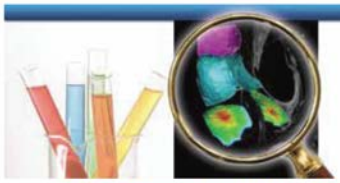

OABiomarker Global Initiative

OARSI

6th International Workshop on Osteoarthritis Imaging combined with the OARSI OA Biomarkers Workshop III - Imaging Biomarker Validation and Qualification

Meeting Chairs: David Hunter, MBBS, PhD, FRACP, Ali Guermazi, MD

Scientific Program Committee: Felix Eckstein, MD, Virginia Byers Kraus, MD, PhD, Elena Losina, PhD, Linda Sandell, PhD

July 12-14, 2012 • Hilton Head Marriott Resort & Spa • Hilton Head Island, South Carolina, USA

Technical Considerations from Radiological Perspective

-What Researchers Need to Know-

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QIC

Disclosures

- Consulting Fees from:
  - Genzyme, Norvartis, AstraZeneca, Merck Serono, and Stryker Biotech
- President of Boston Imaging Core Lab (BICL), LLC
- Content of this presentation is meant to stir debate and discussion. "NOTHING PERSONAL"

Contents

Why Do We Need Clinical Trials?

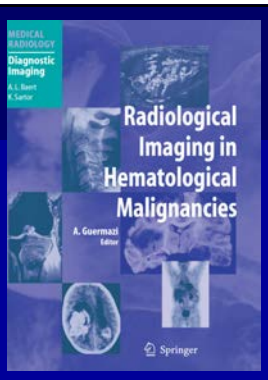
- A researcher tried jalapenos on a stomach ulcer patient, and the ulcer went away.
The researcher published an article:

  "Jalapenos Cure Stomach Ulcers."

- The next patient subjected to the same treatment died. The researcher published a follow-up article:

  "More Detailed Study Reveals That Jalapenos Cures 50% of Stomach Ulcers."

Lee JJ. Design and Analysis of Clinical Trials. In: Cancer - Principles and Practice of Oncology Review. Ed R. Govindan; 2005:98-103



VOLUME 25 · NUMBER 5 · FEBRUARY 10 2007
JOURNAL OF CLINICAL ONCOLOGY
SPECIAL ARTICLE

Use of Positron Emission Tomography for Response Assessment of Lymphoma: Consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma

Malik E. Juweid, Sigrid Stroobants, Otto S. Hoekstra, Felix M. Mottaghy, Markus Dietlein, Ali Guermazi, Gregory A. Wiseman, Lale Kostakoglu, Klemens Scheidhauer, Andreas Buck, Ralph Naumann, Karoline Spaepen, Rodney J. Hicks, Wolfgang A. Weber, Sven N. Reske, Markus Schwaiger, Lawrence H. Schwartz, Josee M. Zijlstra, Barry A. Siegel, and Bruce D. Cheson

From the Department of Radiology, University of Iowa, Iowa City, IA; Department of Nuclear Medicine,

Non Hodgkin Lymphomas

- First classification of Hodgkin disease and Non-Hodgkin lymphomas (NHL) in 1982
- Today NHL are potentially curable malignancies
- More than 70% of patients with newly diagnosed NHL respond to combination radiotherapy and/or chemotherapy regimens
- Appropriate selection of treatment after accurate staging and risk stratification, as well as improved therapy, has resulted in a high success rate in NHL management
- Survival rates of lymphoma patients have increased during the last decades

Table 1. Recent Trends in 5- and 10-Year Relative Survival by Cancer Site According to Modeled Period Analysis: SEER Program, United States, 1998-2003

		5-Year Relative Survival by Modeled Period Analysis						10- Year Relative Survival by Modeled Period Analysis					
		1998		2003		Difference		1998		2003		Difference	
Cancer Site	No.*	%	SE	%	SE	(% units)	*P* for Trend	%	SE	%	SE	(% units)	*P* for Trend
Oral cavity	35,740	57.2	0.9	61.1	0.9	+3.9	< .01	45.8	1.0	50.1	0.9	+4.3	< .01
Esophagus	14,115	14.6	0.8	18.0	0.9	+3.4	.01	9.7	0.7	12.5	0.8	+2.8	< .01
Stomach	27,127	23.7	0.8	25.5	0.8	+1.8	.16	19.0	0.8	20.6	0.8	+1.6	.15
Colon	120,094	62.5	0.5	66.3	0.5	+3.8	< .0001	57.3	0.6	61.7	0.6	+4.4	< .0001
Rectum	48,274	63.6	0.8	66.8	0.8	+3.2	< .01	55.6	0.9	59.7	0.9	+4.1	< .01
Liver	15,287	8.9	0.6	12.4	0.7	+3.5	< .001	5.9	0.6	8.7	0.7	+2.8	< .001
Pancreas	34,467	5.6	0.3	7.1	0.4	+1.5	< .01	3.8	0.3	4.9	0.3	+1.1	< .01
Larynx	13,543	66.3	1.4	61.8	1.5	−4.5	.06	53.7	1.5	49.0	1.6	−4.7	.07
Lung	199,629	16.1	0.2	16.3	0.2	+0.2	.58	10.8	0.2	11.0	0.2	+0.2	.59
Skin melanoma	52,630	90.1	0.6	92.6	0.5	+2.5	< .01	87.4	0.8	90.7	0.6	+3.3	< .01
Breast	232,042	87.7	0.3	90.8	0.2	+3.1	< .0001	80.8	0.4	85.5	0.3	+4.7	< .0001
Cervix uteri	17,114	73.1	1.1	71.8	1.1	−1.3	.45	68.2	1.2	67.4	1.2	−0.8	.67
Corpus uteri	43,982	86.2	0.6	84.9	0.6	−1.3	.21	84.1	0.7	82.8	0.8	−1.3	.25
Ovary	25,536	44.5	1.0	43.8	0.9	−0.7	.65	36.4	0.9	34.8	0.9	−1.6	.28
Prostate	255,598	96.3	0.4	99.8	0.1	+3.5	< .0001	88.8	1.7	98.2	0.3	+9.4	< .0001
Testis	10,736	95.0	0.7	97.0	0.5	+2.0	.048	94.2	0.9	96.4	0.6	+2.2	.04
Urinary bladder	62,455	80.4	0.7	80.2	0.7	−0.2	.85	73.0	0.8	73.8	0.8	+0.8	.53
Kidney	33,184	61.1	0.9	66.9	0.8	+5.8	< .0001	52.9	1.0	59.1	0.9	+6.2	< .0001
Brain	20,514	26.3	0.9	29.8	0.9	+3.5	.01	20.7	0.8	23.8	0.8	+3.1	.02
Thyroid	23,990	96.3	0.5	97.0	0.4	+0.7	.29	95.4	0.6	96.2	0.5	+0.8	.31
Hodgkin's disease	10,552	84.4	1.1	84.8	1.1	+0.4	.81	78.4	1.4	79.7	1.3	+1.3	.54
Non-Hodgkin's lymphoma	60,917	58.2	0.7	65.3	0.6	+7.1	< .0001	47.0	0.8	55.0	0.7	+8.0	< .0001
Multiple myeloma	17,977	32.5	1.1	32.5	1.1	±0.0	.99	14.7	0.8	15.0	0.8	+0.3	.77
Leukemias	36,964	41.0	0.8	45.5	0.8	+4.5	< .001	29.4	0.8	34.8	0.8	+5.4	< .0001

Abbreviation: SEER, Surveillance, Epidemiology, and End Results.
*Patients diagnosed in 1988-2003 whose survival experience is (partly) included in period analyses for the 1998-2003 period.

Brenner et al. J Clin Oncol 2007; 25:3274-3280

FAB NHL Classification

- **B-Cell Neoplasms**
  - B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
  - B-cell prolymphocytic leukemia
  - Lymphoplasmacytic lymphoma
  - Splenic marginal zone B-cell lymphoma (± villous lymphocytes)
  - Hairy cell leukemia
  - Plasma cell myeloma/plasmacytoma
  - Extranodal marginal zone B-cell lymphoma of MALT type
  - Mantle cell lymphoma
  - Follicular lymphoma
  - Nodal marginal zone B-cell lymphoma (± monocytoid B-cells)
  - Diffuse large B-cell lymphoma
  - Burkitt lymphoma/Burkitt cell leukemia
- **T and NK-cell Neoplasms**
  - T-cell prolymphocytic leukemia
  - T-cell granular lymphocytic leukemia
  - Aggressive NK cell leukemia
  - Adult T-cell lymphoma/leukemia (HTLV-I+)
  - Extranodal NK/T-cell lymphoma, nasal type
  - Enteropathy-type T-cell lymphoma
  - Hepatosplenic γδ T-cell lymphoma
  - Subcutaneous panniculitis-like T-cell lymphoma
  - Mycosis fungoides/Sézary syndrome
  - Anaplastic large cell lymphoma, primary cutaneous type
  - Peripheral T-cell lymphoma, not otherwise specified (NOS)
  - Angioimmunoblastic T-cell lymphoma
  - Anaplastic large cell lymphoma, primary systemic

Follicular Lymphoma International Prognostic Index (FLIPI)

- Accurate diagnosis of follicular NHL
  - Based on lymph node/organ biopsy with immunochemistry and t(14;18) translocation
- Five parameters are included in FLIPI
  - Age ≥ 60 years
  - Ann Arbor stage III-IV: based on baseline CT neck-chest-abdomen-pelvis and bone marrow biopsy/aspiration
  - Hemoglobin level < 120 g/L
  - Serum LDH level > upper limit of normal
  - Number of nodal sites > 4
- Patients' stratification and treatment selection: based on whole body PET-CT, with or without DCE-MRI
- Inclusion cost:~$50,000

Solal-Celigny P, et al. Blood. 2004 Sep 1;104(5):1258-65

Lessons Learned from NHL

- Accurate staging based on imaging
  - Follicular lymphoma is an indolent lymphoma
  - Burden of disease based on CT measurements
- Monitoring of the disease
  - Hemoglobin and serum LDH levels
  - Response criteria based on CT measurements
- Residual mass activity:
  - In the past, MRI with gadolinium
  - Currently based on whole body PET-CT or PET-MRI
- Sensitivity for detection of residual mass activity on PET: 100%, specificity: 97%

