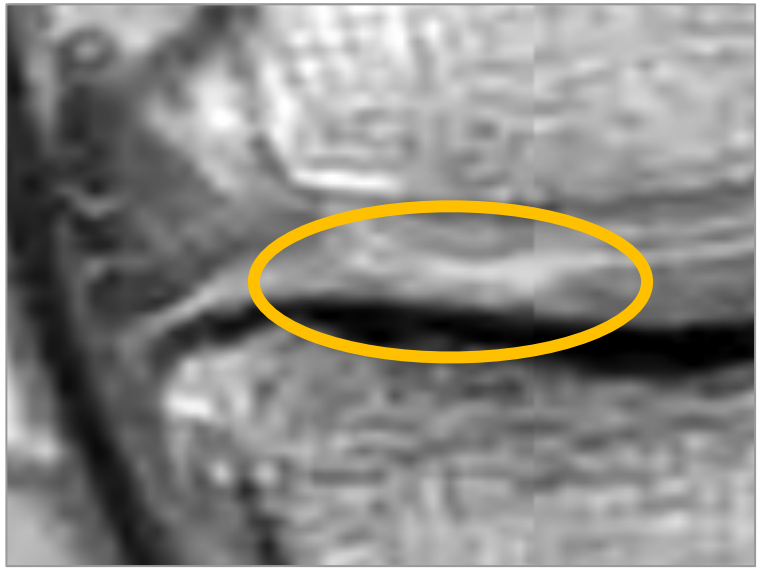
"Regarding enrichment, there is considerable interest in identifying the subset of the patient population for whom an intervention would have a clinically meaningfully favorable benefit-to-risk profile due to greater benefits or fewer adverse outcomes."

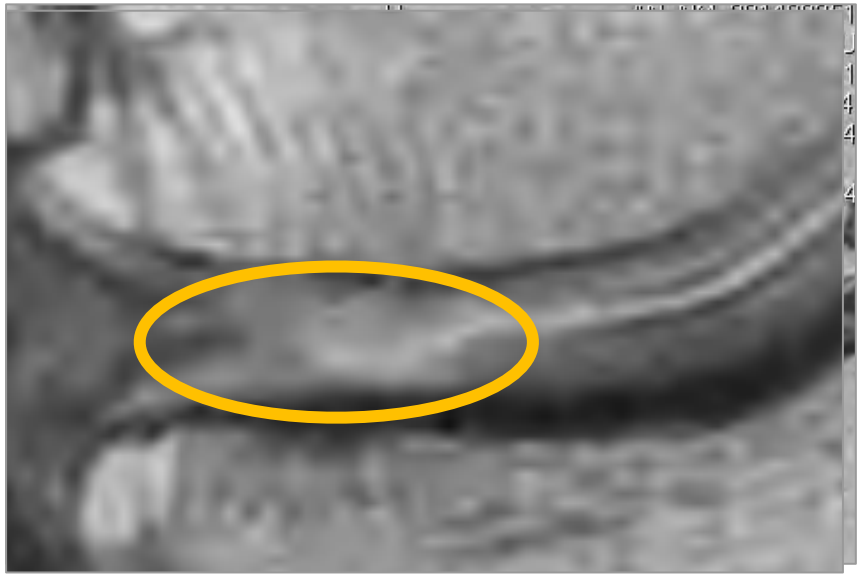
Fleming TR, Powers JH. Stat Med 2012; 31(25): 2973–2984

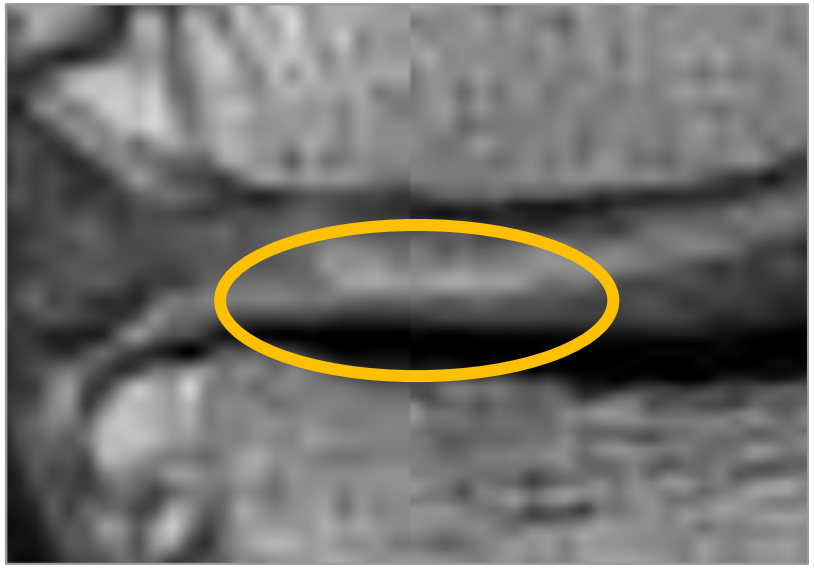
Enrichment:
OA is not one disease!

