Evidence of Surrogacy – What Imaging Data Predicts the Development of Long-Term Clinical Outcomes

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No Conflicts of Interest Related to this presentation to Disclose

Knee Replacement (KR) as a Long-term Clinical Endpoint

Pros:

- Cost-effective procedure with excellent long-term outcomes.
- May be considered as "final disease stage" (i.e., joint death) and is associated with marked pain, greater disability and decreased quality of life
- Exponential increase in KRs with an estimated 3 million/year in the US by 2030
- KR is a very expensive procedure and prevention of KR would have major socioeconomic impact

Cons:

- No clear consensus on indications for KR, but imaging biomarkers may help in the clinical decision making for patients as well use of KR as an outcome measure for clinical studies and clinical trials.
- May be dependent on non-clinical factors such as patients' and providers' preferences as well as access issues such as insurance status

Relationship Between Tibial Cartilage Loss Over Two Years and Subsequent Knee Replacement

	Number of knee replacements (%)	OR	Adjusted OR (95% CI)*†
Rate of tibial cartilage loss <3% per annum (n=37)	3 (8.1)	1	1
Rate of tibial cartilage loss 3-8% per annum (n=40)	7 (17.5)	2.4	2.3 (04. to 12.2)
Rate of tibial cartilage loss >8% per annum (n=38)	8 (22.2)	3.2	7.1 (1.4 to 36.5)

*Multivariate logistic regression adjusting for age, gender, BMI, % tibial cartilage loss, WOMAC score and bone size. † p=0.02 for trend

123 participants, 24 month f/u, 18 KR after 48M

Cicuttini, et al. ARD 2004, Table 4

Relationship Between Bone Marrow Edema and Knee Replacement

	OR*	95% CI
BME of any pattern vs. No BME	8.95	1.49-53.68
Global BME vs. No BME	13.04	2.06-82.58
Global BME vs. all other patterns	5.45	1.02-28.96

*Controlled for age

- Database of 4000 MRIs, 235 cases reviewed
- 25 OA only and 48 OA & BML, 3 year f/u, 15 KR

Scher, et al. Skeletal Radiology 2008, Table 6

Relationship Between Bone Marrow Lesions and Effect of Increasing Grade of Severity of Subchondral Bone Abnormality (BML only or BML and Cyst) and Knee Replacement

Tibiofemoral BMLs	Multivariate odds ratio (95% CI)*	p-value
Total tibiofemoral BMLs	1.57 (1.04, 2.35)	0.03
Medial tibiofemoral BMLs	1.78 (1.16, 2.74)	0.01
Lateral tibiofemoral BMLs	0.82 (0.43, 1.54)	0.54

*Adjusted for age, gender and KL grade.

	Multivariate analysis aOR (95% CI)	p-value
Medial TF compartment	1.99 (1.01 to 3.90)	0.05
Lateral TF compartment	0.96 (0.48 to 1.94)	0.91

109 participants, 24 month f/u, 16 KR

Tanamas, et al. Rheumatology 2010, Table 4

Tanamas, et al. ART 2010, Table 4

Relationship Between Bone Marrow Lesions (Right Knee) and Knee Replacement

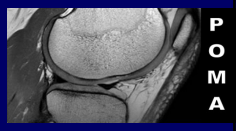
	OR (95% CI)	p-value
Left knee replacement (n=7)		
BML severity (0 to 8)	**2.78 (1.58, 4.90)**	**<0.01†**
BML presence/absence	**12.85 (1.82, 90.91)**	**0.011†**
Right knee replacement (n=8)		
BML severity (0 to 8)	**2.88 (1.84, 4.52)**	**<0.01†**
BML presence/absence #	**22.63 (3.72, α)**	**<0.01†**
Knee replacement right and left (n=12)		
BML severity (0 to 8)	**2.10 (1.13, 3.90)**	**0.019 ‡**
BML presence/absence	5.67 (0.62, 51.77)	0.124‡

Using exact logistic regression because all 8 subjects who had right knee replacement had a BML present; † Adjusted for age and sex; ‡ Further adjusted for body mass index, knee pain, leg strength, cartilage defects, tibial bone area, and radiographic osteoarthritis