Therapy

- Conventional treatments: CHOP, CEOP, DHAP, ESHAP, Mini-BEAM, CP, PFS, CVP…
- Monoclonal antibodies: rituximab (Rituxan [anti CD20]), GA101 and Ofatumumab (fully humanized anti CD20), bevacizumab (Avastin [VEGF])
- Radioimmunotherapy: tositumomab (Bexxar), ibritumomab (Zevalin): anti CD20
- Vaccines: FavID, keyhole limpet hemocyanin-conjugated lymphoma idiotype protein
- Proteasome inhibitor: bortezomib (Velcade)

Stevenson FK, Stevenson GT. Blood 2012;119:3659-67

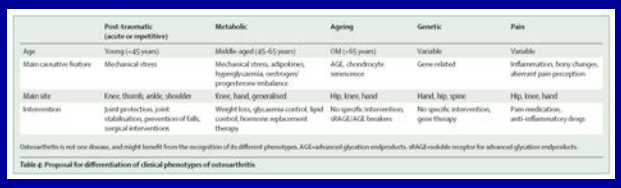
Clinical Trials in OA Today

- Patient inclusion:
  - X-ray KLG criteria
  - Pain
  - No recent trauma
  - No history of RA, lupus erythematosus, gout, septic arthritis…
  - If MRI is included, patient should not have MRI contraindications

– Cost for inclusion: less than $1,000

OA Multiple Faces/Phenotypes

- Post traumatic (acute or repetitive)
- Metabolic
- Ageing
- Genetics
- Pain
- Inflammatory / Non-inflammatory
- Mechanical
- From an imaging perspective: synovitic, osseous, meniscal, cartilaginous, instability/ligamentous…



	Post-traumatic (acute or repetitive)	Metabolic	Ageing	Genetic	Pain
Age	Young (<45 years)	Middle-aged (45-65 years)	Old (>65 years)	Variable	Variable
Main causative feature	Mechanical stress	Mechanical stress, adipokines, hyperglycaemia, oestrogen/progesterone imbalance	AGE, chondrocyte senescence	Gene related	Inflammation, bony changes, aberrant pain perception
Main site	Knee, thumb, ankle, shoulder	Knee, hand, generalised	Hip, knee, hand	Hand, hip, spine	Hip, knee, hand
Intervention	Joint protection, joint stabilisation, prevention of falls, surgical interventions	Weight loss, glycaemia control, lipid control, hormone replacement therapy	No specific intervention, sRAGE/AGE breakers	No specific intervention, gene therapy	Pain medication, anti-inflammatory drugs

Osteoarthritis is not one disease, and might benefit from the recognition of its different phenotypes. AGE=advanced glycation endproducts. sRAGE=soluble receptor for advanced glycation endproducts.

Table 4: Proposal for differentiation of clinical phenotypes of osteoarthritis

"Osteoarthritis is not one disease, and might benefit from the recognition of its different phenotypes".

Bijlsma JW, et al. Lancet 2011;377:2115-26

OA Multiple Faces/Phenotypes

"Even after adjustment for sex, age, and BMI, African Americans were less likely than Caucasians to have hand radiographic OA phenotypes, but more likely to have knee radiographic OA phenotypes involving the TF joint."

Nelson AE, et al. Arthritis Rheum 2011;63:3843-52

"Such differences suggest that OA pathogenesis might proceed via unique gender-specific pathways based on underlying hormonal and anatomic differences. As we seek to better understand the metabolic and inflammatory contributions to OA, it is imperative that we continue to carefully evaluate for potential differences by gender."

Huffman KM, Kraus WE. Osteoarthritis Cartilage 2012;20:603-4

"The prevalence of symptomatic knee OA in rural areas of China is much higher than reported from urban regions of China or in the Framingham cohort. The higher representation of bilateral and lateral compartment disease in China suggests a unique phenotype to OA."

Kang X, et al. Arthritis Rheum 2009;61:641-7

Who Is At Risk? Who Will Benefit?

- MRI as a screening tool? How do we find fast progressors?

Risk factor	Reference	Adjusted Odds Ratio[4] (95% confidence intervals)
Effusion[1] (WORMS ≥ 1)[1]	Effusion absence (WORMS score = 0)	1.79 (0.76-4.23)
Synovitis[1] (modified WORMS ≥ 1)[1]	Synovitis absence (modified WORMS score = 0)	0.68 (0.32-1.45)
Meniscal damage[2]	No meniscal damage	1.98 (0.76-5.15)
Meniscal extrusion[2]	No meniscal extrusion	3.62 (1.29-10.12)*
Prevalent cartilage damage (WORMS ≥ 2)[3]	Absence of cartilage damage in subregion (WORMS =0 or 1)	15.90 (5.08-49.79)*
BML (WORMS ≥ 1)[3]	No BML in subregion (WORMS =0)	4.58 (1.08-19.44)*

Risk factors for ***TF*** cartilage loss at 6 months

Risk factor	Reference	Adjusted Odds Ratio[3] (95% confidence intervals)
Effusion (WORMS ≥ 1)[1]	Effusion absence (WORMS score = 0)	3.54 (1.30-9.64)*
Synovitis (modified WORMS ≥ 1)[1]	Synovitis absence (modified WORMS score = 0 in both synovitis subregions)	0.79 (0.28-2.07)
Prevalent cartilage damage (WORMS ≥ 2)[2]	No cartilage damage in subregion (WORMS score = 0 or 1)	4.32 (1.35-13.85)*
BML (WORMS ≥ 1)[2]	No BML in subregion (WORMS score =0)	1.61 (0.67-3.84)

Risk factors for ***PF*** cartilage loss at 6 months

Roemer FW, et al. Arthritis Rheum 2012;64:1888-98.

Who Is At Risk? Who Will Benefit?

- MRI as a screening tool?

MRI Characteristics		Cartilage status at follow-up			Slow Cartilage Loss	Fast Cartilage Loss
		No cartilage loss N=257 (74.1%)	Slow cartilage loss N=70 (20.2%)	Fast cartilage loss N=20 (5.8%)	Multi-adjusted* OR [95% CI] p-value	Multi adjusted* OR [95% CI] p-value
BML	Grade 0	226 (87.9%)	57 (81.4%)	17 (85%)	1.0 (reference)	1.0 (reference)
	Any grade >1	31 (12.1%)	13 (18.6%)	3 (15%)	1.79 [0.83,3.87] 0.14	1.00 [0.24, 4.10] 0.99
Synovitis/ effusion	Grade 0	106 (41.2%)	24 (34.2%)	3 (15%)	1.0 (reference)	1.0 (reference)
	Any grade >1	151 (58.8%)	46 (65.7%)	17 (85%)	1.37 [0.75, 2.50] 0.30	3.36 [0.91, 12.4] 0.07
Meniscal damage	Grade 0	218 (84.9%)	44 (62.9%)	11 (55%)	1.0 (reference)	1.0 (reference)
	Any grade >1	39 (15.1%)	26 (37.1%)	9 (45%)	3.25 [1.70,6.25] <0.01	3.19 [1.13, 9.03] 0.03
Meniscal extrusion	Grade 0	196 (76.3%)	39 (55.7%)	8 (40%)	1.0 (reference)	1.0 (reference)
	Any grade > 1	61 (23.7%)	31 (44.3%)	12 (60%)	2.02 [1.12, 3.63] 0.02	3.62 [1.34, 9.82] 0.01
High grade lesions	Grade <1	211 (82.1%)	42 (60%)	7 (35%)	1.0 (reference)	1.0 (reference)
	Grade >2	46 (17.9%)	28 (40%)	13 (65%)	3.28 [1.78, 6.03] 0.01	8.99 [3.23, 25.1] <0.01

Risk factors for ***rapid TF cartilage loss*** at 30 months

Roemer FW, et al. Radiology 2009;252:772-80

Current Recommendation by OARSI FDA ASC Working Group

- XR is used for:
  - Kellgren Lawrence grade (diagnosis of radiographic OA)
  - Osteophytes
  - JSW (= indirect visualization of cartilage)
- XR-based outcome = FDA approved
  - Currently no FDA-approved MRI-based outcome
- JSW is still a recommended option for trials of structural modification
  - But need to be aware of limitations of XR

Conaghan P et al. Osteroarthritis Cartilage 2011; 19:606-10

Use of X-ray in Clinical Trials – Inclusion and Strtification

- KLG 0
  - No JSN, no osteophyte = supposedly normal knee
- KLG 1
  - No JSN, equivocal tiny osteophyte = almost normal knee
- KLG 2
  - No JSN, unequivocal osteophyte = marginal osseous proliferation, without cartilage loss or damage to the joint

    Still there in no consistency since some researchers include possible joint space narrowing

KLG 0 - MRI Prevalence of OA Features when Any Score > 0

Any score > 0	Males (%)	Females (%)
Cartilage morphology	70.5	68.8
Menisci (medial & lateral)	34.2	15.9
Osteophytes	91.2	90.2
Ligaments (cruciate & collateral)	10.0	6.9
Bone marrow edema	50.6	52.3
Bone attrition	31.4	27.4
Subchondral cysts	23.5	25.4
Effusion	34.7	30.6
% of knees with any abnormality	95.0	95.2

Guermazi A, et al. Arthritis Rheum 2007;56:S128-129

KLG 0 - MRI Prevalence of OA Features at Higher Threshold

Unequivocal score	Males (%)	Females (%)
Cartilage ≥ 3 in any subregion	43.3	46.3
Menisci ≥ 2 in any subregion	13.0	5.5
Osteophytes ≥ 2 in any subregion	14.0	10.0
Ligts, any cruciate ≥ 1, any coll. ≥ 2	3.3	0.8
BM edema ≥ 2 in any subregion	15.8	16.5
Bone attrition ≥ 2 in any subregion	8.0	8.5
SC cysts ≥ 2 in any subregion	3.8	4.3
Effusion ≥ 2	5.1	2.3
% of knees with any unequivocal Ab.	55.8	52.7

Guermazi A, et al. Arthritis Rheum 2007;56:S128-129

KLG 1 - MRI Prevalence of OA Features when Any Score > 0

Any score > 0	Males (%)	Females (%)
Cartilage morphology	71.8	70.3
Menisci (medial & lateral)	36.7	18.1
Osteophytes	91.7	90.3
Ligaments (cruciate & collateral)	11.9	7.7
Bone marrow edema	52.5	52.6
Bone attrition	32.4	27.9
Subchondral cysts	25.2	26.0
Effusion	36.0	32.0
% of knees with any abnormality	95.3	95.5