- Enrichment by MRI for superior structural disease characterization considering mode of action of product
- Enrichment for certain structural MRI-defined phenotypes: Inflammation, Bone, Cartilage, Atrophic etc.
- Enrichment for “Subjects-at-Risk” defined by structure and symptoms

Enrichment by MRI:
Superior structural disease characterization

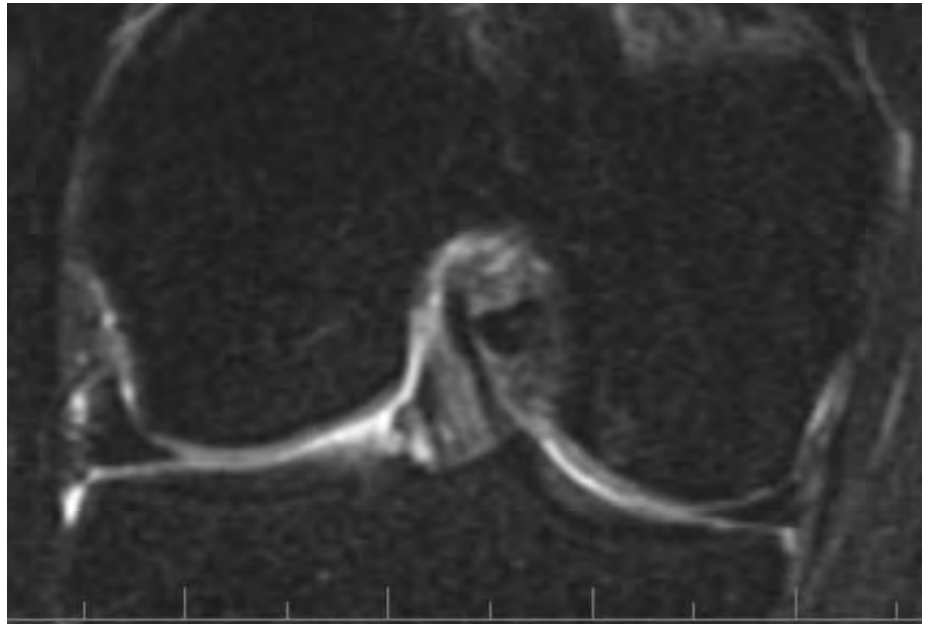


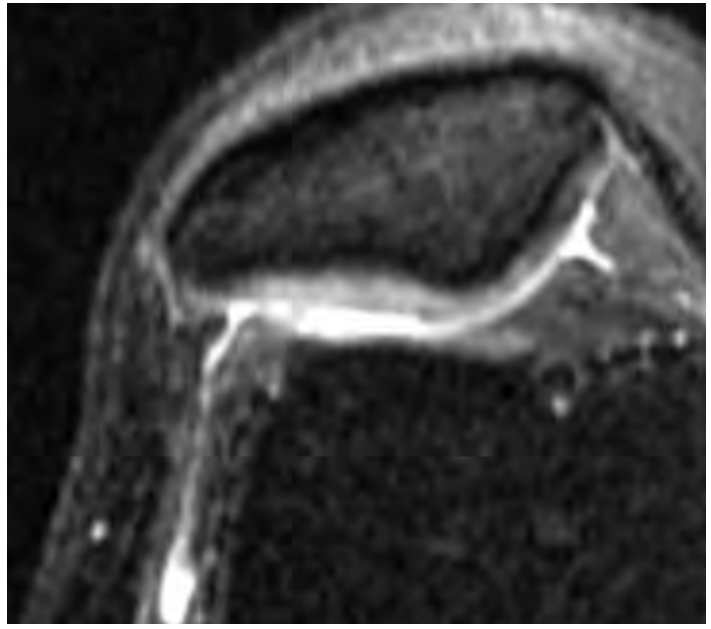


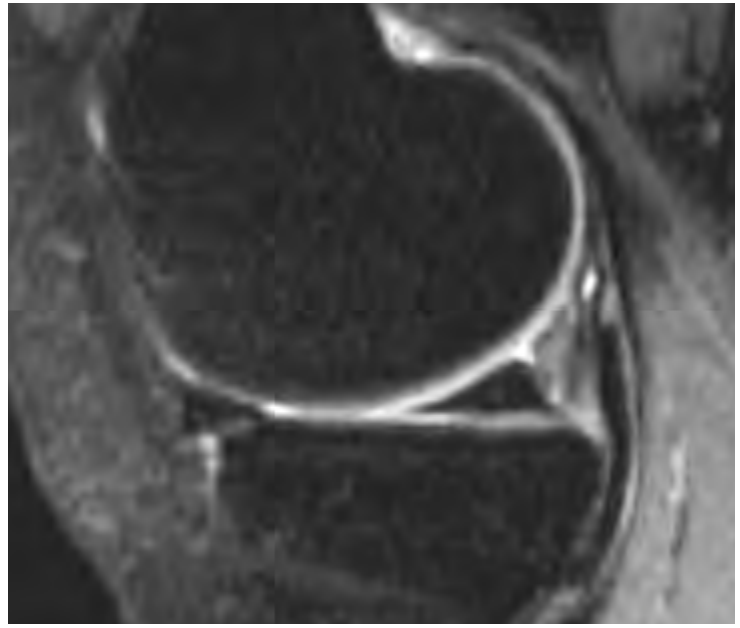


Anabolic compound: Cartilage damage => Cartilage can grow!