- Tasmanian Older Cohort (TASOAC) study
- 205 participants, 5 year f/u, 12 KR

Dore, et al. ART 2010, Table 5

Pivotal Osteoarthritis Initiative MRI Analyses (POMA)



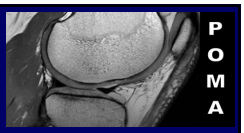
- To examine the relationship between features of joint morphology and disease progression to important clinical outcomes, for example, knee replacement

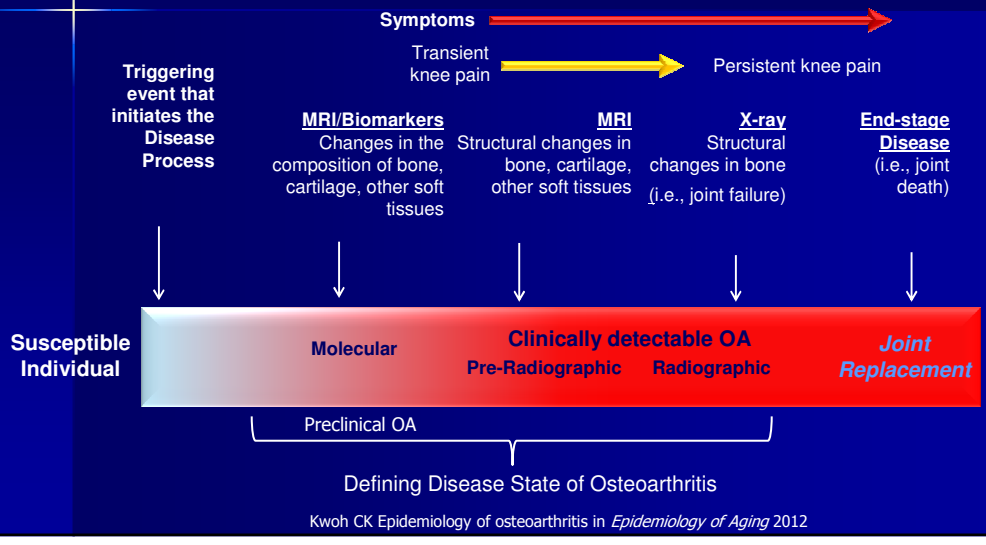
  Joint morphologic features to be evaluated:
  - Quantitative MRI measures
    - Carilage morphometry (Chondrometrics)
    - Subchondral Bone Shape (Qmetrics)
  - Semi-Quantitative MRI measures (BICL)
    - Cartilage morphology
    - Bone marrow lesions
    - Effusion/synovitis
    - Meniscal abnormalities

