### Novel Imaging of Juvenile Inflammatory Arthritis AMC-experience Seeking the truth

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CES 👹

# Learning objectives

- To illustrate the various new imaging strategies we explored
- To enhance synergetic approach
- To explain way of working in AMC-Amsterdam

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Historic Overview

# 4C's

- Coincidence
- Curiousness
- Collaboration
- Community





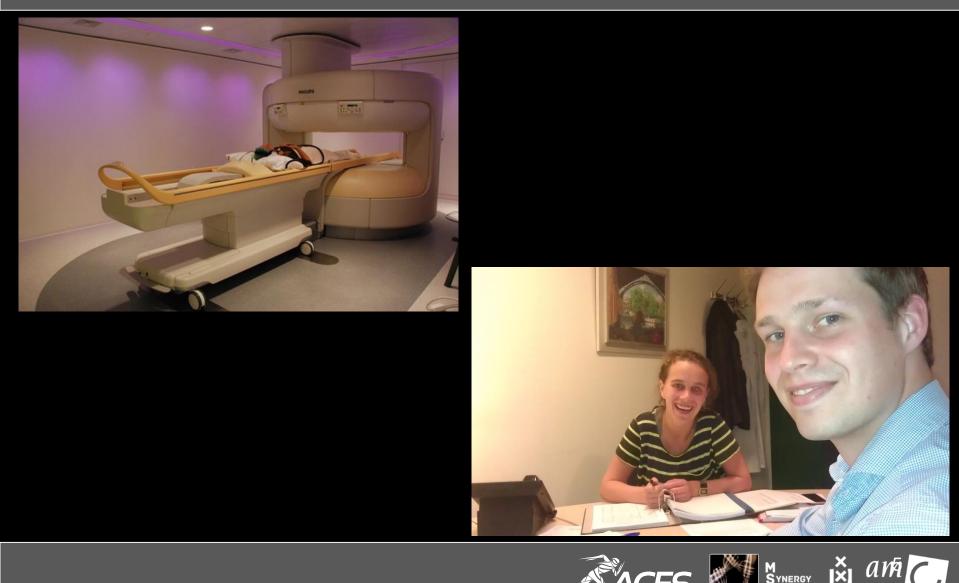
# COMMUNITY means Synergy 1+1=3

- Technicians
- Physicists
- Medical students
- PhD students
- Residents





# Coincidence 2006







Imaging important role in:

- Assessment of disease activity
- Checking response to therapy
- Monitoring disease progression

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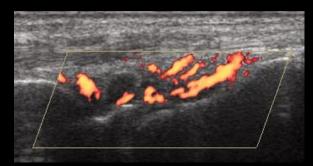
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Evaluation of complications

# Imaging in JIA

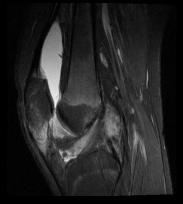
### Imaging modalities

- Radiography
- Ultrasound





Magnetic Resonance Imaging





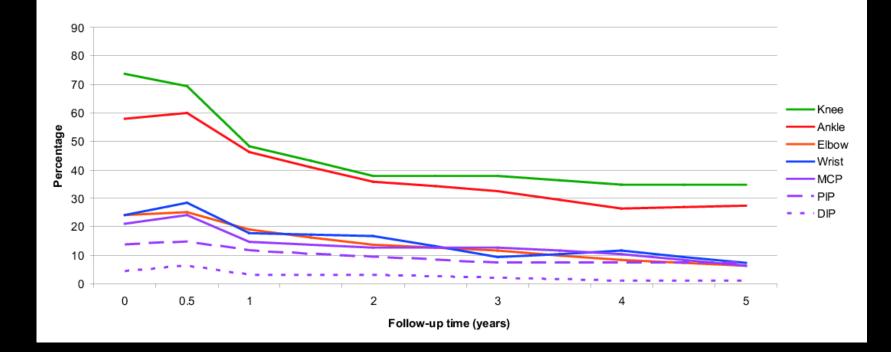
# MRI in JIA

Magnetic Resonance Imaging

- Most sensitive tool for detecting synovitis
- State of the art imaging modality able to visualize bone marrow changes



### BACKGROUND

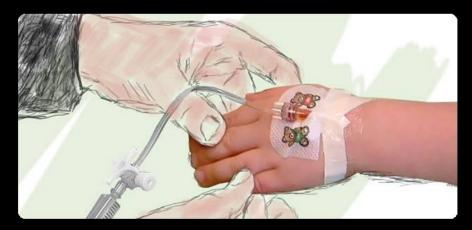


<sup>1</sup> Hemke et al. – Rheumatol Int. 2014



# CURIOUS





- Feasibility (Open) MRI<sup>1</sup>
- IV contrast necessary<sup>2</sup>
- Bilateral scanning no additional value<sup>2</sup>
- Juvenile Arthritis MRI Scoring (JAMRIS) system<sup>3</sup>

<sup>1</sup> Hemke et al. – 2012 <sup>2</sup> Hemke et al. – 2013 <sup>3</sup> Hemke et al. – 2012



# JIA features on MRI

Soft-tissue

-'Synovitis'

-Effusion

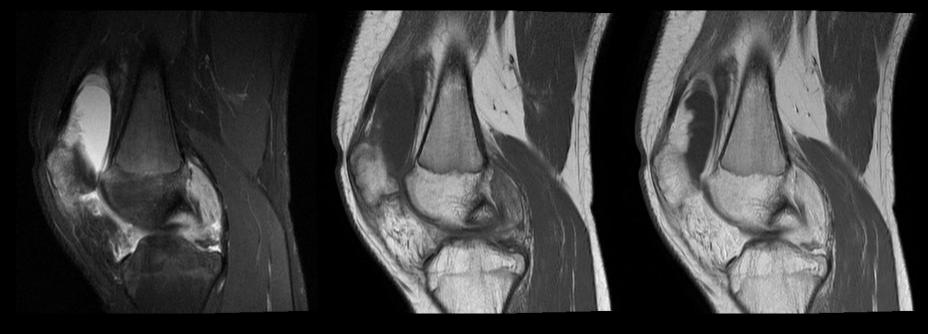
-Tenosynovitis

Osteochondral

- Bone marrow edema
- Cartilage
- Erosions



# Marked synovial hypertrophy

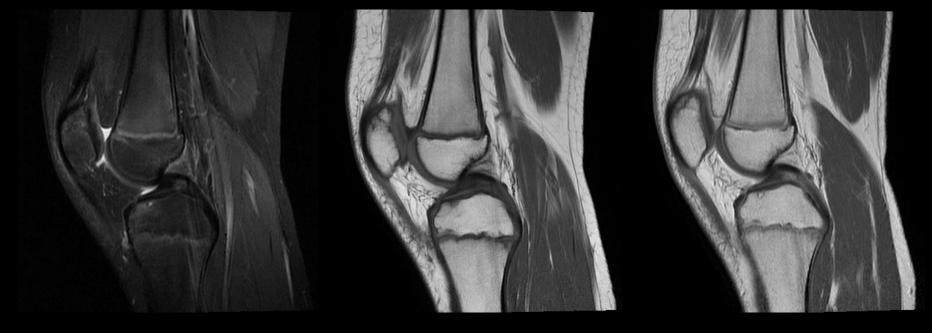


#### T2W fatsat

T1W -Gd SeFciostoreeadchigg((⊕@)d)

T1W + Gd

# Subtle synovial hypertrophy



#### T2W fatsat

T1W -Gd SeFciostoreeadchigg((⊕@)d)

T1W + Gd

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### Methods

Patients

- 46 JIA patients included
- 28 (61%) female patients
- Mean age 12 years (SD 2.8)



# Methods

MRI dataset independently scored by 2 readers

- First reading consisted of unenhanced images only (-Gd)
- Second reading consisted of complete data set; contrast-enhanced and unenhanced images (+Gd)



### Methods

Sequence	Plane	FS	Gd	TR (ms)	TE (mm)	ST (mm)	Gap (mm)	FOV (mm)	Matrix	Time (min)
T2 SPIR	Sag	+	-							
T2 SPIR	Cor	+	-							
T2 SPIR	Ax	+	-		c				-l)	
T1 TSE	Sag	-	-		č	Secon	d readi	ng (+G	a)	
T1 TSE	Sag	-	+							
T1 SPIR	Ax	+	+							