Enrichment by MRI: Superior structural disease characterization







- An anabolic compound can only work if there is cartilage loss => exclude knees without cartilage loss

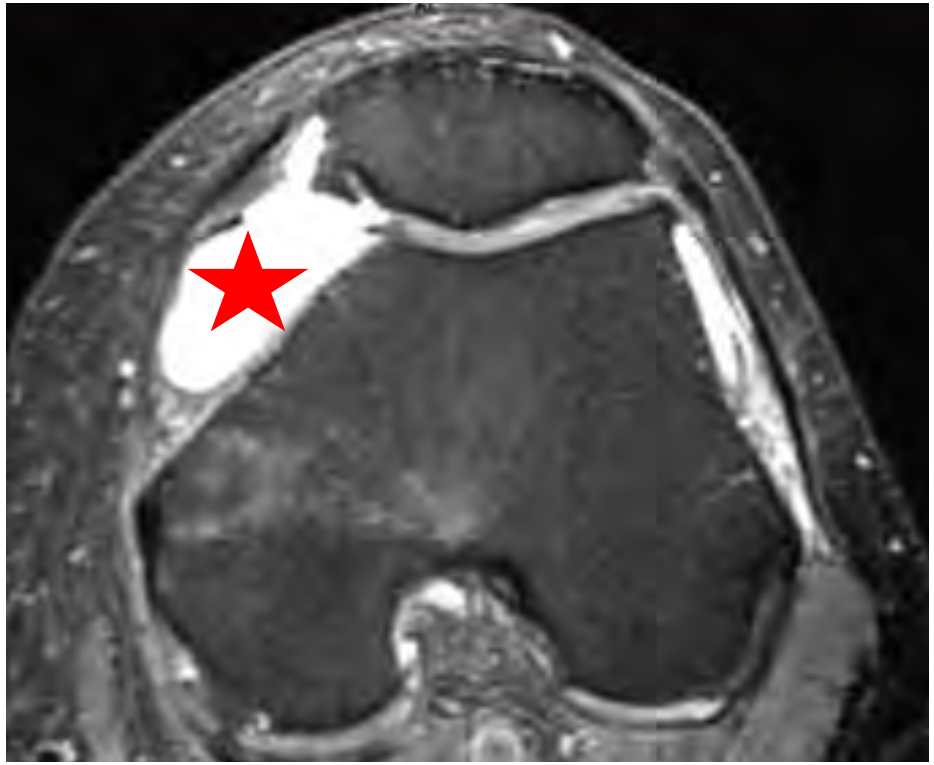
=> 30 % of KL2 knees in OAI/FNIH study had no medial TF cartilage damage!

Enrichment by MRI: Superior structural disease characterization

- An anticatabolic compound can only work if there is something to preserve! = consider excluding wide spread full thickness cartilage loss!

Roemer FW, et al. Association of knee OA structural phenotypes to risk for progression: a secondary analysis from the Foundation for National Institutes of Health Osteoarthritis Biomarkers study (FNIH). Osteoarthritis Cartilage. 2020 Sep;28(9):1220-1228