KLINIKUM AUGSBURG · BOSTON UNIVERSITY · THE UNIVERSITY OF SYDNEY · Qmetrics TECHNOLOGIES · NOVARTIS

Natural History of OA

OAI osteoarthritis initiative a knee health study



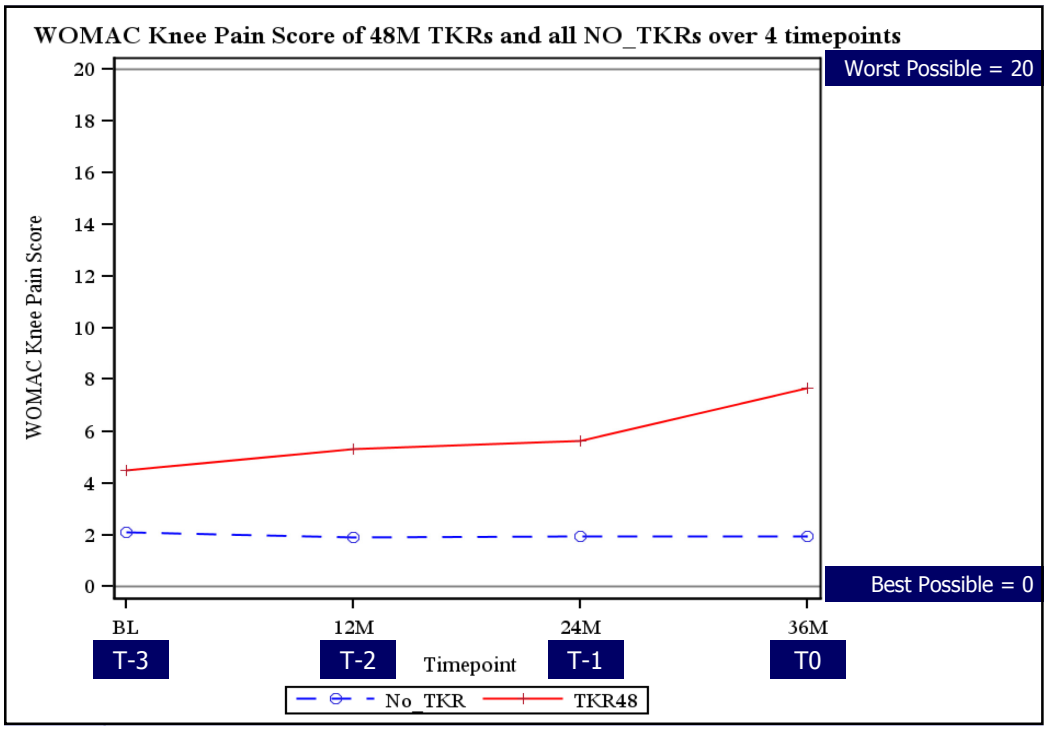


Kwoh CK Epidemiology of osteoarthritis in *Epidemiology of Aging* 2012

Methods – Knee Selection

- Knees from ~100 OAI participants that underwent TKR (~120 knees) and had MRIs available for the time point prior to TKR (i.e., "T0") and at two time points prior TKR (i.e., "T0" and "T-1") were studied.

- For example, a TKR reported at the 48 month (M) visit: T0=36M visit, T-1=24Mvisit.
- TKR Knees were matched with control knees from OAI participants that did not undergo TKR for radiographic disease stage, gender, and age within 5 years at study enrollment and had data available at the same T0 and T-1 follow-up visits.

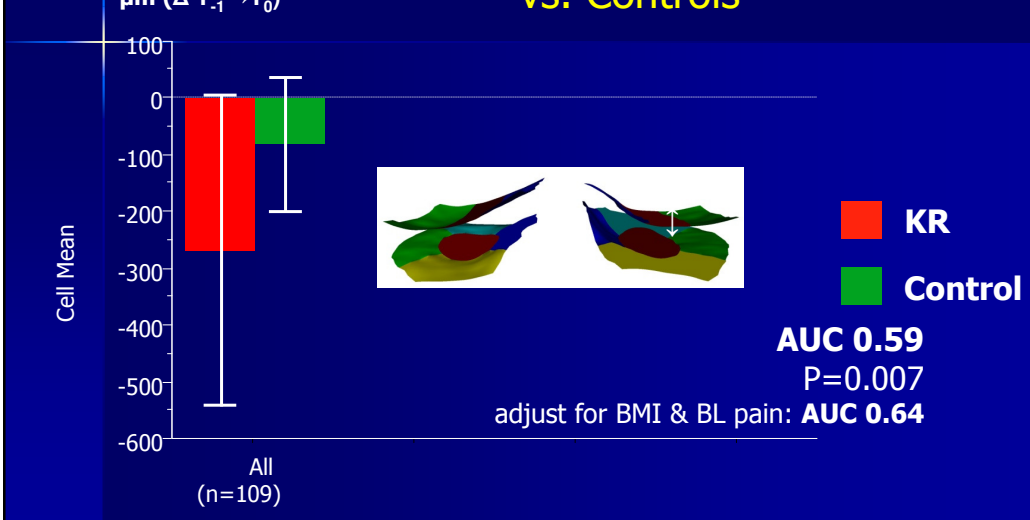


Cross-Sectional Differences (T0) in Quantitative Parameters of Femorotibial Cartilage Structure in Knees Undergoing KR vs. Controls