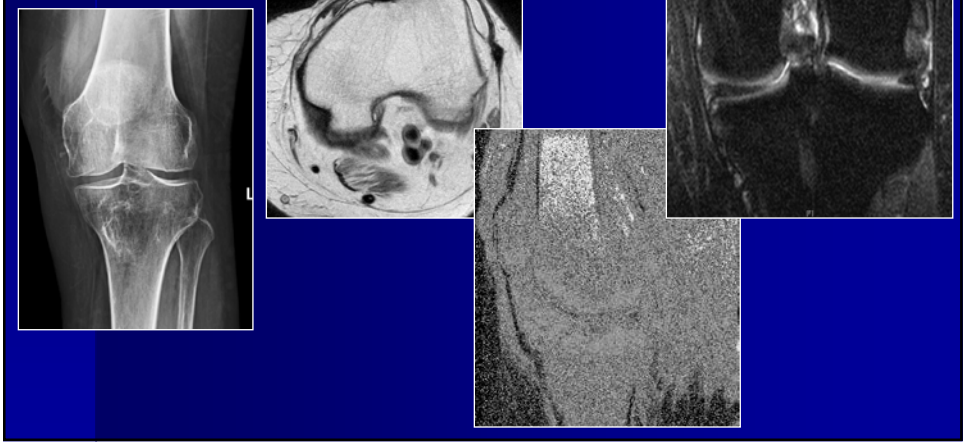
Guermazi A, et al. Arthritis Rheum 2007;56:S128-129

KLG 1 - MRI Prevalence of OA Features at Higher Threshold

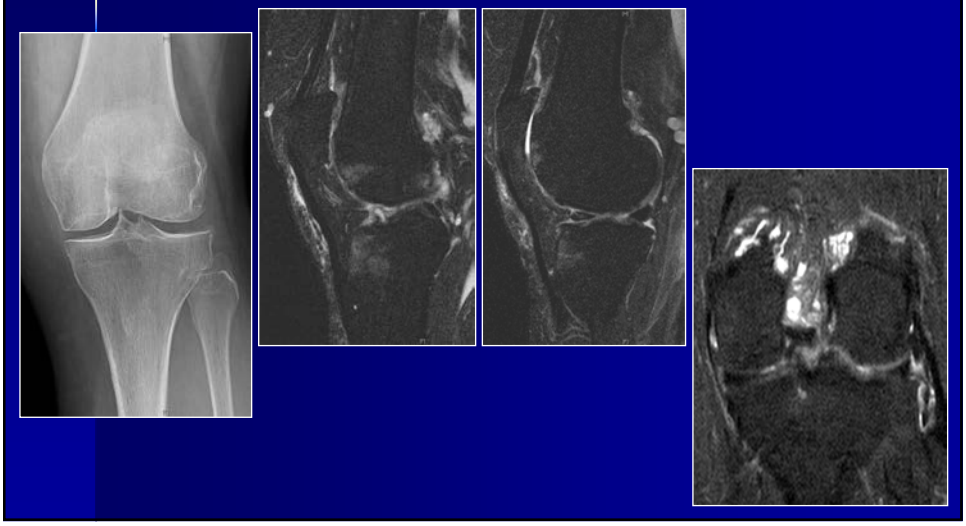
Unequivocal score	Males (%)	Females (%)
Cartilage ≥ 3 in any subregion	45.6	48.2
Menisci ≥ 2 in any subregion	15.2	6.6
Osteophytes ≥ 2 in any subregion	14.5	12.1
Ligts, any cruciate ≥ 1, any coll. ≥ 2	3.4	0.7
BM edema ≥ 2 in any subregion	16.9	17.0
Bone attrition ≥ 2 in any subregion	8.3	8.5
SC cysts ≥ 2 in any subregion	4.1	4.9
Effusion ≥ 2	5.5	2.7
% of knees with any unequivocal Ab.	58.2	54.6