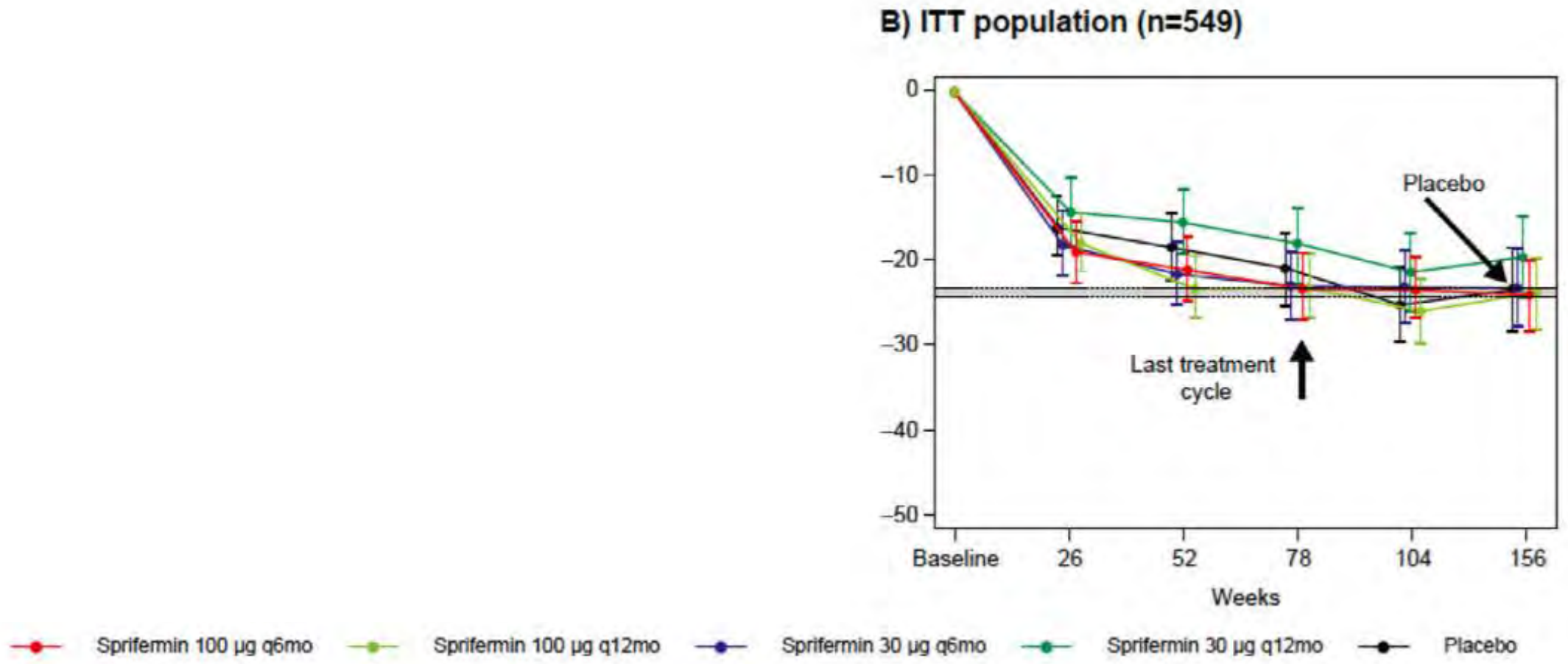
Enrichment for structural MRI-defined phenotypes



Target inflammation => Inflammation should be present!

Roemer FW, et al. MRI-based screening for structural definition of eligibility in clinical DMOAD trials: Rapid OsteoArthritis MRI Eligibility Score (ROAMES) . Osteoarthritis Cartilage. 2020 Jan;28(1):71-81

Enrichment for Subjects-at-Risk

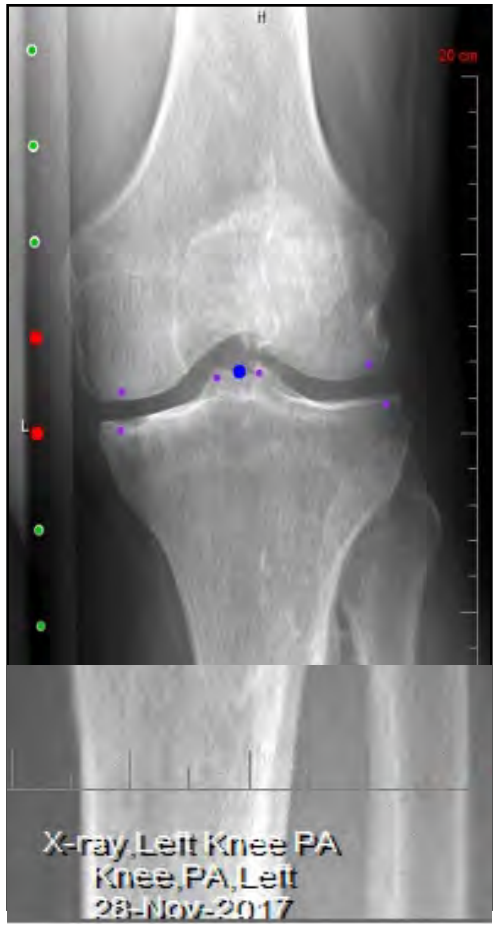


Selection for low mJSW and moderate-to-high pain at baseline (i.e. „Subjects-at-Risk“) demonstrated translation of structure modification into symptomatic benefit

Guehring H, et al. Seminars in Arthritis and Rheumatism 51 (2021): 450-456

Structural Endpoint/Surrogate Outcome

X-ray highly dependent on standardized image acquistion!