	Percent	25%	Median	75%	p-value
(Central) medial compartment					
cMFTC	-42	-1.92	-0.56	0.63	0.0005
MFTC	-26	-1.20	-0.37	0.39	0.0013
Femorotibial cartilage plates					
MF.ThC	-5	-0.42	-0.10	0.16	0.0167
cMF.ThC	-46	-0.82	-0.17	0.21	0.0009
cMF.VC	-30	-579	-91.8	227	0.0196
MT.dAB%	NA	0.00	2.95	19.04	0.0002
cMF.dAB%	1310	-2.52	0.00	38.97	<0.0001
MT.tAB	4	-0.59	0.67	1.82	0.0011
cMF.tAB	7	-0.67	0.22	1.48	0.0296

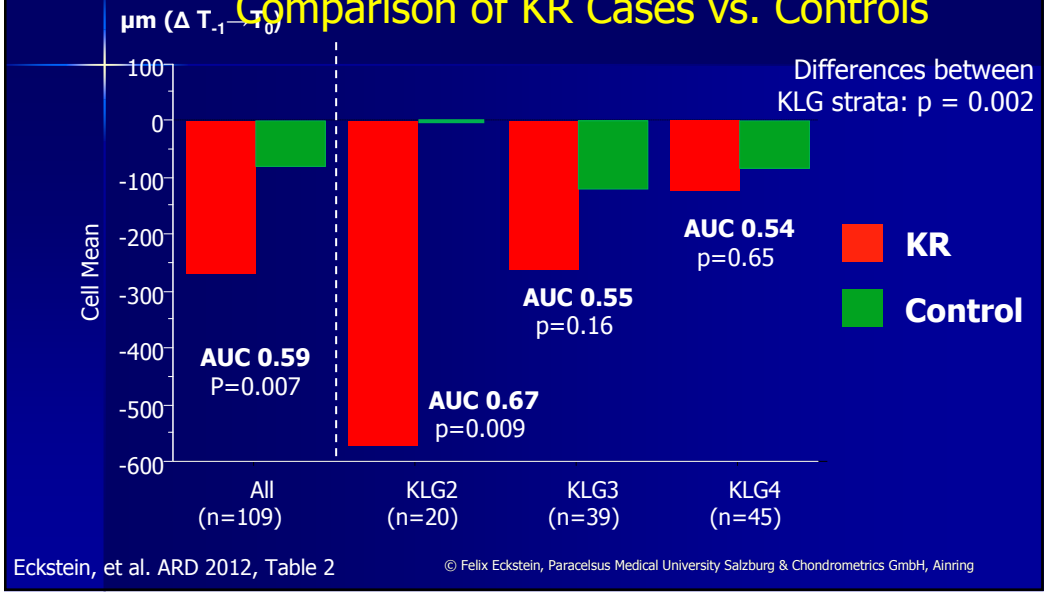
Eckstein, et al. ARD 2012, Table 3

Changes (from T-1 to T0) in cMFTC Prior to Knee Replacement (KR): Comparison of KR Cases vs. Controls



