Imaging in Genetic Cardiomyopathy

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With very special thanks to James Moon

Conflict of Interest

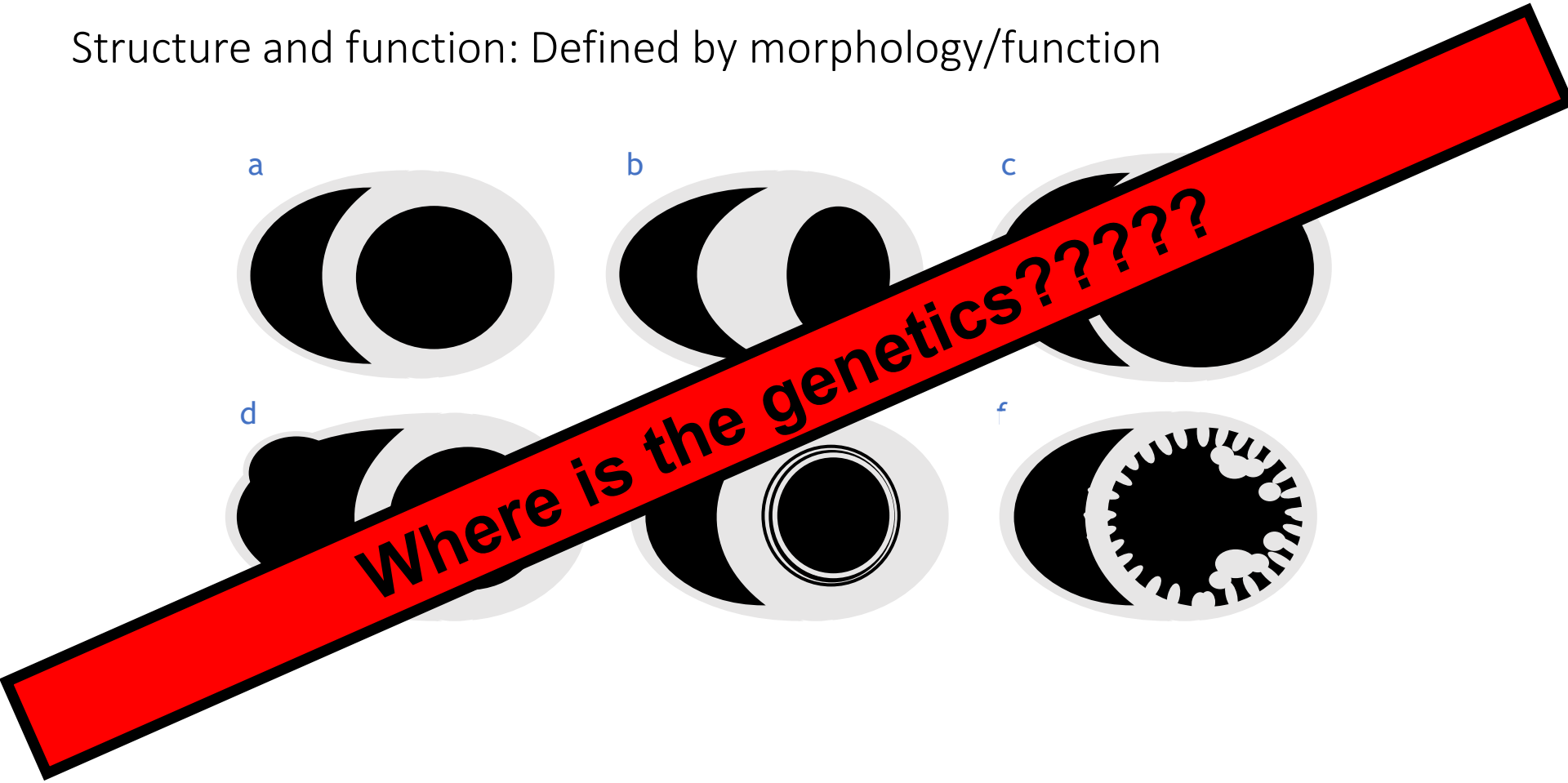
I am a founder/Director of MycardiumAI

‘Genetic Cardiomyopathy’

- Genetics
- Based on genes
- Cardiomyopathy
- Anything wrong bu tery disease

But this isn’t what we currently do…..