## Results

Diagnostic accuracy of MRI without Gd-enhancement compared with Gd-enhanced MRI as the reference standard

	Sensitivity	Specificity	PPV	NPV
Synovial hypertrophy	0.60	0.98	0.90	0.85
Bone marrow changes	0.89	0.99	0.97	0.94
Cartilage lesions	0.73	1.00	1.00	0.95
Bone erosions	1.00	1.00	1.00	1.00

PPV: positive predictive value

NPV: negative predictive value



### Results

### Reliability

	Single measure ICC			
	-Gd	+Gd		
Synovial hypertrophy	0.76	0.88		
Bone marrow changes	0.87	0.88		
Cartilage lesions	1.00	0.97		
Bone erosions	0.93	0.93		

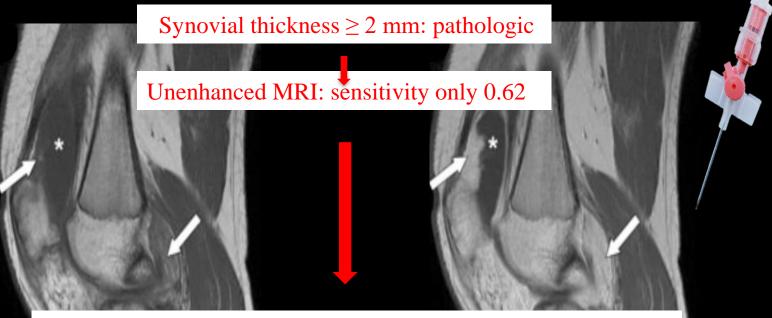
ICC: Intraclass Correlation Coefficient



# Summary

#### T1W GBCA -

#### T1W GBCA +



Thus: contrast essential for reliable examination of synovium

#### Synovial enhancement and thickening!





Hemke, Eur Radiol. 2013&2017

# **Contrast enhanced MRI in JIA**

Conclusions; omitting Gd contrast injection:

- Is unimportant in the assessment of
  - Bone marrow changes
  - Cartilage lesions
  - Bone erosions
- Decreases the reliability in the evaluation of

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- Synovial hypertrophy

# JAMRIS system for the knee

Synovial hypertrophy

Bone marrow changes

Cartilage lesions

Bone erosions



### Juvenile Arthritis MRI Scoring (JAMRIS) system for the knee

#### Synovial hypertrophy score (maximal synovial thickness)

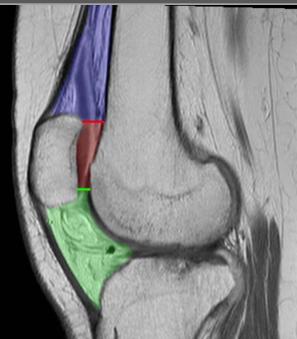
	•			
Location	0-2mm	2-4mm	>4mm	
Retropatellair				
Suprapatellar recesses				
Infrapatellar fat pad				
Cruciate ligaments				
Medial posterior-condylar				
Lateral posterior-condylar				

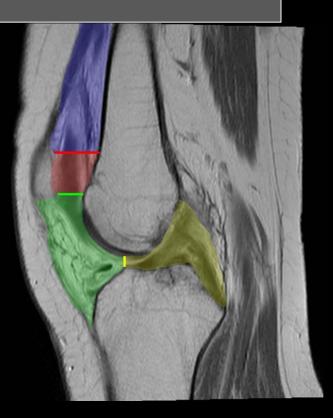
Bone marrow change score (involvement of bone volume)						
None	<10%	10-25%	>25%			
	None	None       <10%	None         <10%         10-25%			

Cartilage lesion score (involvement of cartilage surface area)						
Location	None	<10%	10-25%	>25%		
Patella, lateral						
Patella, medial						
Femur, medial condyl						
Femur, lateral condyl						
Femur, medial weight-bearing region						
Femur, lateral weight-bearing region						
Tibia, medial tibia plateau						
Tibia, lateral tibia plateau						

Bone erosion score (involvement of bone volume)					
Location	None	<10%	10-25%	>25%	
Patella, lateral					
Patella, medial					
Femur, medial condyl					
Femur, lateral condyl					
Femur, medial weight-bearing region					
Femur, lateral weight-bearing region					
Tibia, medial tibia plateau					
Tibia, lateral tibia plateau					

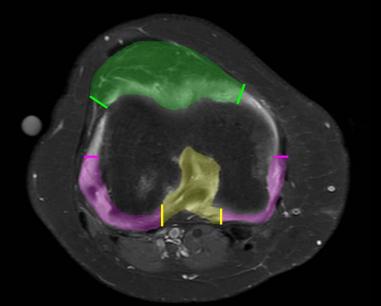
# Synovial thickness

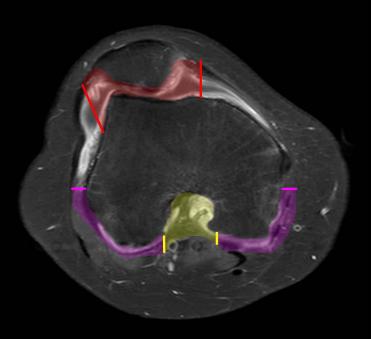




- Patellofemoral, red
- Suprapatellar recesses, blue
- Infrapatellar fat pad, green
- Adjacent to the ACL & PCL, yellow

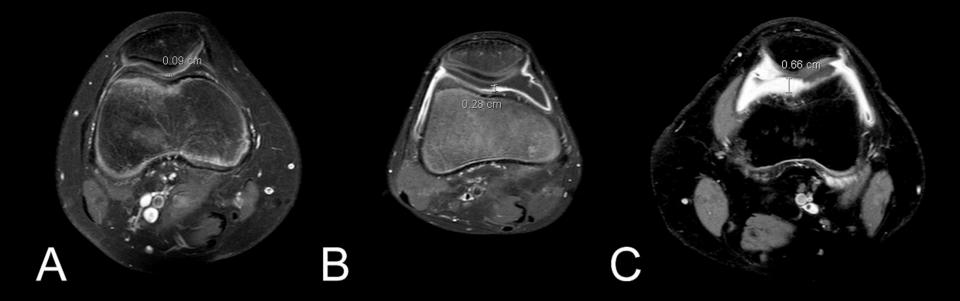
# Synovial thickness





- Patellofemoral, red
- Infrapatellar fat pad, green
- Adjacent to the ACL & PCL, yellow
- Medial- & lateral posterior-condylar, pink

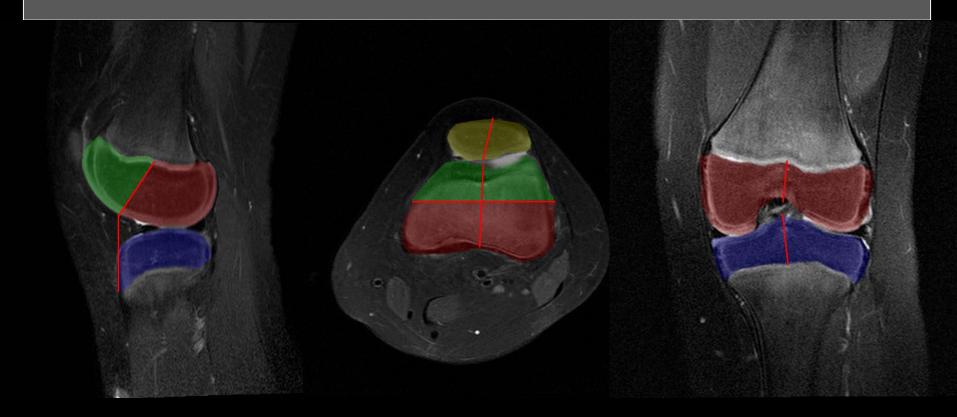
# Example synovial hypertrophy



Patellofemoral

- Grade 0; <2 mm (A)
- Grade 1; ≥2-4 mm (B)
- Grade 2; >4 mm (C)

### Bone marrow changes



- Femur; weight-bearing region, red
- Femur; condylar, green
- Tibia plateau, blue
- Patella, yellow

### Example bone marrow changes



Femur, lateral weight-bearing region

- Grade 0; none (A)
- Grade 1; <10% of bone volume (B)
- Grade 2; 10-25% of bone volume (C)
- Grade 3; >25% of bone volume (D)