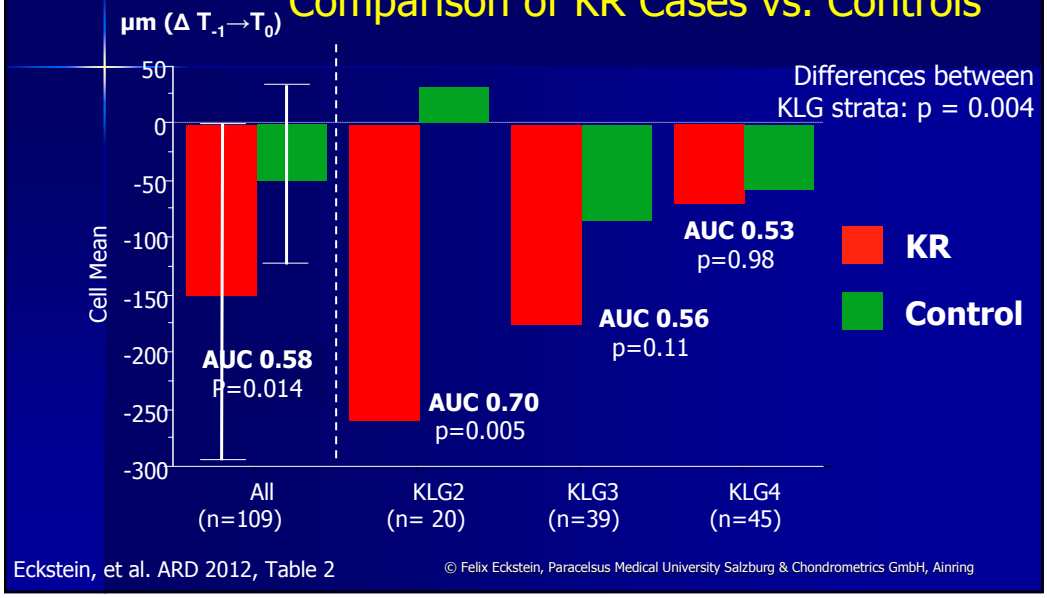
Eckstein, et al. ARD 2012, Table 2

Changes (from T-1 to T0) in cMFTC Prior to Knee Replacement (KR) by KL Strata: Comparison of KR Cases vs. Controls



Eckstein, et al. ARD 2012, Table 2

Changes (from T-1 to T0) in MFTC Prior to Knee Replacement (KR) by KL Strata: Comparison of KR Cases vs. Controls

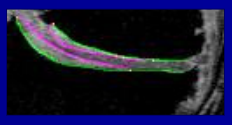


Eckstein, et al. ARD 2012, Table 2

Changes (from T-1 to T0) in Other (Exploratory) Endpoints Prior to Knee Replacement (KR): Comparison of KR Cases vs. Controls

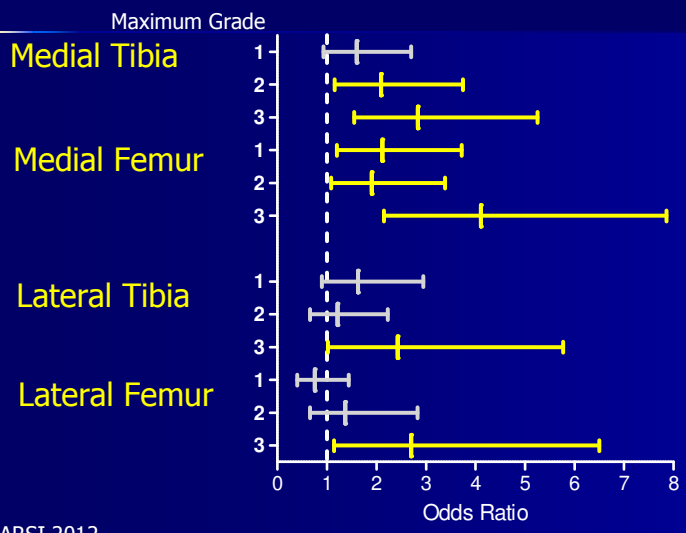
	Thickness (ThCtAB)	Volume (VC)	Denuded area (dAB)
MT	0.005	0.01	0.01
cMF	0.10	0.06	0.04
LT	0.13	0.26	0.07
cLF	0.25	0.11	0.23

Wilcoxon Signed Rank Test

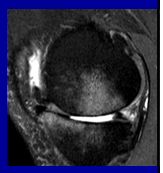


Eckstein, et al. ARD 2012, Table 2

Relationship Between Medial or Lateral BMLs (T0) and Knee Replacement (Plate Analysis)