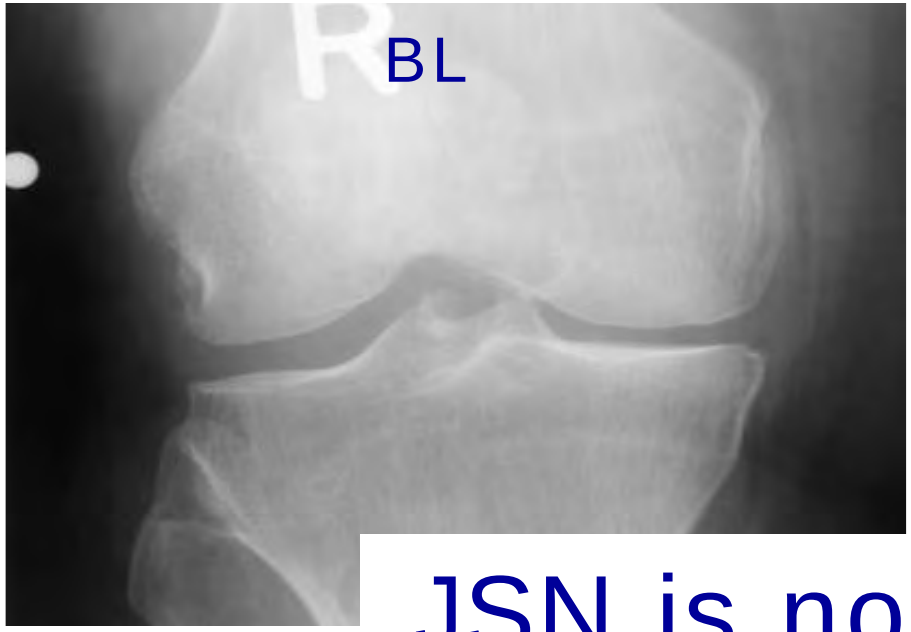


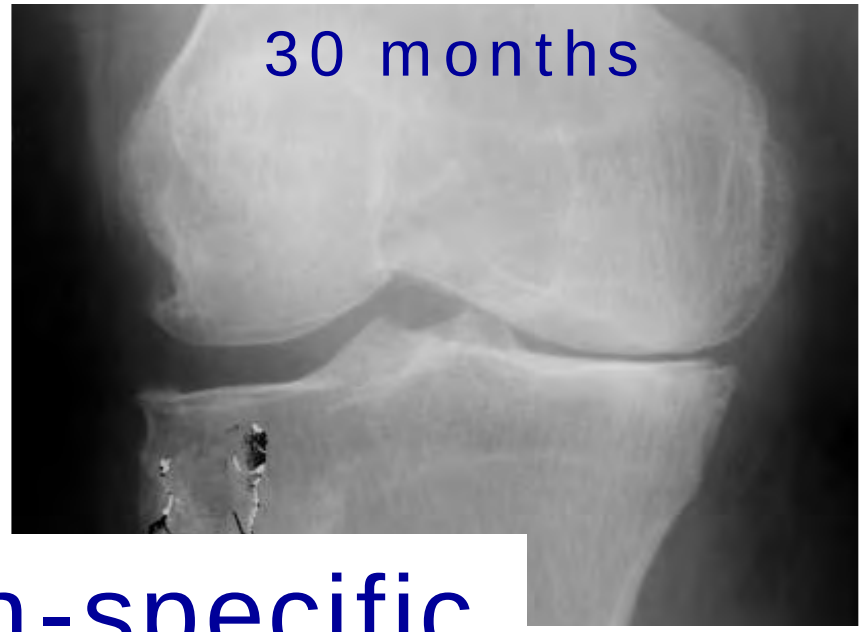
11 degrees

12 degrees

13 degrees

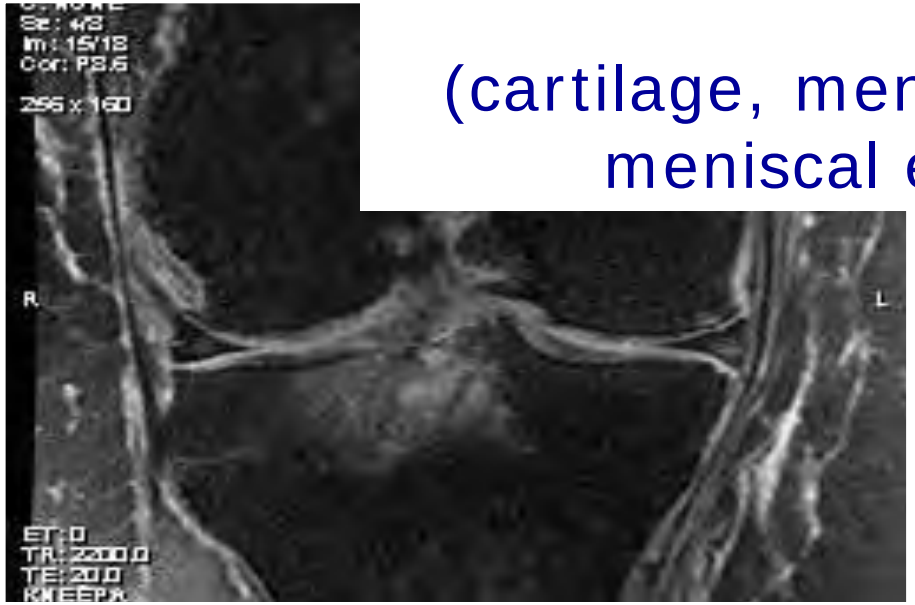
Roemer FW, et al. Nat Rev Rheumatol. 2018;14:372-380.