# JAMRIS system for the knee

Highly reliable

Inter-observer ICC 0.86-0.95 Intra-observer ICC 0.92-1.00

Feasible

Median scoring time 6.6 min

Responsive

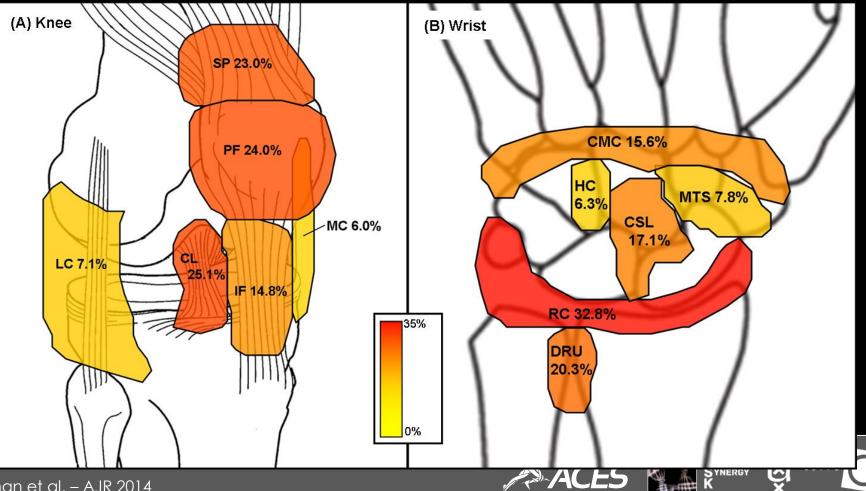
Substantial effect synovial hypertrophy scores Standardized Response Mean (SRM) -0.65

## Predeliction

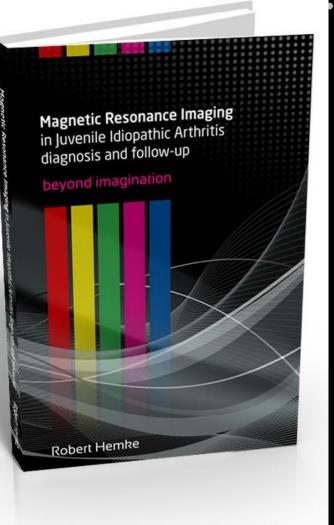
110 MRI knee & 43 MRI wrist

Clinically active (5 criteria)

Presence of synovitis?

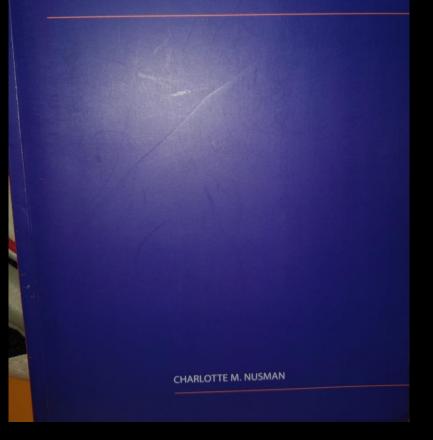


Nusman et al. – AJR 2014



INNOVATING IMAGING IN JUVENILE IDIOPATHIC ARTHRITIS: AN ONGOING QUEST

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## International presentations RSNA





### COLLABORATION - I OMERACT







### COLLABORATION II Amsterdam & Partners

International collaboration is inevitable

Together we can find the truth

Join forces of existing groups

**'Amsterdam November Meeting' – ANOME** 

### $\rightarrow$ KNEE & WRIST



# PARTICIPANTS (11)

Name	Country	Profession	Joint(s)
Andrea Doria	Canada	Radiologist	Large & small
Nikolay Tzaribachev	Germany	Ped. Rheumatologist	Large & small
Mario Maas	Netherlands	Radiologist	Large & small
Marion van Rossum	Netherlands	Ped. Rheumatologist	Large & small
Robert Hemke	Netherlands	Radiologiy resident	Large & small
Charlotte Nusman	Netherlands	PhD student	Large & small
Charlotte van Gulik	Netherlands	PhD student	Large & small
Karen Rosendahl	Norway	Radiologist	Small
Lil-Sofie Ording-Muller	Norway	Radiologist	Small
Derk Avenarius	Norway	Radiologist	Small
Clara Malattia	Italy	Ped. Rheumatologist	Small
Anouk Barendregt	Netherlands	PhD student	Large & small





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## ANOME-MEETINGS

	ANOME 1	ANOME 2	ANOME 3	ANOME 4
Date	22-24 Nov 2013	26-28 Sep 2014	8-9 Nov 2014	3-4 Oct 2015
Focus joint	Knee & wrist	Knee	Wrist	Wrist
Achievements	Agree knee scoring	Reliability st. knee	MRI protocol wrist	Agree wrist scoring
	Discuss wrist scoring	5 readers, n=20	Calibration session	Inventory intern.
			wrist	collaborations
Outcome	Paper J Rheumatol.	Poster @ ESPR	Letter-to-editor in	MS in preparation
		Oral @ NVVR	J Rheumatol.	



#### ANOME - WRIST

Previous efforts:

RAMRIS<sup>1</sup>, paediatric-targeted MRI scoring system<sup>2</sup> and Revised scores<sup>3,4,5</sup> Well-established: Synovitis, tenosynovitis Difficulties in osteochondral domain<sup>6</sup>

MRI protocol

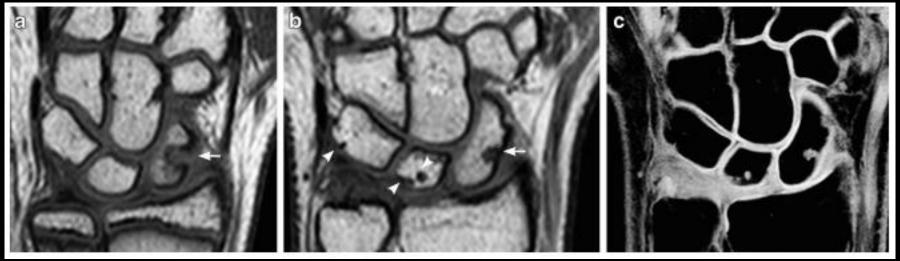
<sup>1</sup>Østergaard et al. – J Rheumatol. 2003
 <sup>2</sup>Malattia et al. – Ann Rheum Dis. 2011
 <sup>3</sup>Damasio et al. – Pediatr Radiol. 2012
 <sup>4</sup>Tanturri de Horatio et al. – Pediatr Radiol. 2012
 <sup>5</sup>Lambot et al. – Pediatr Radiol. 2013
 <sup>6</sup>Ording-Muller et al. – Pediatr Radiol. 2013



#### OSTEOCHONDRAL DOMAIN

- Normal bony depressions mimicking erosions
- Overestimation of structural damage