MOAKS
Grade 2: >33-66%



MOAKS
Grade 3: >66%

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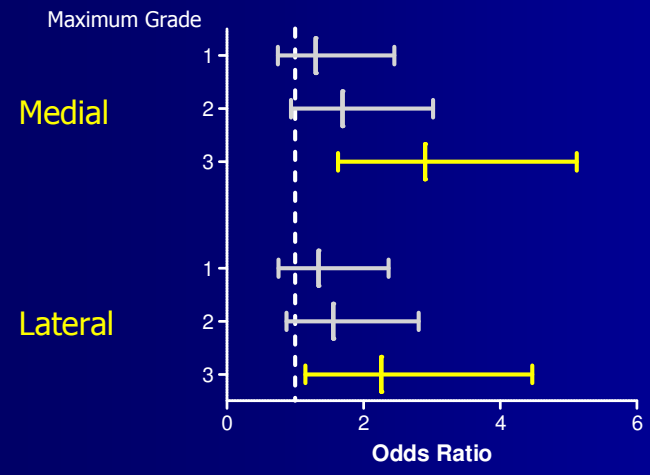
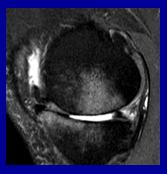
Relationship Between BMLs (T0) and Knee Replacement (Compartment analysis)





MOAKS
Grade 3: >66%

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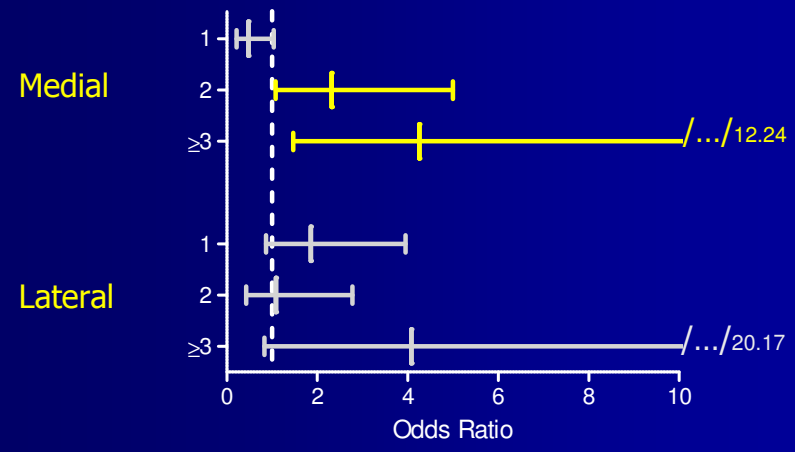
Relationship Between Number of Subregions with Worsening BMLs (from T-1 to T0) and KR



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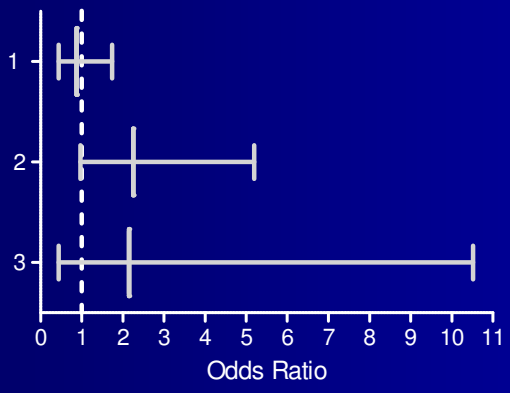
Relationship Between Hoffa-Synovitis (T0) and Knee Replacement



MOAKS
Grade 2

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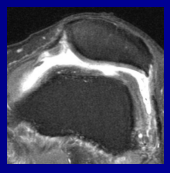
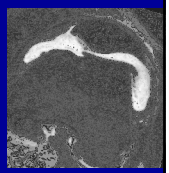
Relationship Between Effusion-Synovitis (T0) and Knee Replacement

MOAKS
Grade 2



MOAKS
Grade 3



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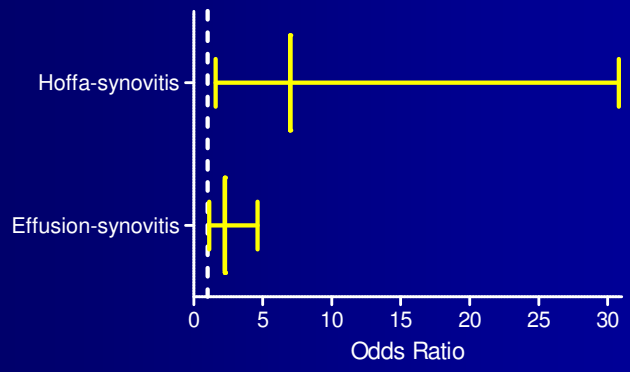
Relationship Between Worsening Hoffa-Synovitis or Effusion Synovitis (T-1 to T0) and Knee Replacement