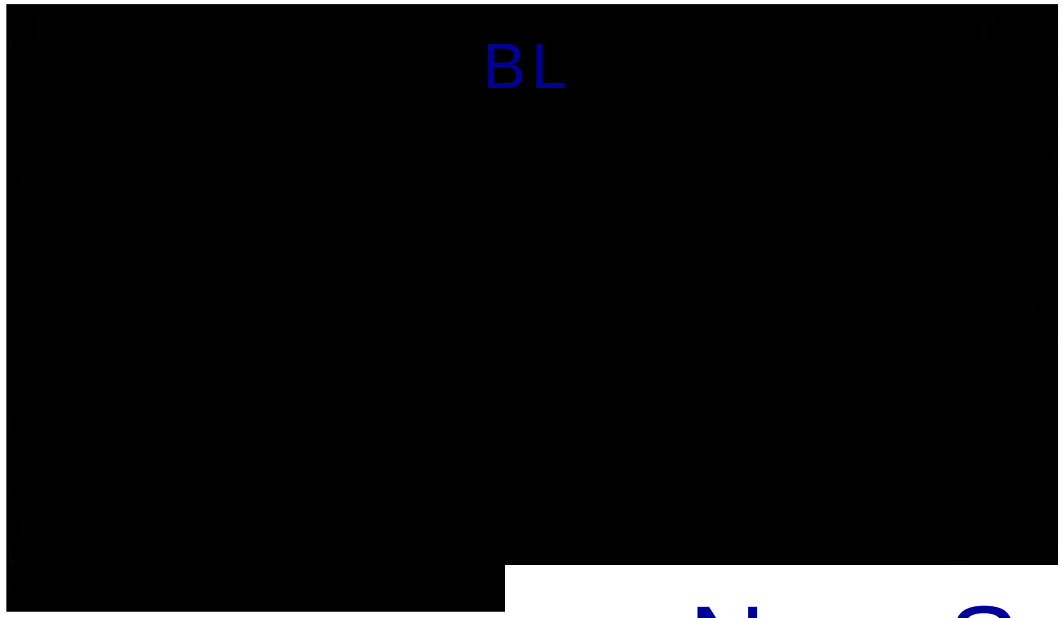


JSN is non-specific

(cartilage, meniscus damage, meniscal extrusion)



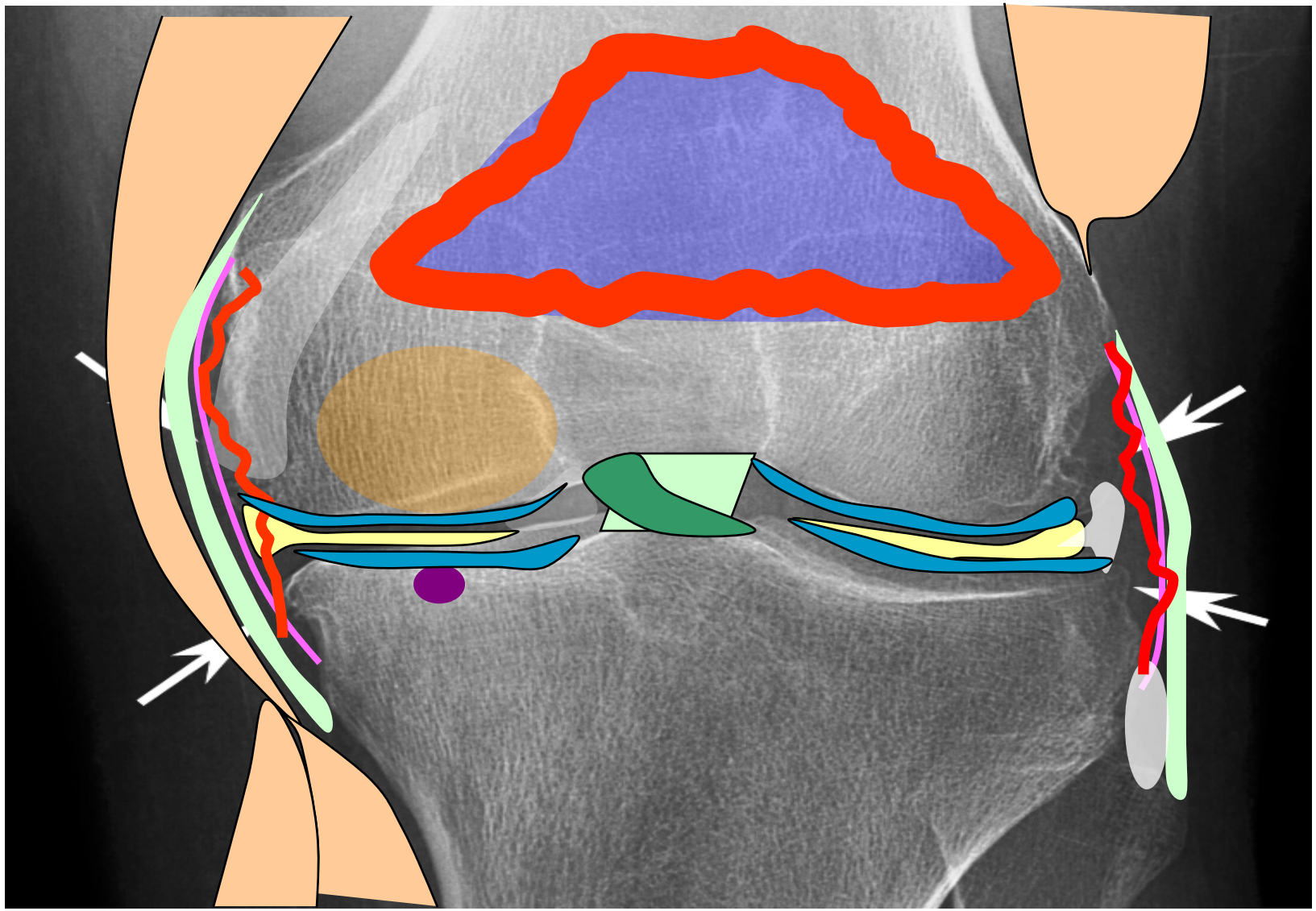
Amin S, et al. Arthritis Rheum 2005;52:3152-9
Crema MD et al. Osteoarthritis Cartilage 2014;22:1743-7