Guermazi A, et al. Arthritis Rheum 2007;56:S128-129

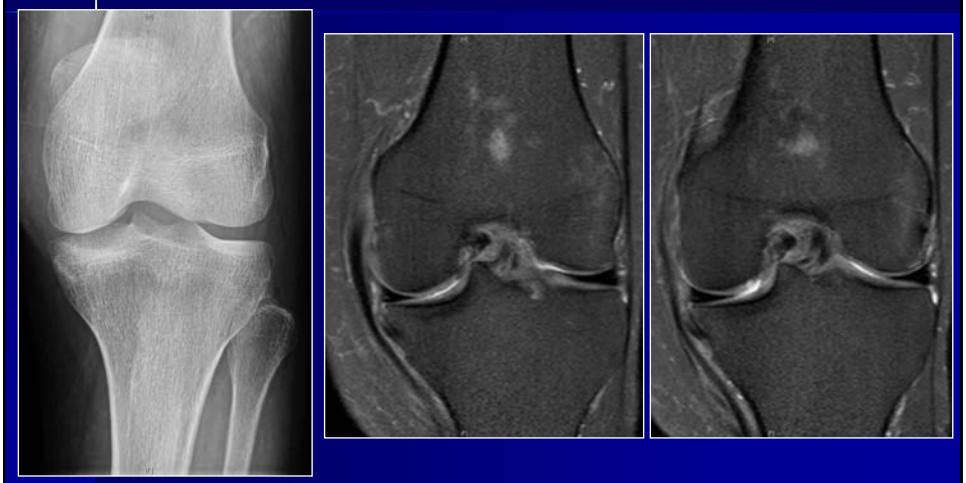
KLG 2 - Examples



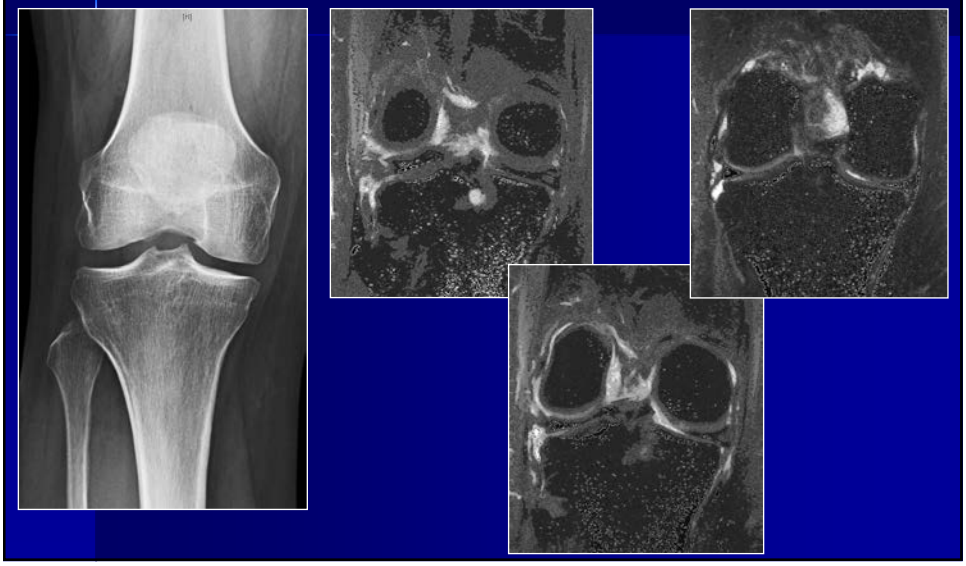
KLG 2 - Examples

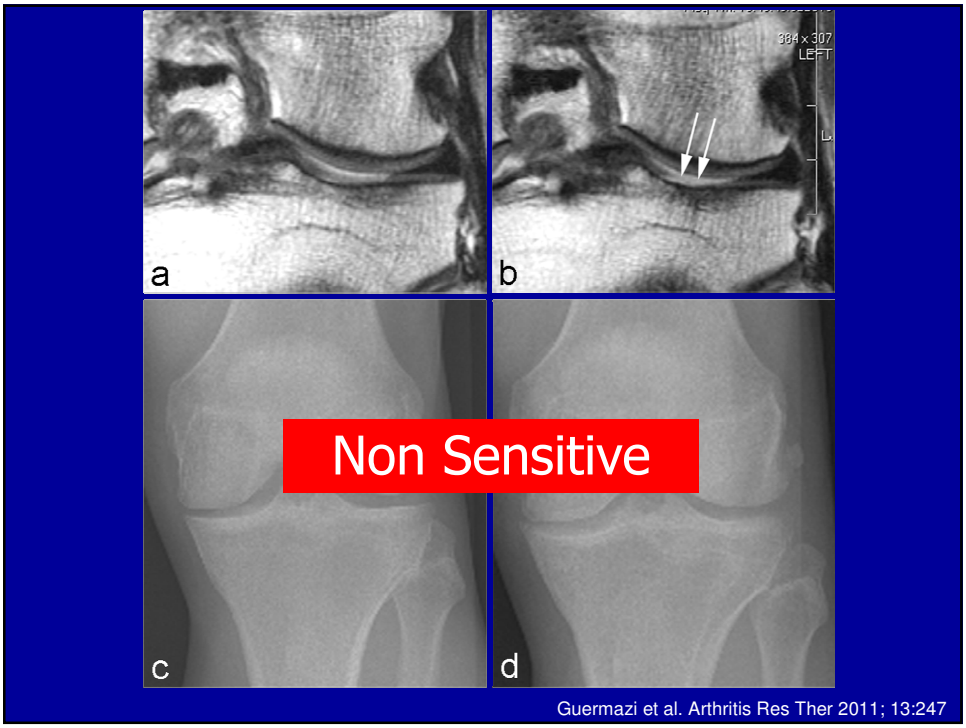


KLG 2 - Examples

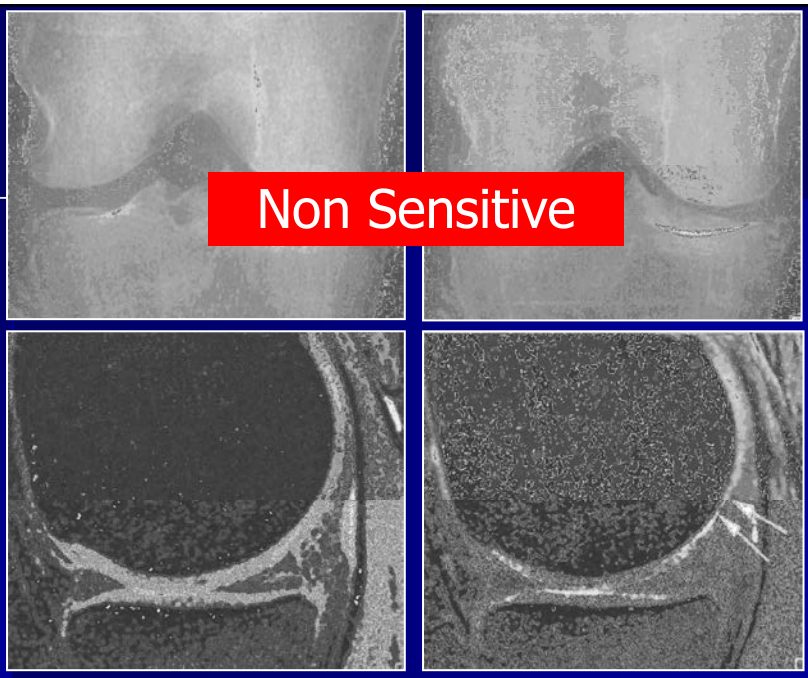


KLG 2 - Examples

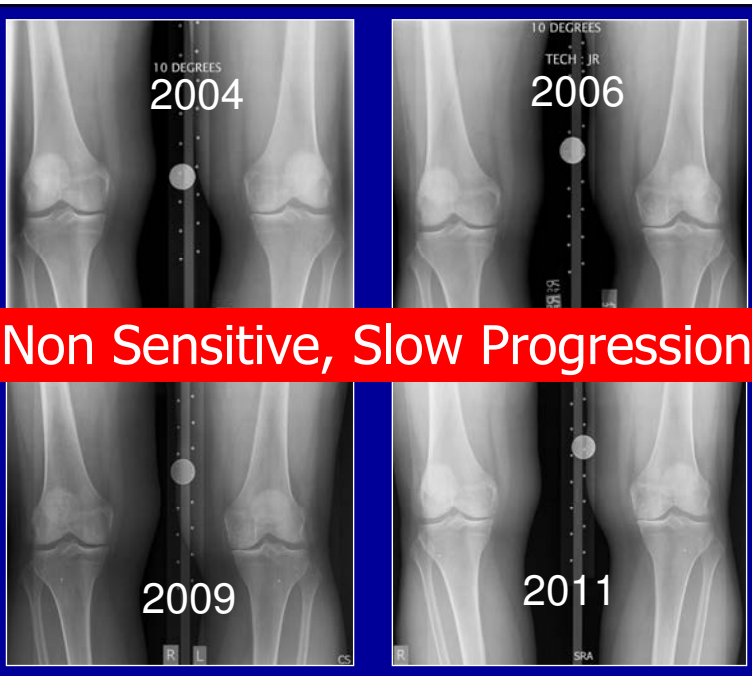




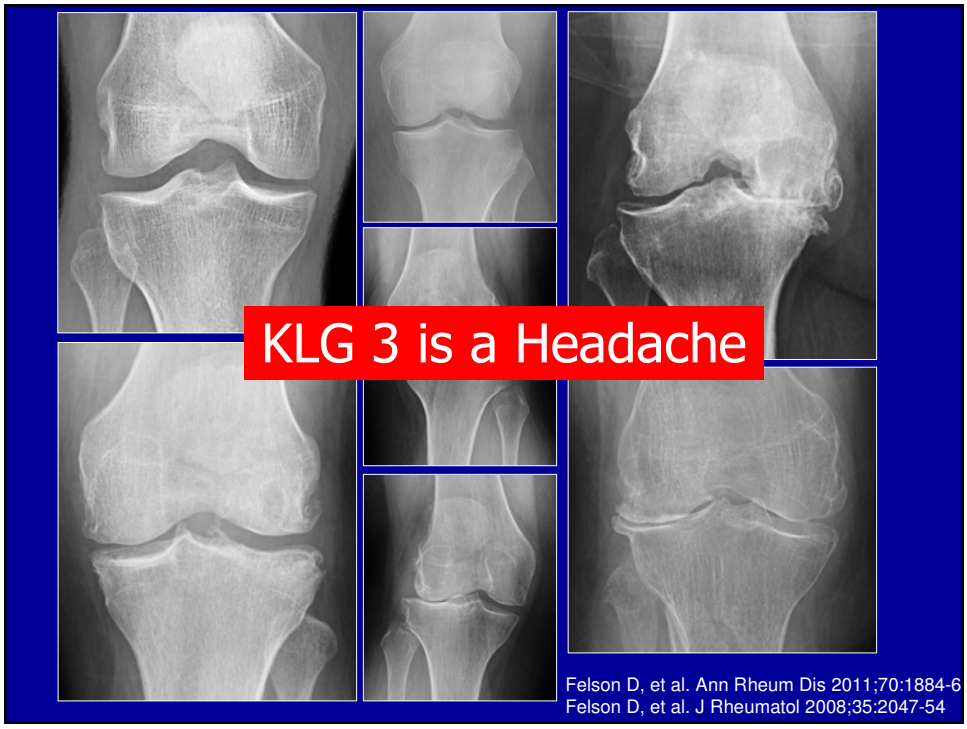
Guermazi et al. Arthritis Res Ther 2011; 13:247



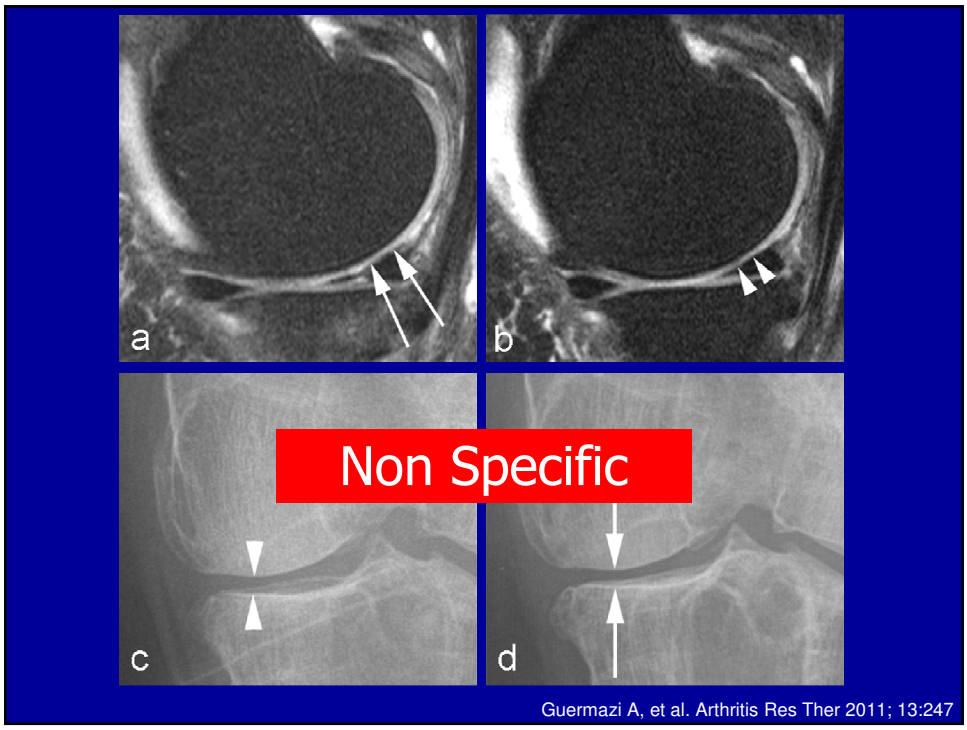
Roemer FW, et al. Osteoarthritis Cartilage 2009;17(Suppl 1):S224



Felson D, et al. Progression of osteoarthritis as a state of inertia. Ann Rheum Dis 2012 Jun 30



Felson D, et al. Ann Rheum Dis 2011;70:1884-6
Felson D, et al. J Rheumatol 2008;35:2047-54



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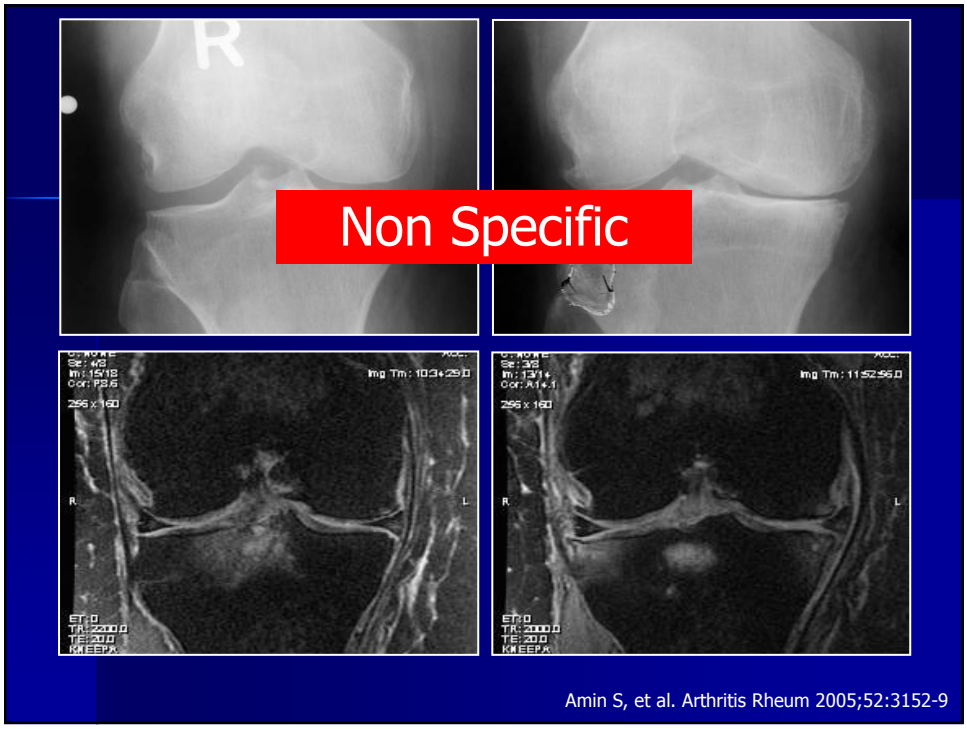
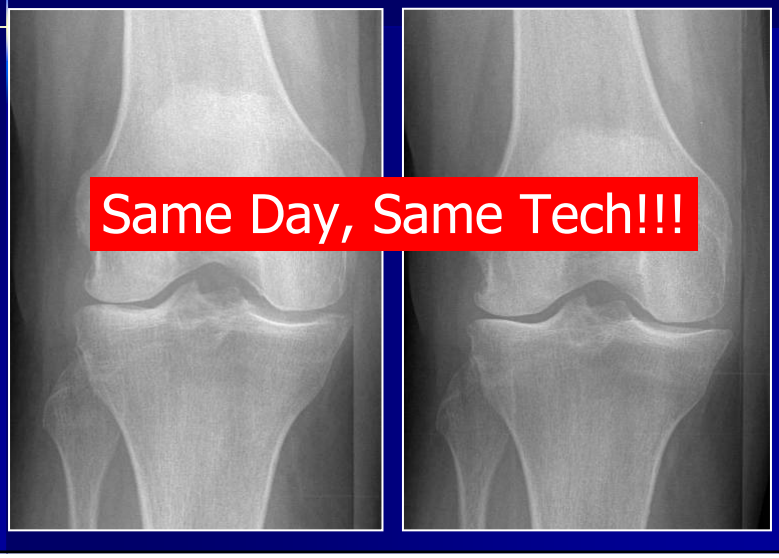