Worsening by at least 1 grade



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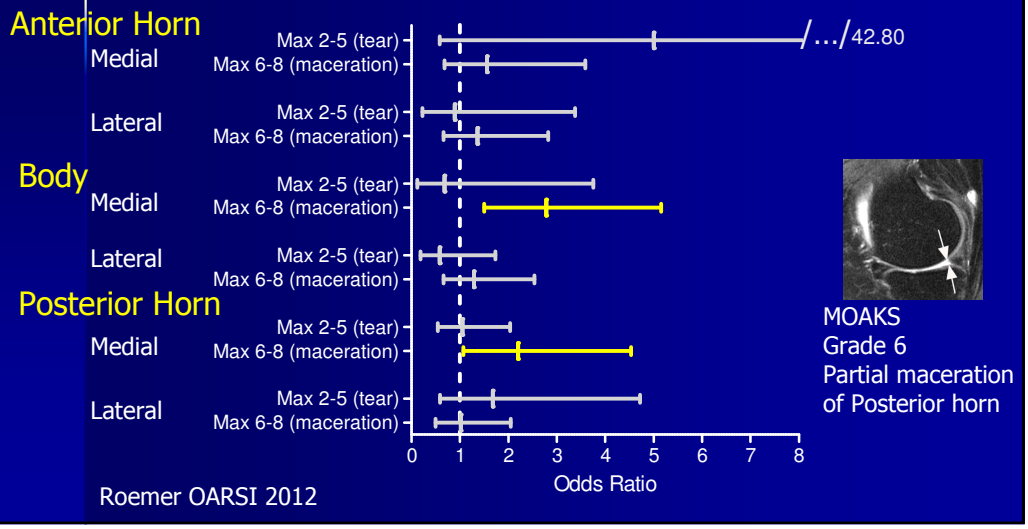
Relationship Between Meniscal Damage (T0) and Knee Replacement



MOAKS
Grade 6
Partial maceration
of Posterior horn

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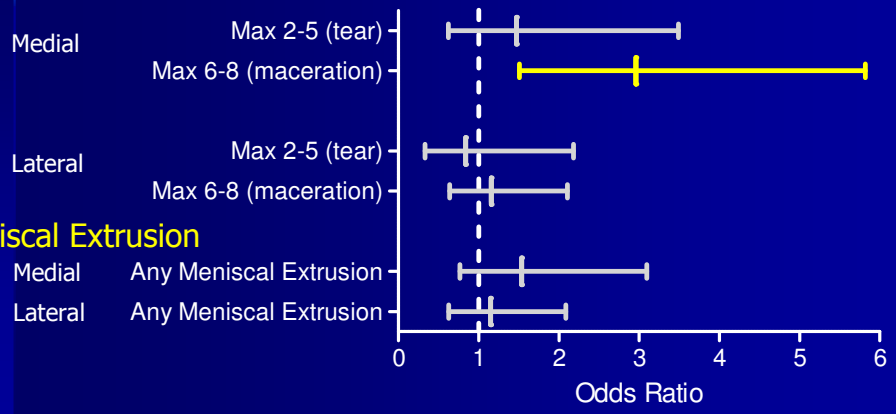
Relationship Between Meniscal Damage (T0) and Knee Replacement

Maximum Grade in any of 3 locations



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Statistical Parameter Mapping: Comparison of Mean Bone Curvature Between KR Cases and Controls