Non-Sensitive

(slow; only central joint visualized)

Tissues involved in the OA process



Cartilage

Meniscus

Subchondral cyst

PCL/ACL

MCL/LCL

Bone marrow lesion

Capsule

Effusion

Periarticular cyst

Synovitis

Muscle

Methods of MRI OA Assessment

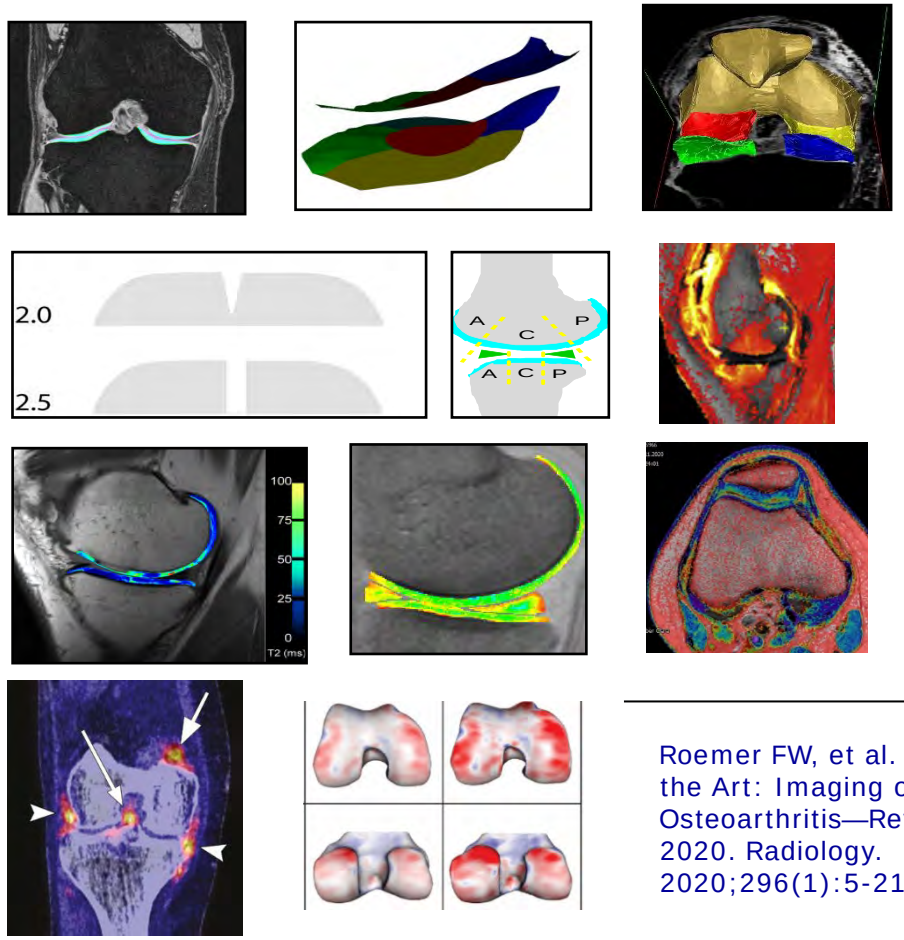
- Different imaging approaches to OA joint assessment using MRI available:

established

- Quantitative Analysis
  (cartilage, meniscus, muscle)
- Semiquantitative Analysis
  (all joint tissues, eligibility)
- DCE MRI (synovitis/inflammation)

exploratory

- Compositional Analysis
  (cartilage, meniscus, muscle)
- Bone Shape
- Metabolic Imaging (PET-CT/MRI)