Amin S, et al. Arthritis Rheum 2005;52:3152-9

Positioning Is Problematic



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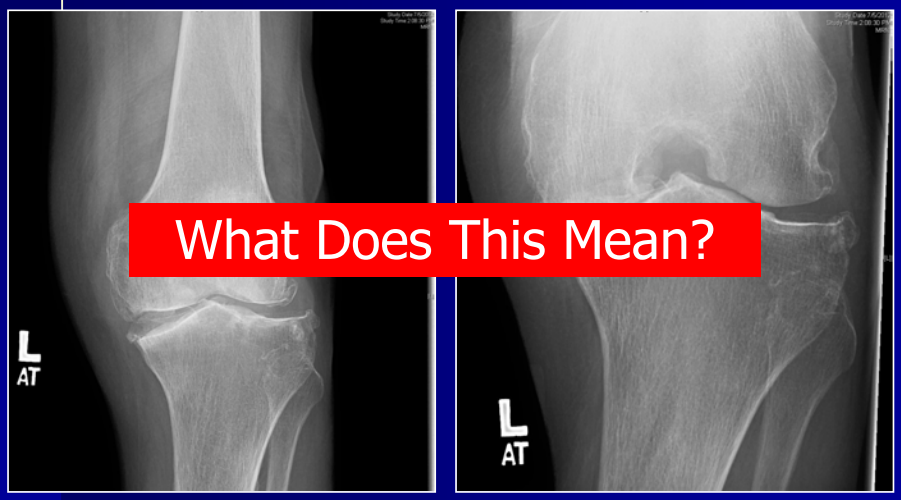
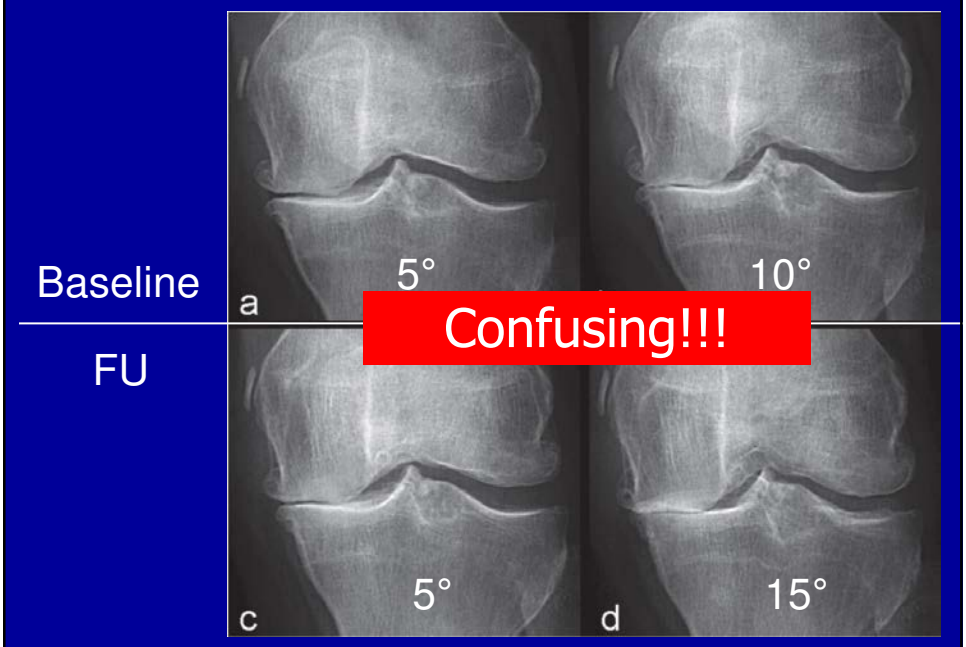


What Does This Mean?



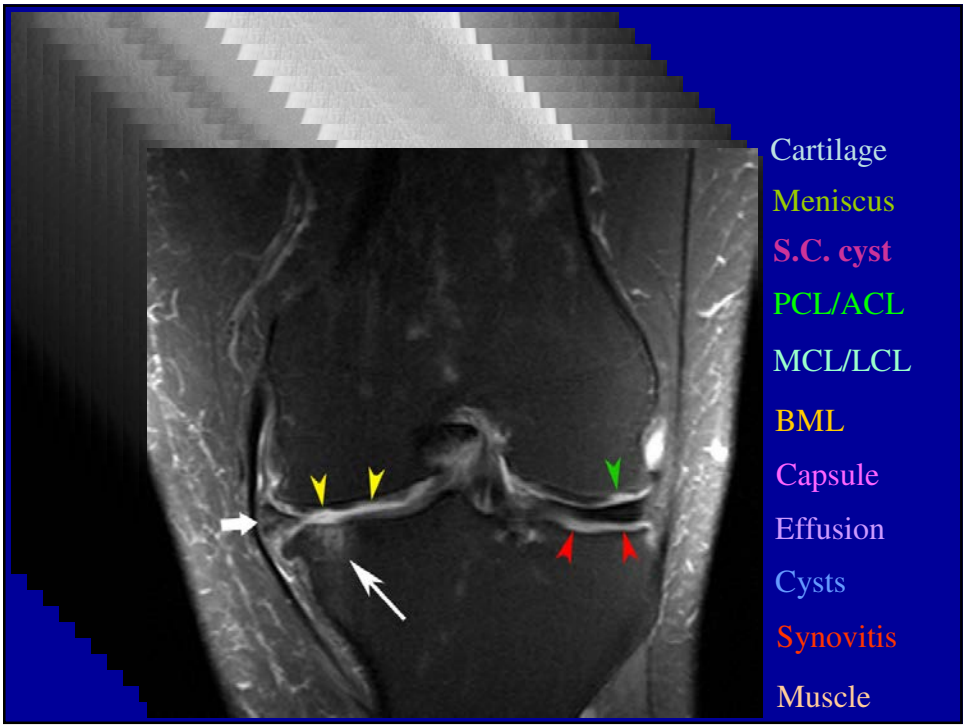
Confusing!!!

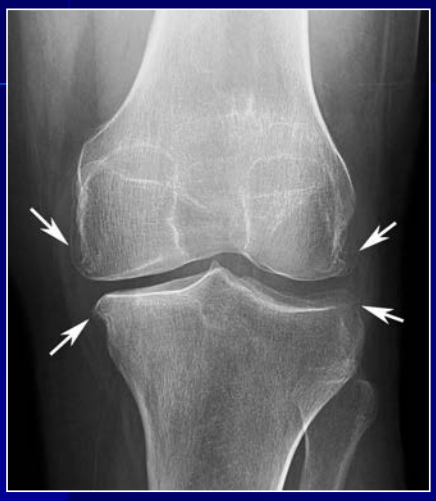
Guermazi et al. Arthritis Res Ther 2011; 13:247

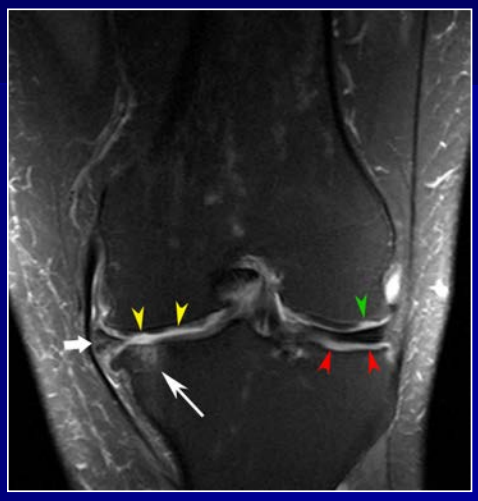
Fluctuation of Knee MRI Features

- Changes in scores of BML's and synovitis were associated with the fluctuation of frequent knee pain and pain severity
  - Effect of BML's was greater than that of synovitis
- Improvement of BML's over time was associated with concomitant reduction in pain presence and pain severity
- Worsening of synovitis and effusions over time was associated with an increase in knee pain presence and severity
- "These findings have implications for the development of new treatment and prevention strategies for the management of symptoms of knee OA."
- No x-ray feature fluctuation. X-ray is "ONE WAY ROAD" to an increase in KLG

Zhang Y, et al. Arthritis Rheum 2011;63:691-699







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- How about key features of OA, e.g. BMLs, meniscus, synovitis…?

Time to Say "Au Revoir" to the X-ray!