Avenarius et al. – Pediatr Radiol. 2015



13-year old boy

4-years later

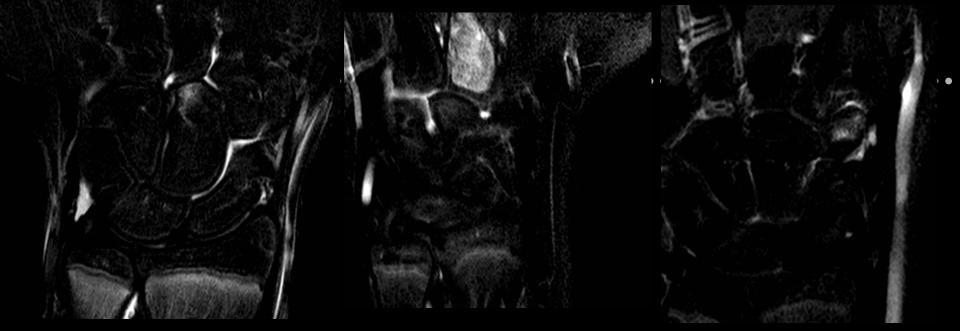
Cartilage coverage

ACES

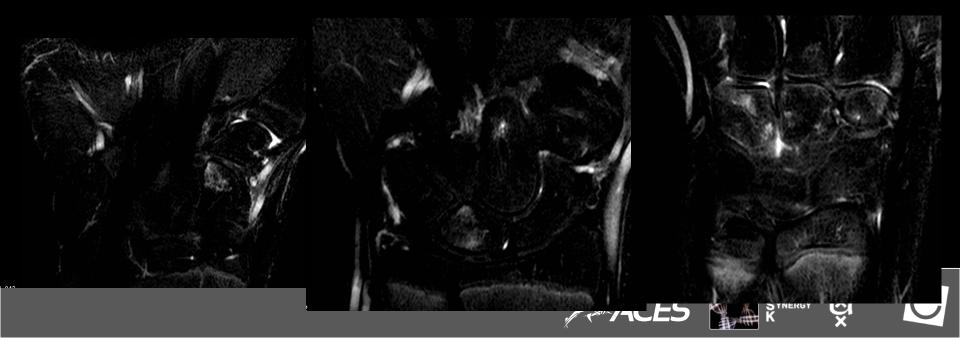
#### OSTEOCHONDRAL DOMAIN

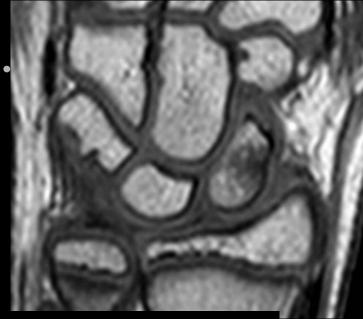
ACES M SYNERGY & AM

- No current scoring method for MRI available yet
- Possibilities:
  - Back to conventional radiography
  - Cartilage-sequences
  - Healthy MRI atlas

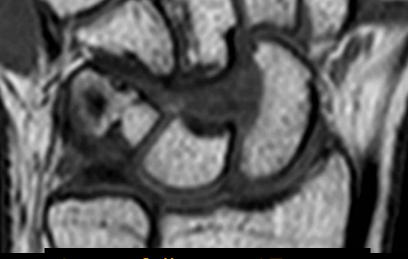


35% edema





#### Healthy child 13 years



4 year follw up- 17 years

WATS cartilage sequention. Depressions show cartilage layer







# COLLABORATION III: Amsterdam Pediatric rheumatologists –Building database



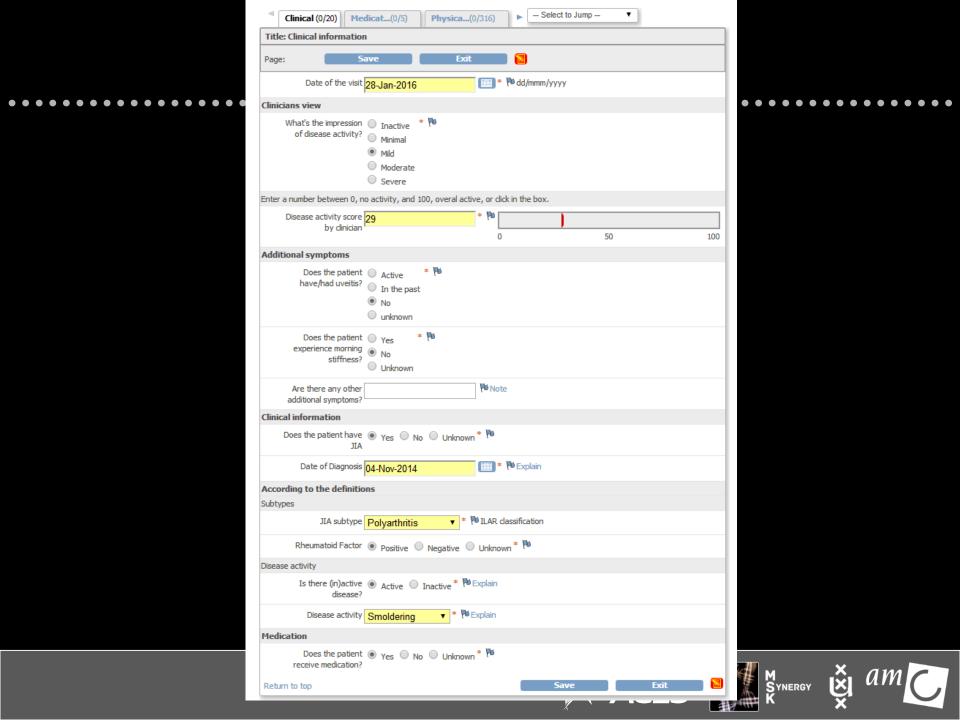
#### Database features

- Modern and safe
- enables multicenter study
- 747 unique patients
- Clinical assessment / Imaging / Immunology

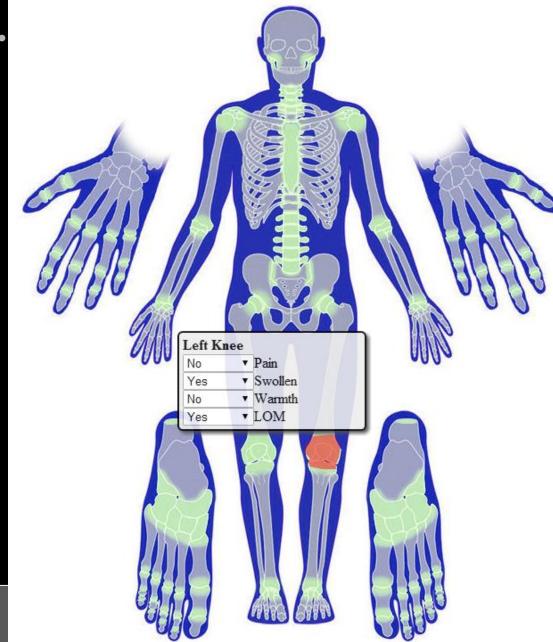










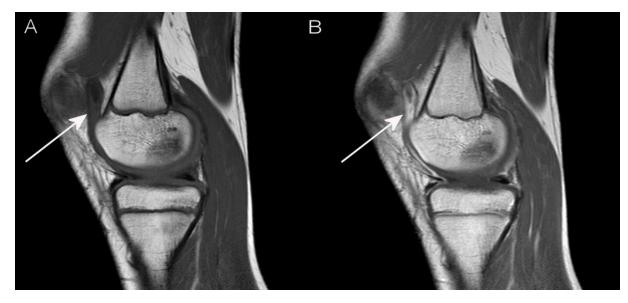


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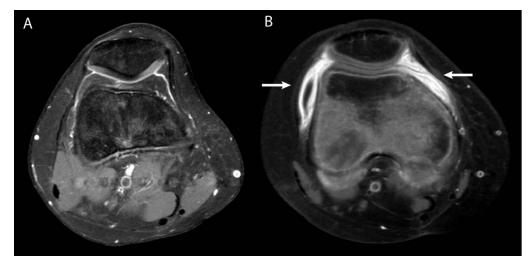


#### Introduction

- Increased use of MR imaging in assessment of disease activity in JIA patients
- Discrepancies between MR imaging and clinical assessment pose a dilemma



An example of the sagittal TI-weighted MRI sequence pre-(a) and post-(b) contrast of the right knee in a 10-year old female with clinically inactive JIA of the oligoarticular subtype, with enhancing and thickened synovium at the patellofemoral region (arrow)



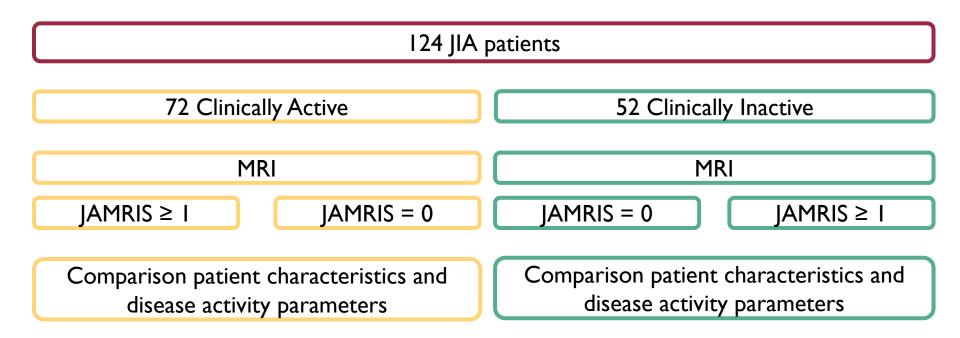
Two examples of children with clinically active JIA as depicted with an axial, contrast-enhanced, TI fat saturated MRI sequence. (A) a 15-year old girl without signs of synovitis on MRI, (B) an 8-year old girl with enhanced, thickened synovium at the patellofemoral region (arrows).