Roemer FW, et al. State of the Art: Imaging of Osteoarthritis—Revisited 2020. Radiology. 2020;296(1):5-21

Role of target tissue and mode of action

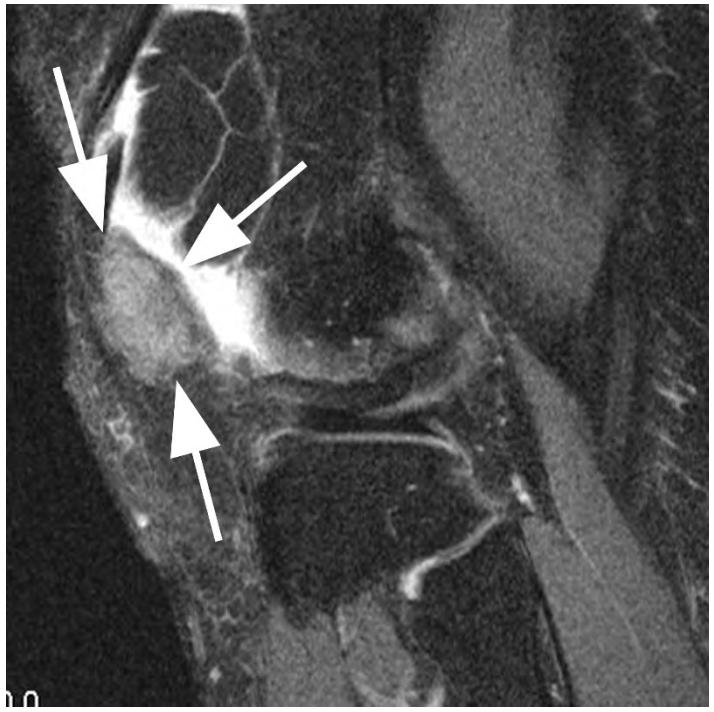
Possible Outcome Measures depending on target tissue:

- Cartilage: q MRI, SQ MRI, compostional MRI (early disease, tissue quality)
- Inflammation: DCE MRI, non-enhanced SQ MRI (Hoffa- effusion-synovitis, contrast-enhanced SQ MRI (11 point scoring), effusion volume assessment, possibly metabolic imaging like PET MRI/CT
- Subchondral Bone: SQ MRI, volume assessment, perfusion parameters (DCE MRI), bone structure, bone shape

Safety

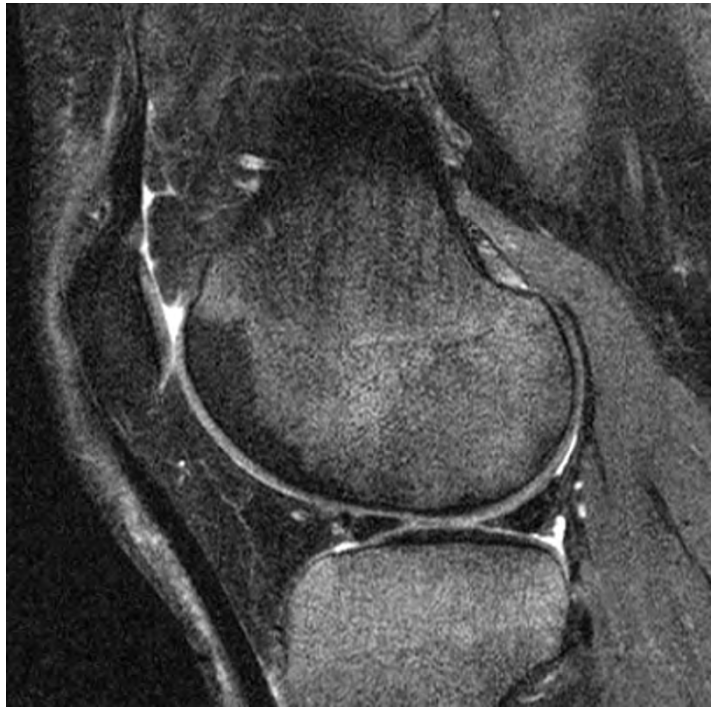
Safety

Many structural safety findings are not visualized by X-ray!



Tumor (GCTTS)

Osteonecrosis



Systemic disease
(leukemia)

Summary: X-ray vs. MRI

X-ray: Needed for baseline disease characterization (severity)

X-ray: Non-sensitive to change and non-specific

X-ray: Challenging to acquire in reproducible fashion in clinical trials

X-ray: Does not show findings that may be affecting efficacy (at BL) or considered safety concerns (on-trial)

MRI: Ready for Screening Purposes/ Eligibility

MRI: Eligibility - Helps in Enrichment

MRI: Endpoint - MRI-Methods are complementary; choice depending on mode of action, target tissue and length of trial

Thank You!