- Why we perform x-ray?
  - OP and JSN (indirect visualization of cartilage)
- Sensitivity to change?
  - None = "too slow" in longitudinal studies
- Specificity?
  - None = meniscal subluxation can mimic cartilage loss
- Positioning in multicenter studies?
  - Difficult or even problematic
- How about key features of OA, e.g. BMLs, meniscus, synovitis…?
  - Can't visualize them

Guermazi A et al. Arthr Res Ther 2011: 13:247

Imaging of OA Using MRI

- Choice of appropriate MRI pulse sequences is essential for scientifically meaningful interpretation of MRI-derived data
  - Cartilage
  - Bone marrow lesions (BML)
  - Meniscus
  - Synovitis

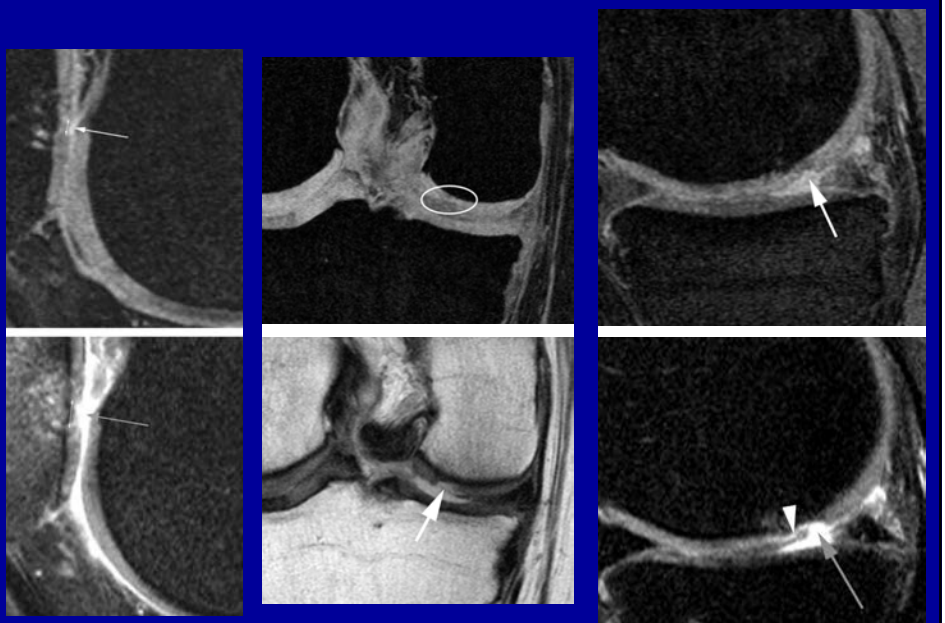
Choice of MRI Pulse Sequence

- Cartilage damage
  - Semiquantitative (SQ)
    - Grading of cartilage damage (e.g. grade 0–6)
    - Assessment of early OA:
      - T2w or lw or PDw fs FSE sequence should be used
      - GRE (e.g. DESS, FLASH, SPGR) is not suitable
  - Quantitative (Q)
      - Segmentation of the entire cartilage for volume/thickness measurement
      - GRE sequence is suitable

Focal Cartilage Defect

- Manifests in routine MRI as a focal lesion with acutely angled margins
- Lesion of the cartilage without change in thickness or cartilage surface is called signal change and only visible on T2-w
- GRE sequences are unsuited to detect subtle cartilage abnormalities including cartilage focal defects
  - Very prone to susceptibility artifact making it difficult to differentiate true focal defect from signal change due to artifact
  - GRE are suitable for quantitative cartilage segmentation
- Water sensitive sequences are ideal for focal defect assessment

Recht MP, et al. Am J Roentgen 2005;185:899-914
Hayashi D, et al. Arthritis Rheum 2010;62:3830-1
Bauer JS, et al. Invest Radiol 2008;43:604-611

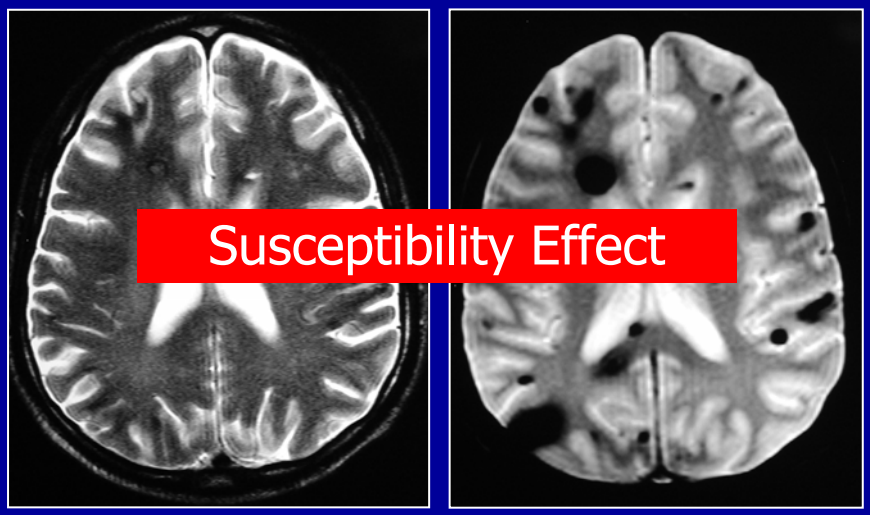


Hayashi D, et al. Arthritis Rheum 2010;62:3830-3831
Roemer FW, et al. Eur J Radiol 2011;80:e126-131

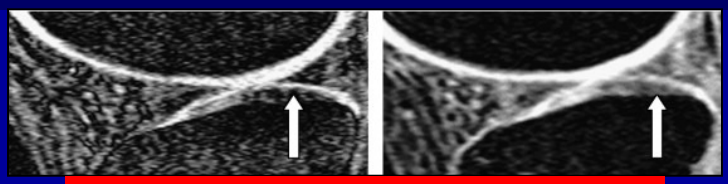
MRI Sequences Acronyms

Type of sequence	Philips	Siemens	GE	Hitachi	Toshiba
Fast SE	Turbo SE	Turbo SE	Fast SE	Fast SE	Fast SE
Ultra fast SE	SSH-TSE UFSE	SSTSE HASTE	SS-FSE	FSE - ADA	(Super)FASE DIET
Gradient echo (GE)	FFE	GRE	GRE	GE	FE
Spoiled GE	T_1 -FFE	FLASH	SPGR MPSPGR	RSSG	RF-spoiled FE
Ultra fast GE	T_1-TFE T_2–TFE THRIVE	TurboFLASH VIBE	FGRE Fast SPGR FMPSPGR VIBRANT FAME LAVA	SARGE	Fast FE RADIANCE QUICK 3D
Ultrafast GE with magnetization preparation	IR-TFE	T_1 /T_2- TurboFLASH	IR-FSPGR DE-FSPGR		Fast FE
Steady state GE	FFE	FISP	MPGR, GRE	TRSG	FE
Contrast enhanced steady state GE	T_2-FFE T_2	PSIF	SSFP		FE
Balanced GE	Balanced FFE	True FISP	FIESTA	BASG	True SSFP

Application of GRE in Neuroradiology

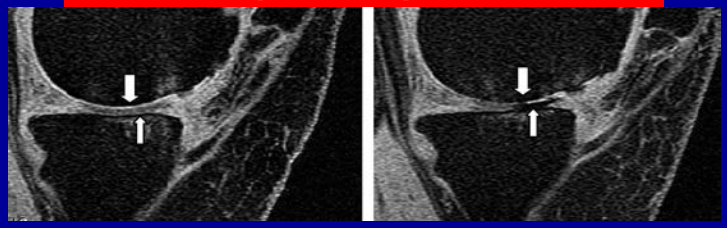


Why Is GRE Not Suitable for SQ Assessment of Cartilage Damage?



Sagitta… …ect from grade … …w-up.

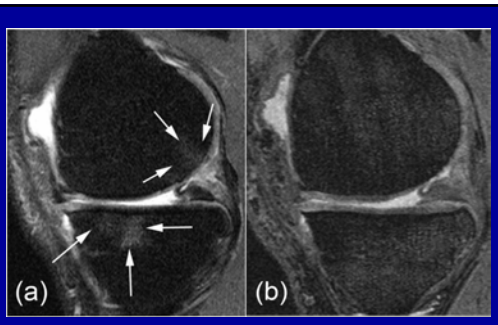
Susceptibility Artifact

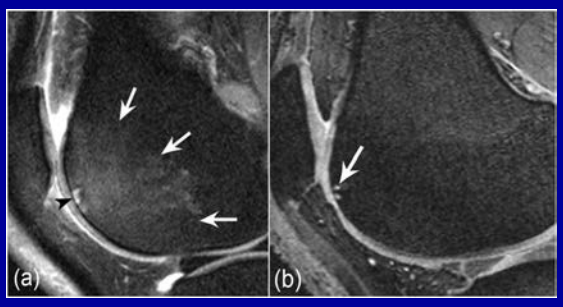


MRI show a cartilage defect score at both medial tibia and medial femur progressed from grade 3 at baseline to grade 4 at FU.

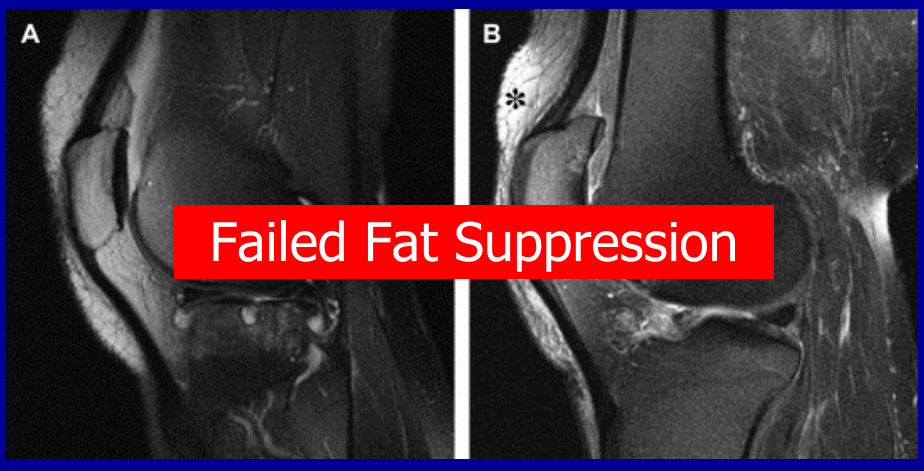
Choice of MRI Pulse Sequence

- Bone marrow lesions (BML)
  - Aka 'bone marrow edema pattern'
  - GRE sequences are insensitive to marrow abnormalities
    - May lead to underestimation of BML size or failure to detect BML
  - T2w/Iw/PDw fs FSE or STIR sequence should be used



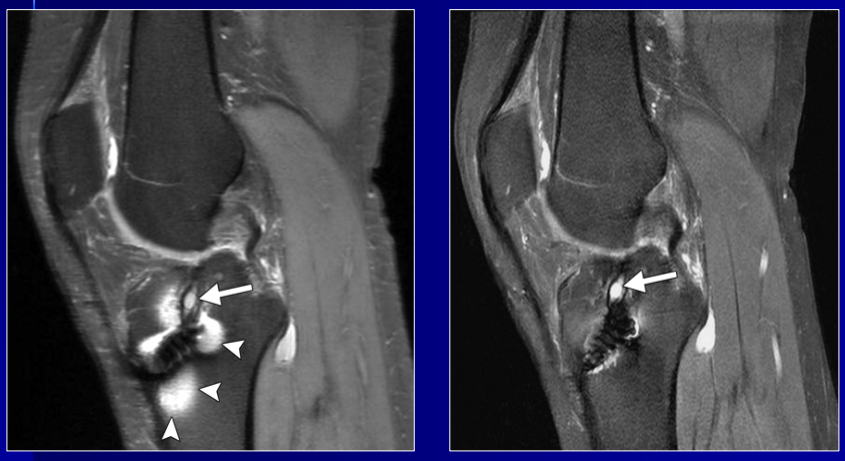


Hayashi D, et al. BMC Musculoskel Dis 2011;12:198
Crema MD, et al. Rheumatology 2011;50:996-997