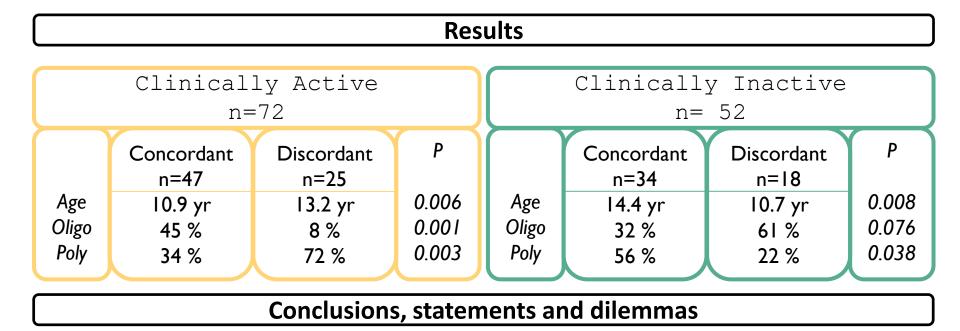
#### Objective

- To explore the frequency of mismatching results between clinical assessment and MRI
- To define the group(s) of JIA patients in which the clinical assessment is discrepant with the MRI
- To form hypotheses on the meaning and cause of these discrepancies

#### Methods

- Prospectively collected data
- Clinical and laboratory assessment, followed by contrast enhanced MRI of the knee
- 1.0 T MRI
- A JAMRIS ≥ 1 means presence of synovial thickening





- Nearly 35% of the JIA patients showed discordant findings
- MRI may prevent overtreatment in <u>clinically active</u> patients
- The meaning of synovial thickening in the <u>clinically inactive</u> patient is still unknown.

#### References

- 1. van Gulik EC, Welsink-Karssies MM, van den Berg JM, Schonenberg-Meinema D, Dolman KM, Barendregt AM, et al. Juvenile idiopathic arthritis: magnetic resonance imaging of the clinically unaffected knee. Pediatric radiology. 2018;48(3):333-40.
- 2. van Gulik EC, Hemke R, Welsink-Karssies MM, Schonenberg-Meinema D, Dolman KM, Barendregt AM, et al. Normal MRI findings of the knee in patients with clinically active juvenile idiopathic arthritis. Eur J Radiol. 2018;102:36-40.

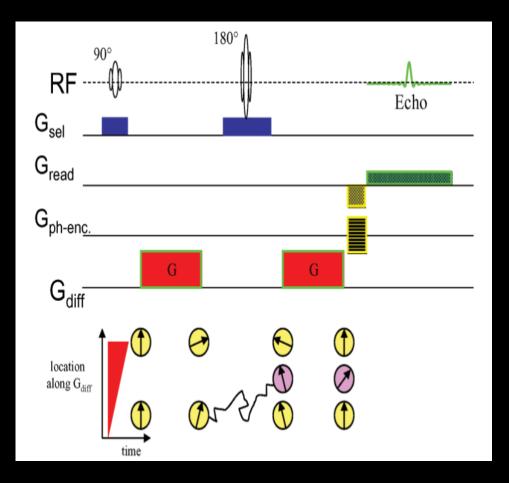
# Essentials of Diffusion-weighted imaging (DWI)

Advantage: non-contrast technique!











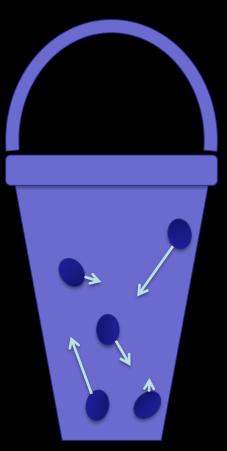


Le Bihan, J Magn Reson Imaging 2006







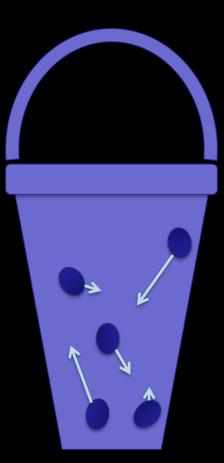


Free diffusion





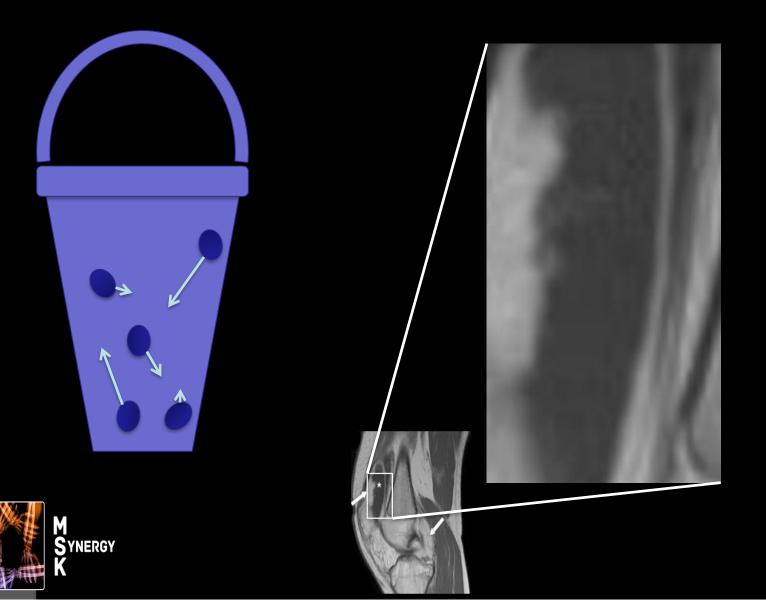






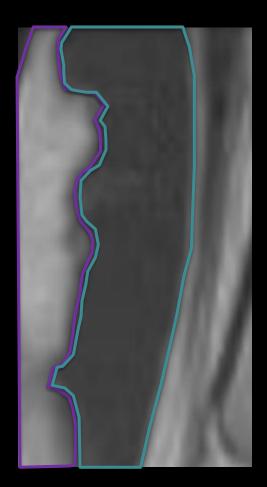






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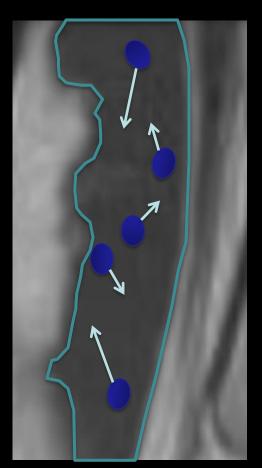