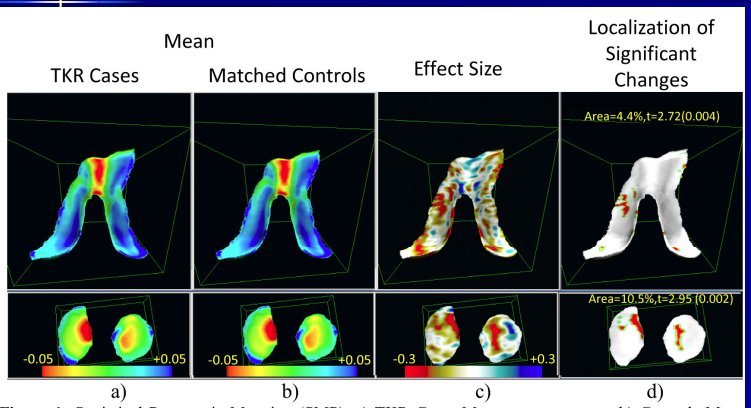


Figure 1: Statistical Parametric Mapping (SMP). a) TKR Cases Mean curvature map. b) Controls Mean curvature map. d) Effect size map: [mean difference]/[paired standard deviation]. d) Location of the statistical significant differences in curvature adjusted for false discovery ($p<0.05$).

Flattening of:
cMF (2.7%)

and
MT (10.5%)

Tamez-Peña, OARSI 2012

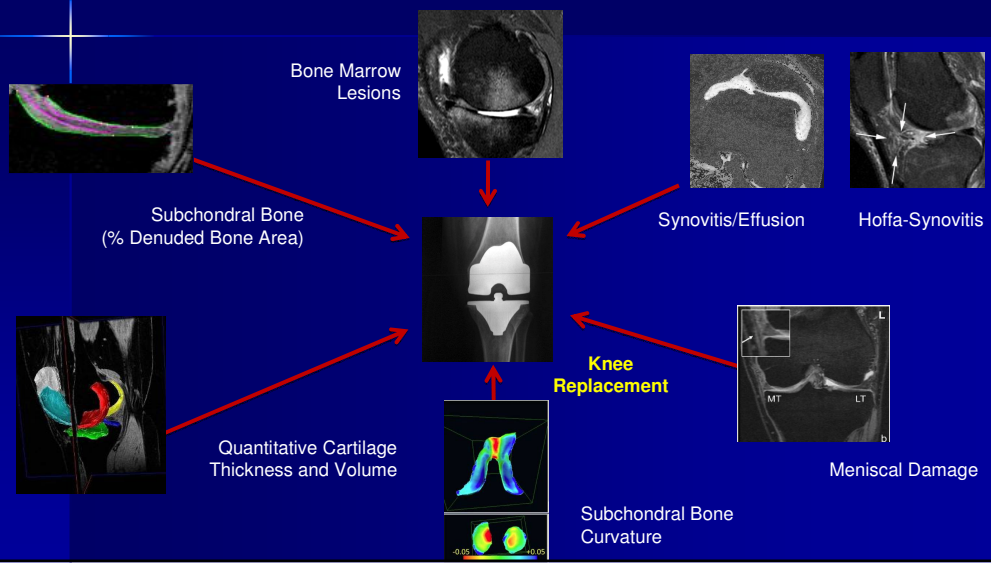
ROC Analysis of the Curvature of the Bone-Cartilage Interface: Comparison Between KR Cases and Controls

(127 Case-Control Pairs at T0)

	TKR Cases	Matched Control (Gender, Age and cKLG)	Paired Difference	Curvature Adjusted ROC [Gender, Age, Height & KL]	T0 Logistic Model [Gender, KL, Age, BMI, Pain and Curvature]
	Mean (Std)	Mean (Std)	p-value	AUC(p-value)	AUC
Femur	0.024(0.004)	0.025(0.004)	0.000	0.52(0.657)	0.77
Entire Tibia	-0.008(0.006)	-0.009(0.004)	0.002	0.62(0.001)	0.76
cMF	0.024(0.006)	0.027(0.006)	0.000	0.66(0.000)	0.79
cLF	0.025(0.004)	0.026(0.005)	0.036	0.57(0.066)	0.77
MT	-0.009(0.007)	-0.012(0.005)	0.003	0.62(0.001)	0.77

Tamez-Peña OARSI 2012

Presence and/or Worsening of Morphologic Features on MRI Increases the Risk of Knee Replacement



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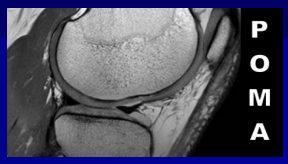

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OAI Confirmed KRs