Peterfy C, et al. Osteoarthritis Cartilage 2006;14 Suppl A:A95-111

Fat Suppression (Fat Saturation vs. IDEAL)

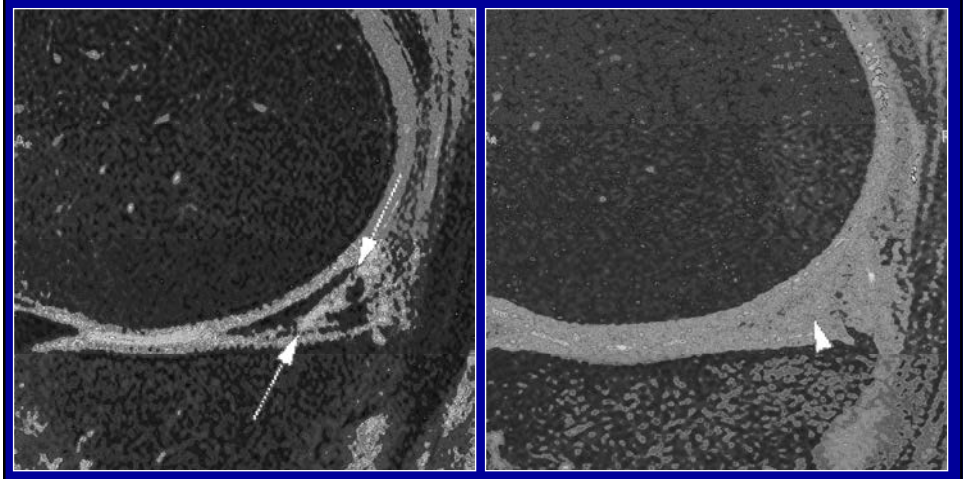


Choice of MRI pulse Sequence

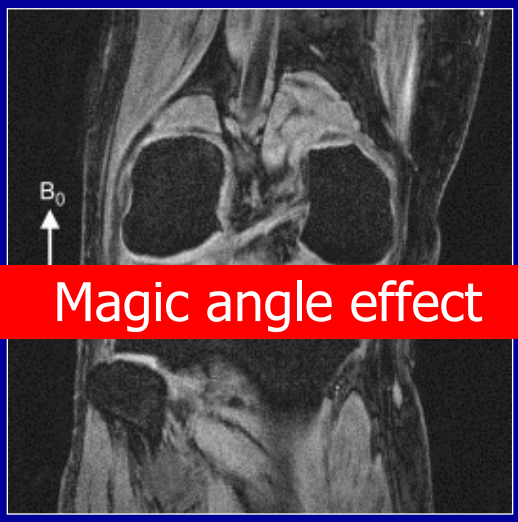
- Meniscus
  - Both coronal and sagittal planes are used
  - Slice thickness should be no more than 3mm
  - Ideally, Iw FSE with a long TR should be used
  - Long TE sequences (e.g. T2w FSE) and GRE sequence are relatively insensitive for meniscal tears

Sequence	TE (ms)
T2-weighted (T2w)	≥80
Proton density-weighted (PDw)	≤10
Intermediate-weighted (Iw)	~35

Englund M, et al. Nature Rev Rheumatol 2012 May 22



MRI Artifact on Short TE Sequence



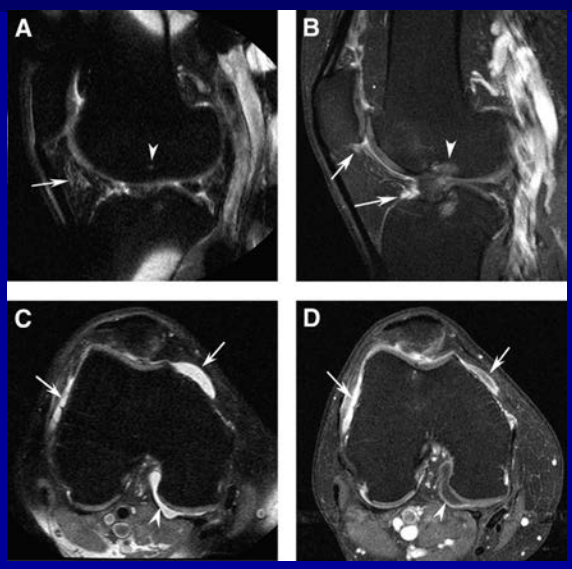
Peterfy C, et al. Osteoarthritis Cartilage 2006;14 Suppl A:A95-111

Choice of MRI Pulse Sequences

- Synovitis
  - True extent can only be appreciated by CE T1w sequence
  - Can also be assessed on non-enhanced MRI as 'Hoffa-synovitis' and 'effusion-synovitis'
    - but joint fluid and inflamed synovium cannot be differentiated
  - T2w/Iw/PDw fs FSE sequence should be used
  - GRE sequence not suitable
    - Prone to chemical shift artifact

Loeuille D, et al. Osteoarthritis Cartilage 2011;19:1433-9

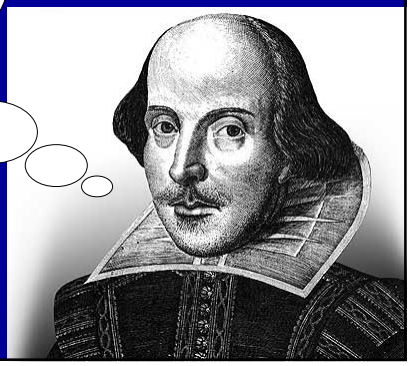
CE-MRI vs. Unenhanced MRI



Hayashi D, et al. Semin Arth Rheum 2011;41:116-30

Assessment of Synovitis in OA

To Gd,
Or Not To Gd,
That Is The Question!



The Case for Gd in RA

- Synovitis is reliable and valid measure of RA activity
- DCE-MRI improves sensitivity to early pathology and to change
  - Useful in phase I & II studies for sensitive assessment of compound anti-inflammatory effectiveness
  - Useful as outcome measure in phase III & IV studies
- MRI may have an important role in clinical practice
  - Differential diagnoses of early unclassified polyarthritis
  - Sensitive monitoring of therapeutic response
  - Prognostication of patients

Østergaard M, Ejbjerg B. Semin Musculoskelet Radiol 2004;8:287-99

Why Not Use Gd in OA?

- Extra imaging time
  - Add 5-10 min to usually 45-50 min exam
- Expensive
  - Add $50 to $400-500 per exam
- Not without risk to the participant
  - Very low risk of nephrogenic systemic fibrosis (NSF)
  - Exclude patients with renal insufficiency
  - Extremely rare allergy

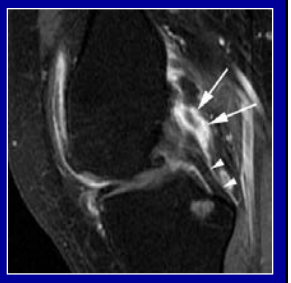
Role of CE-MRI for Synovitis in OA

- Synovitis in OA is a known source of pain
- Gd administration is recommended if we aim to assess comprehensively synovitis thickening in OA participants
- CE-MRI-based SQ scoring system published
- Could be useful in clinical trials as a marker of therapeutic response
  - Potential DMOAD?

Guermazi A, et al. Ann Rheum Dis 2011;70:805-11

How to Include Patients with Synovitis in Clinical Trials?

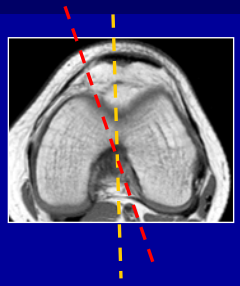
- KLG 2-3?
- Pain: other structures can be painful
- Palpation: Most of the synovitis is located deep in the notch posterior to the PCL (71.2% vs. 59.5% supra-patellar)
- Synovial biopsy: gold standard
  - Invasive since multiple areas should be biopsied
  - Unethical in long longitudinal trials
- Inflammation biomarkers: does systemic biomarker translates to a local OA joint inflammation?
- Imaging:
  - Scintigraphy: non specific
  - Ultrasound-Doppler: difficult for longitudinal FU, improper for deep-located synovitis
  - CE-MRI: ideal for inclusion and FU

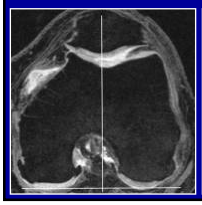


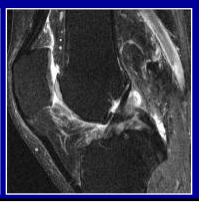
Roemer F, et al. OAC 2010;18:1269-74

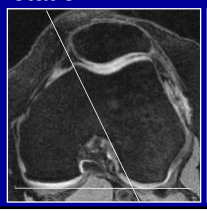
Orientation of Image Acquisition

- In multicenter trials, all imaging centers need to ensure the correct orientation of image acquisition: "Easy To Achieve"
  - Axial, coronal, sagittal
- One imaging center in multicenter study had a problem
  - Sagittal images were actually acquired in an 'oblique sagittal' plane
  - Problem for reading and data interpretation