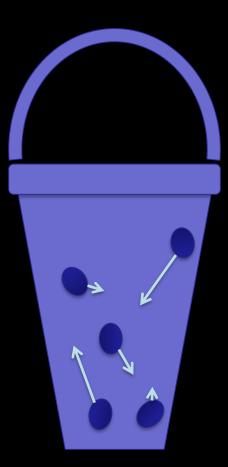




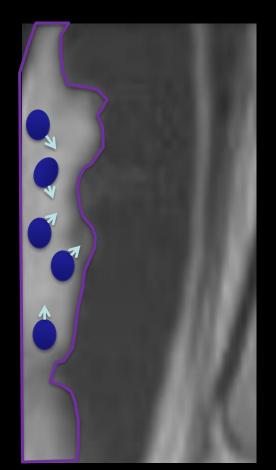


Effusion: 'free' diffusion







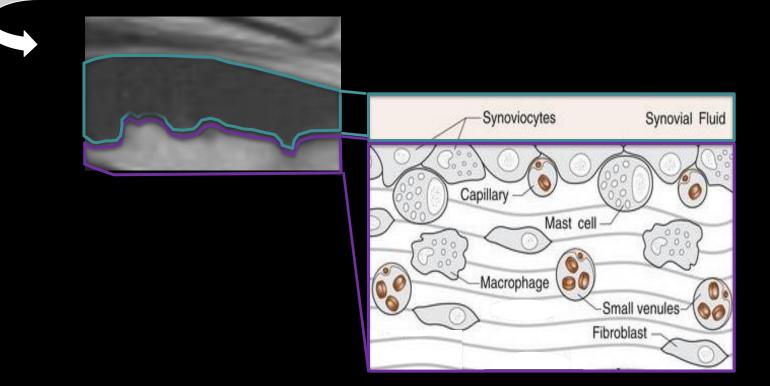


Synovium: restricted diffusion





### What are we looking at?







https://musculoskeletalkey.com/rheumatoid-arthritis-and-the-hand/

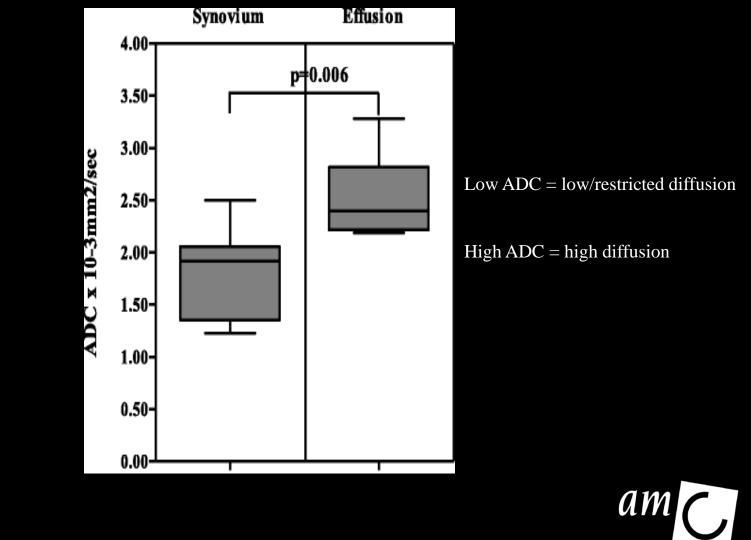
# Assessment of synovium using DWI

- Layers with different composition fluid (acellular) vs. solid (cellular)
- Diffusion of H<sub>2</sub>O through synovium depends on microarchitecture -> increased cellularity in synovitis





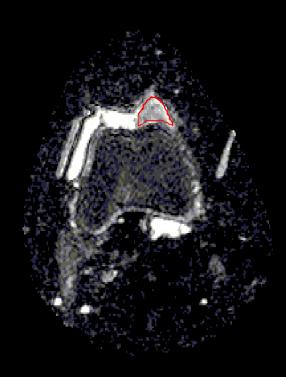
#### 1. Diffusion synovium $\neq$ effusion





Barendregt, Skeletal Radiol 2015

### 2. Diffusion higher in inflamed synovium

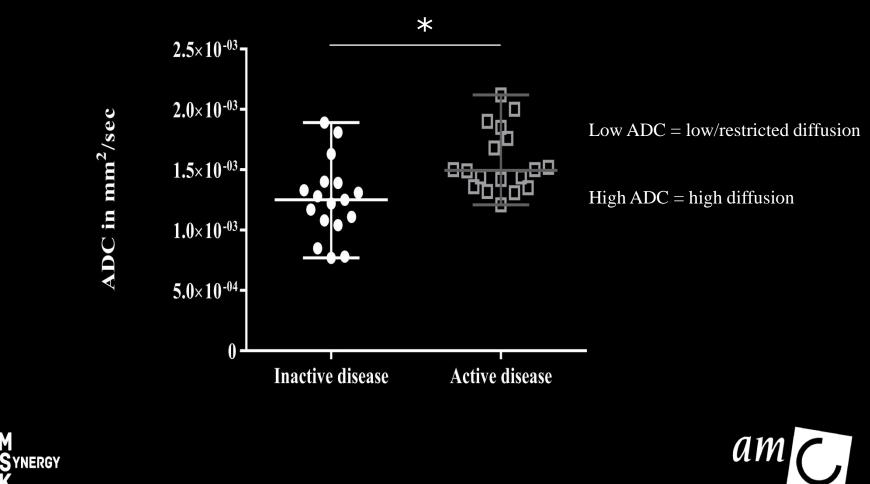






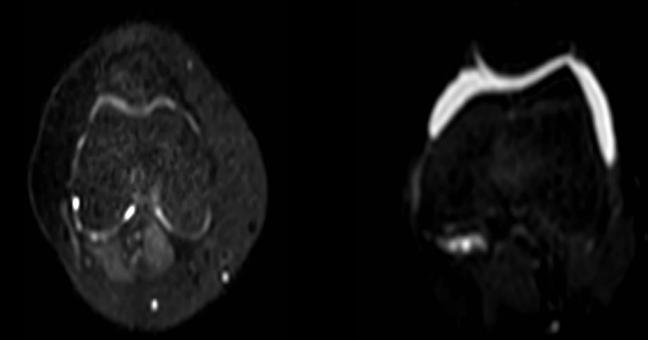
Barendregt, Eur Radiol 2017

### 2. Diffusion higher in inflamed synovium



Barendregt, Eur Radiol 2017

### Now: 3 Tesla DWI



#### Inactive disease



Active disease

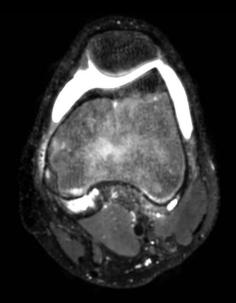


## 3 T. MRI, active JIA

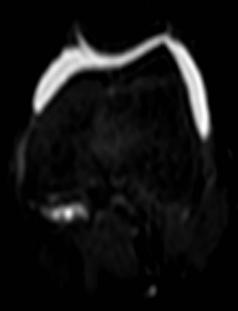
T2W

#### T1W GBCA +

#### DWI







Case: 15-y ơ 2 yrs prog. pain in right hip and knees ANA - ESR 22 Oligo-art. JIA





#### To conclude

- On going quest
- Collaboration key
- Young talents are crucial

























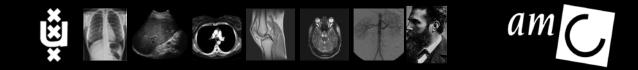




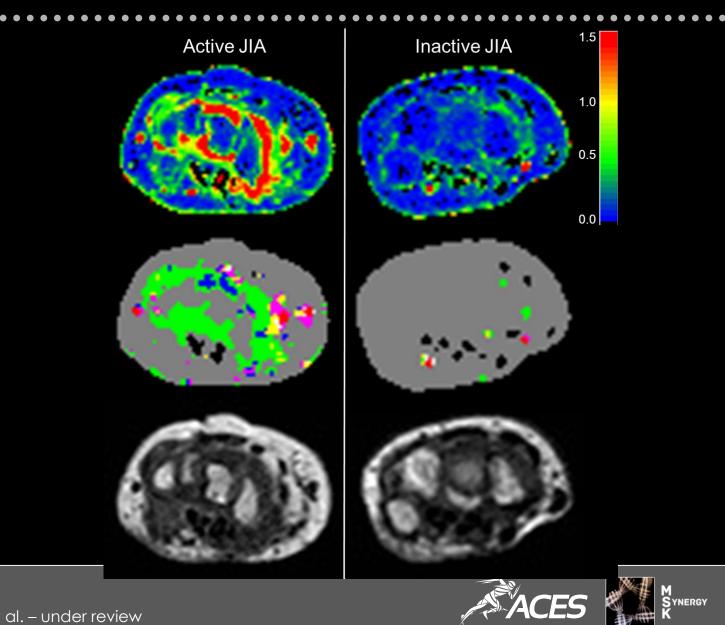
#### Objective

To compare descriptive DCE-MRI features and the relative number of TIC shapes in clinically active and inactive JIA patients





#### DCE-MRI in wrist



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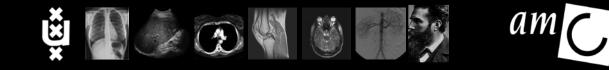
Nusman et al. – under review

#### Conclusion

The DCE-MRI pixel-by-pixel TIC-shape method is able to differentiate groups of clinically active and inactive JIA patients by:

- TIC shape 4 and 5
- Maximal enhancement, slope, iAUC, enhancing volume

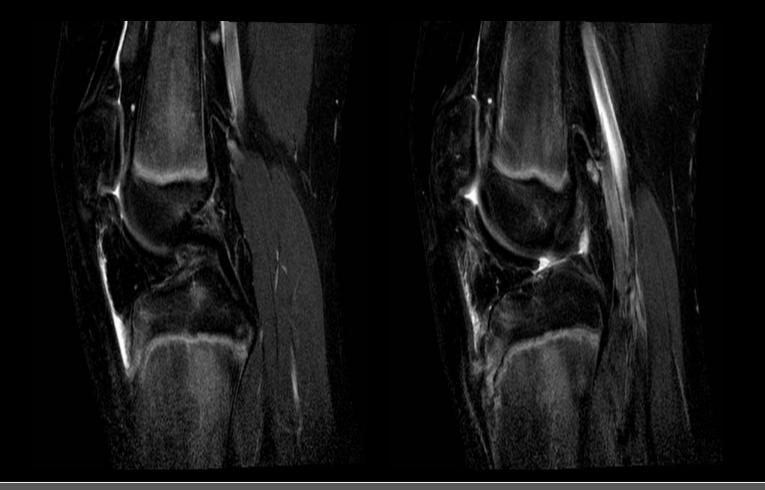




#### Case 1)

- 14-year old boy with history of right tibial # (after trauma)
- Bilateral knee pain < 1,5 y, unable to play football</li>
- Swelling: +, morning stiffness: mild, night pain: +
- No infection, no thick bite, no IBD-features, no weight loss.
- Great-grandmother: RA
- PE: tibial tubercle painful on examination, warm and swollen.

#### Case 1 – sagittal T2 SPIR

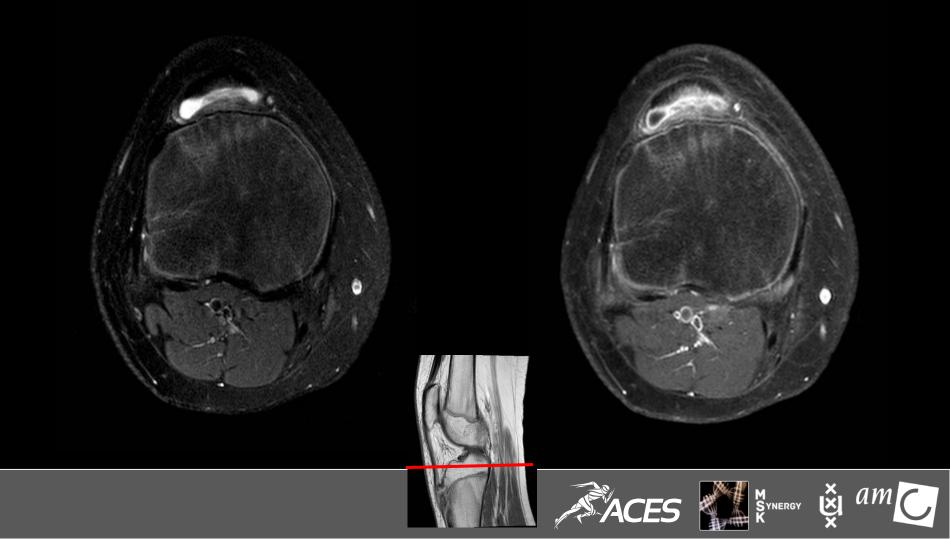




# Case 1 – sagittal T1 without and with iv contrast



## Case 1 – axial T2 and axial T1 fatsat with contrast





Osgood schlatter disease: no inflammation



#### Case 2 –

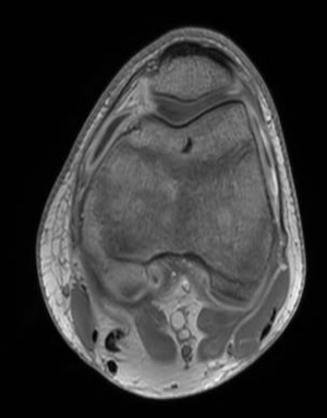
- 16-year old boy, length: 1,96 m
- 3x acute knee swelling left after minor trauma. Crepitations +
- No other joint complaints
- PE: left knee swollen, LOM in flexion. Hypermobility.
- DDx: hypermobility, Marfan's syndrome, coagulation disorder, JIA?



#### Case 2 – sagittal DIXON water

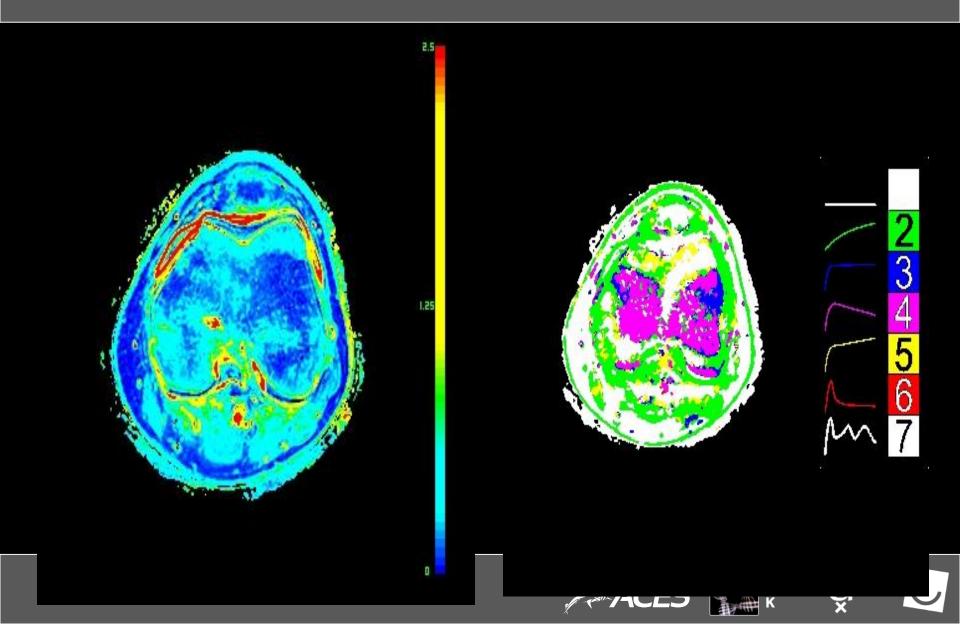


#### Case 2 – axial DIXON in phase +





#### Case 2 – quantitative MRI - DCE



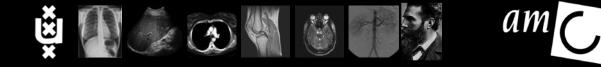
#### DCE-MRI

DCE-MRI is the time-dependent registration of changes in MR signal intensity during and after intravenous injection of a contrast agent

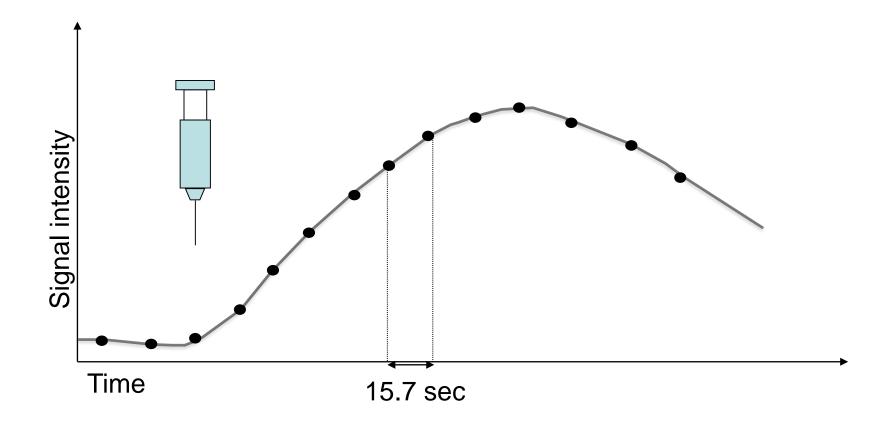


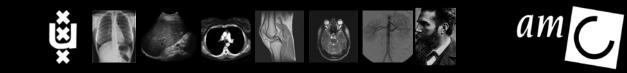


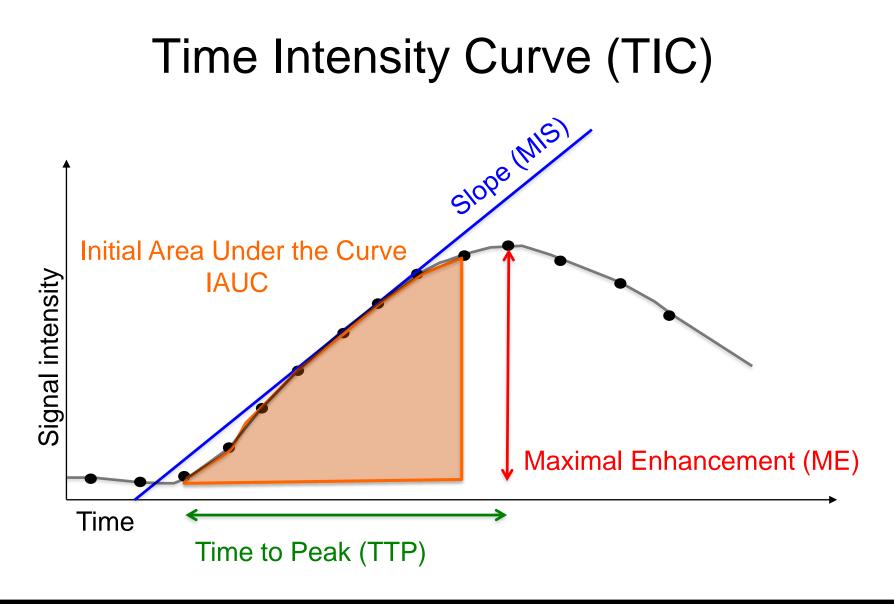
Department of Radiology Academic Medical Center University of Amsterdam The Netherlands

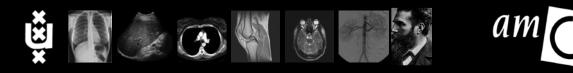


#### Time Intensity Curve (TIC)



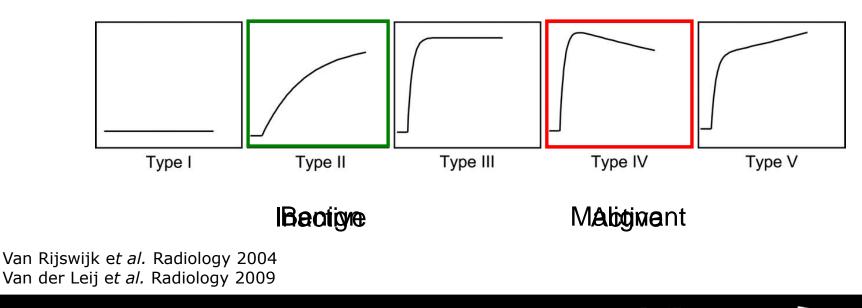






#### **Time Intensity Curves**

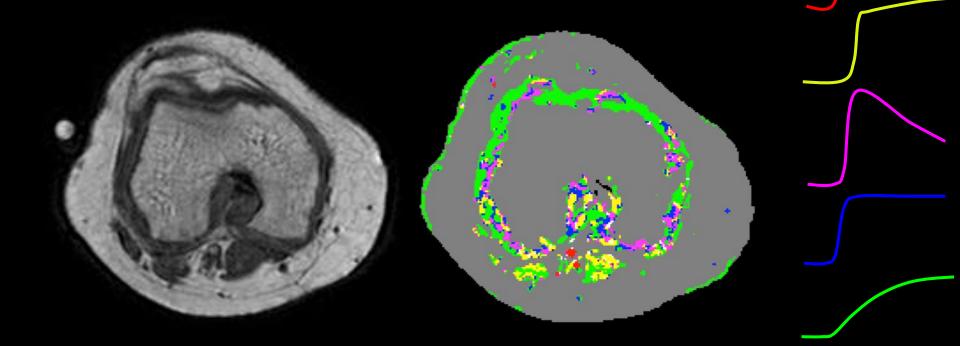
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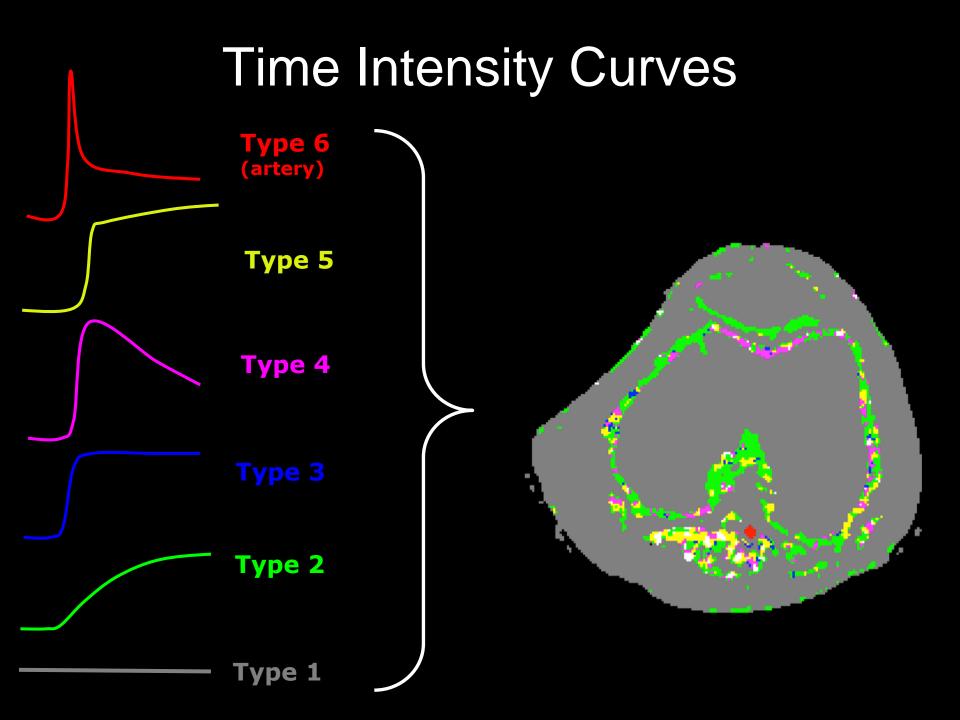


aw

#### Color-code TIC shape map

DCE T1-weighted images TIC shape color-code map

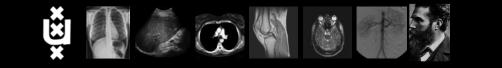




### Example

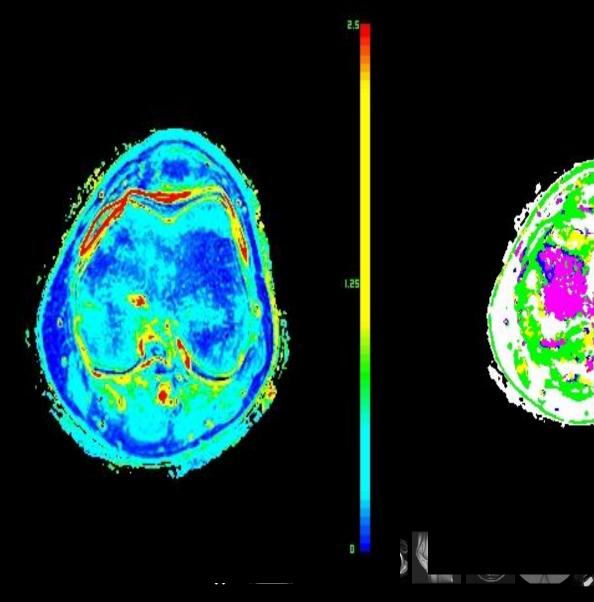
#### Active disease

Inactive disease





### Case 2 – quantitative MRI - DCE

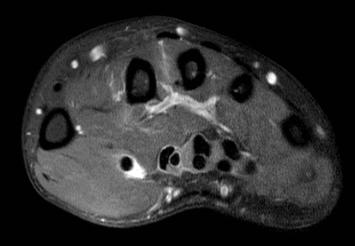


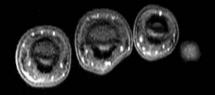
#### Case 3)

- 18-year old girl, poly-articular RF&ACPA+ JIA diagnosed at age 15
- March 2017: flare in multiple joints, start MTX and anti-TNF
- January 2018: poly-articular flare (bilateral wrist, MTPs)
  - MRI wrist: inflammation status as compared to earlier MRI? Damage?

#### Case 3 – axial T1 fatsat after contrast

#### (0047.0040)







#### Case 3 – coronal DIXON (2018)