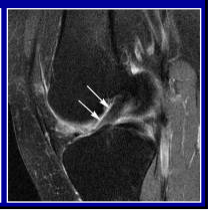
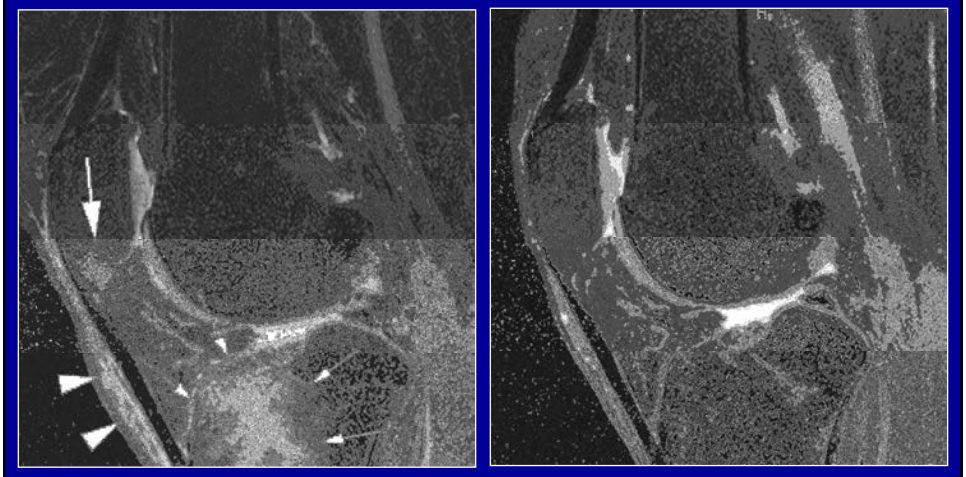


Image Interpretation – The case of BML's

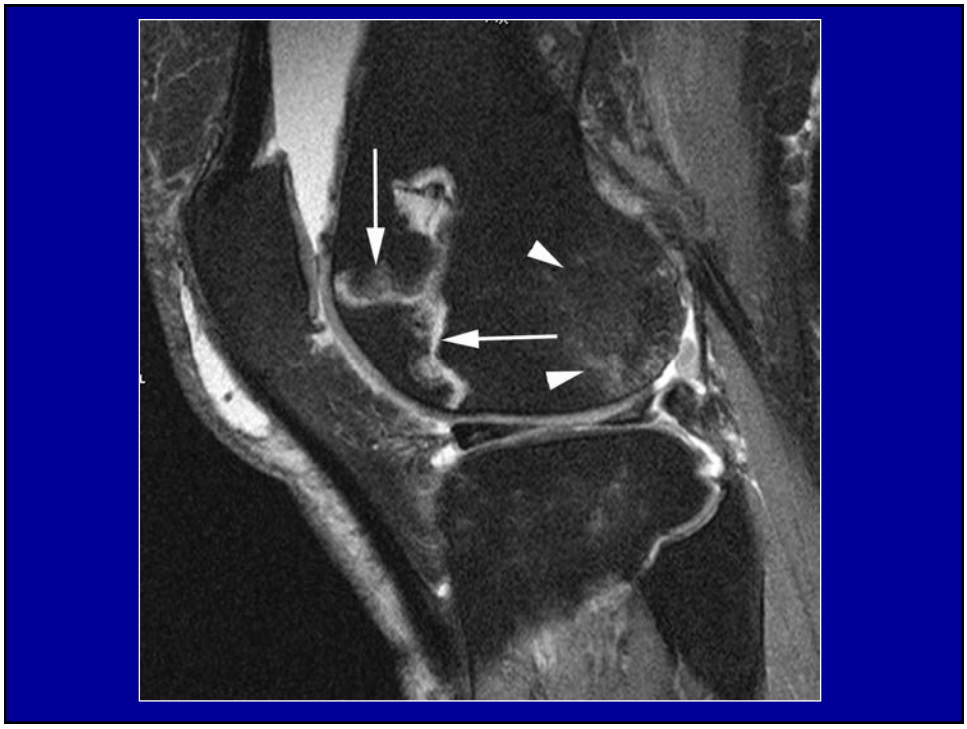
Traumatic	Non-traumatic
• Fracture (subchondral / osteochondral) • Contusion / "bone bruise" • Stress reaction and overuse • Insufficiency fracture • SONK • OCD	• Infarct / avascular necrosis • Transient BME / idiopathic • Infection • Rheumatic • Infiltration • Peritumoral • Chondropathy / Osteoarthritis • Tendinopathy • Enthesiopathy • Physiologic red marrow / normal

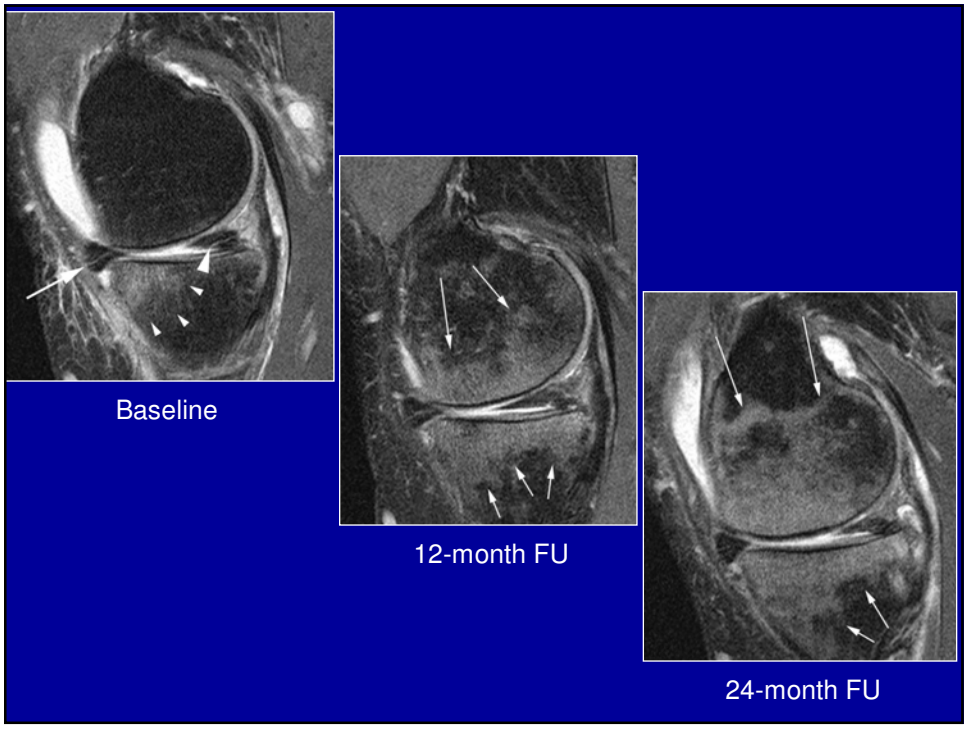
Roemer FW, Frobell R, Hunter DJ, et al. Osteoarthritis Cartilage 2009; 171115-31

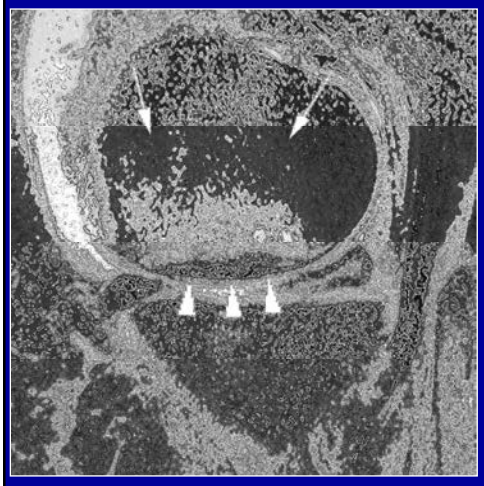
Image Interpretation



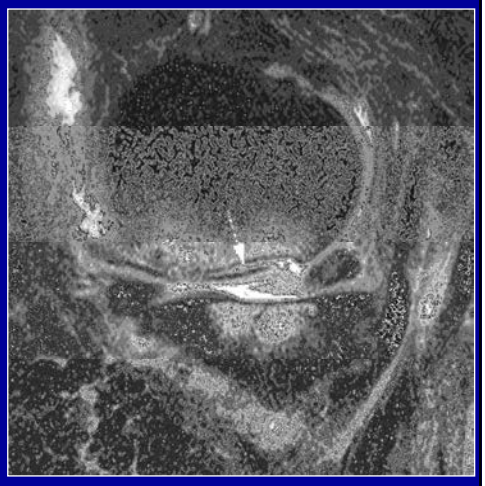
Baseline 12-month FU




Baseline
12-month FU
24-month FU

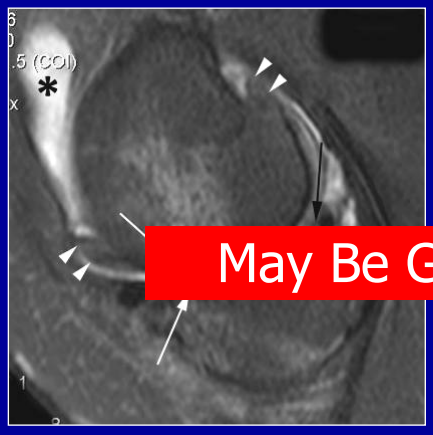


Baseline

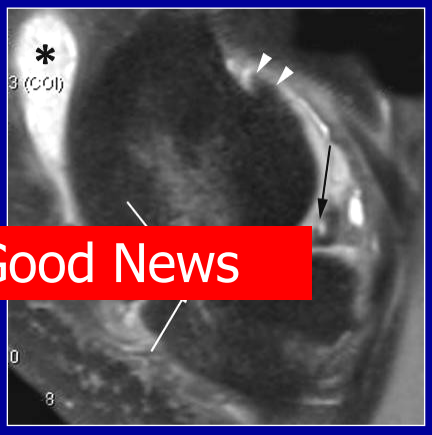


12-month FU

In the Future: All in One?



2D FSE Iw SPAIR



3D FSE Iw SPAIR

In the Future: All in One?

Parameters	Sagittal Intermediate-weighted (2D) FSE SPAIR	Coronal Intermediate-weighted (2D) FSE SPAIR	Axial Intermediate-weighted (2D) FSE SPAIR	Sagittal source 3D FSE SPAIR Intermediate-weighted
Repetition time (ms)	2342	2342	3045	2500
Echo time (ms)	50	50	50	35
Matrix	224 x 176	224 x 176	224 x 176	300 x 258
FOV (cm)	16	16	16	18
Slice thickness (mm)	4	4	4	0,6 x 0,6 x 0,7
Echo train (n)	14	14	14	65
Excitations (n)	4	4	4	1
Bandwidth	395	386	429	255
Acquisition time	2 min 43 sec	2 min 30 sec	2 min 58 sec	4 min 38 sec

Summary

- X-ray for inclusion and as an outcome measure is not appropriate. (Pain for inclusion is also not appropriate)
- Use of MRI is complex; careful trial design and interpretation necessary

Experts Consensus Is Needed Urgently

appropriate. We are not taking into account the complexity of the disease

- Need to focus on the “right” patients for given compound
- Try to include subjects at higher risk (since OA is a slow progressive disease)