Structure and function: Defined by morphology/function



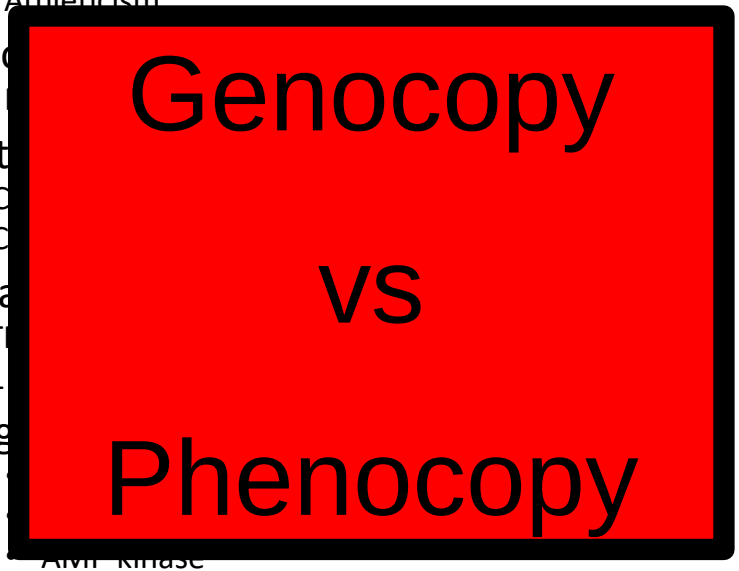
Genetics: Hypertrophy

HCM

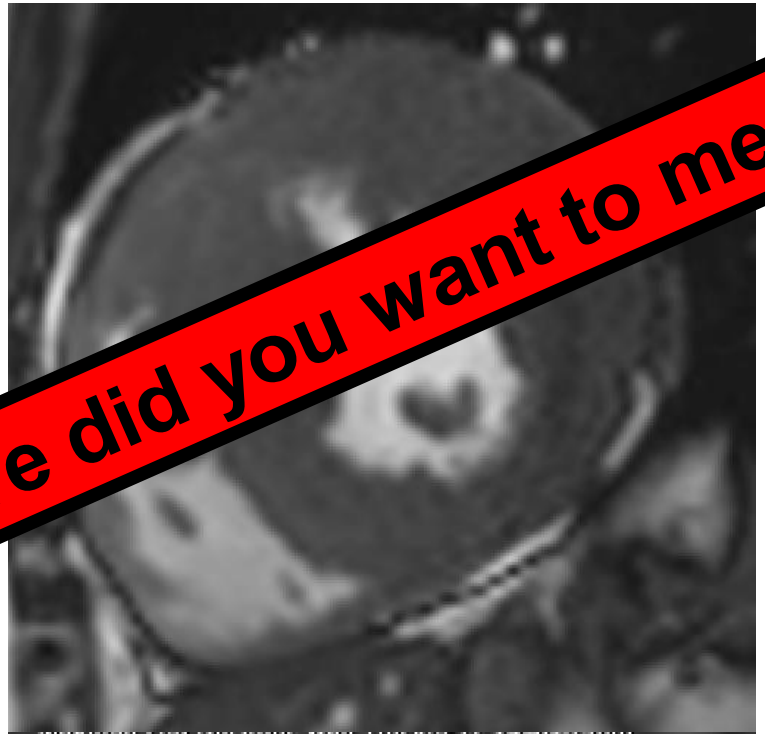
- Hypertrophy
- Phenocopies
- Wall Thickness
- Fibrosis
- Other Techniques
- Disease and treatment

Heart Muscle and Hypertrophy

- Ascertainment: not LVH
  - Age/Ethnicity/obesity
- Physiological
  - Athleticism
- Afterl
  -
- Genet
  - HC
  - DC
- Infiltra
  - TT
  - AL
- Storag
  - AMP-Kinase
- Acute oedema
- Other



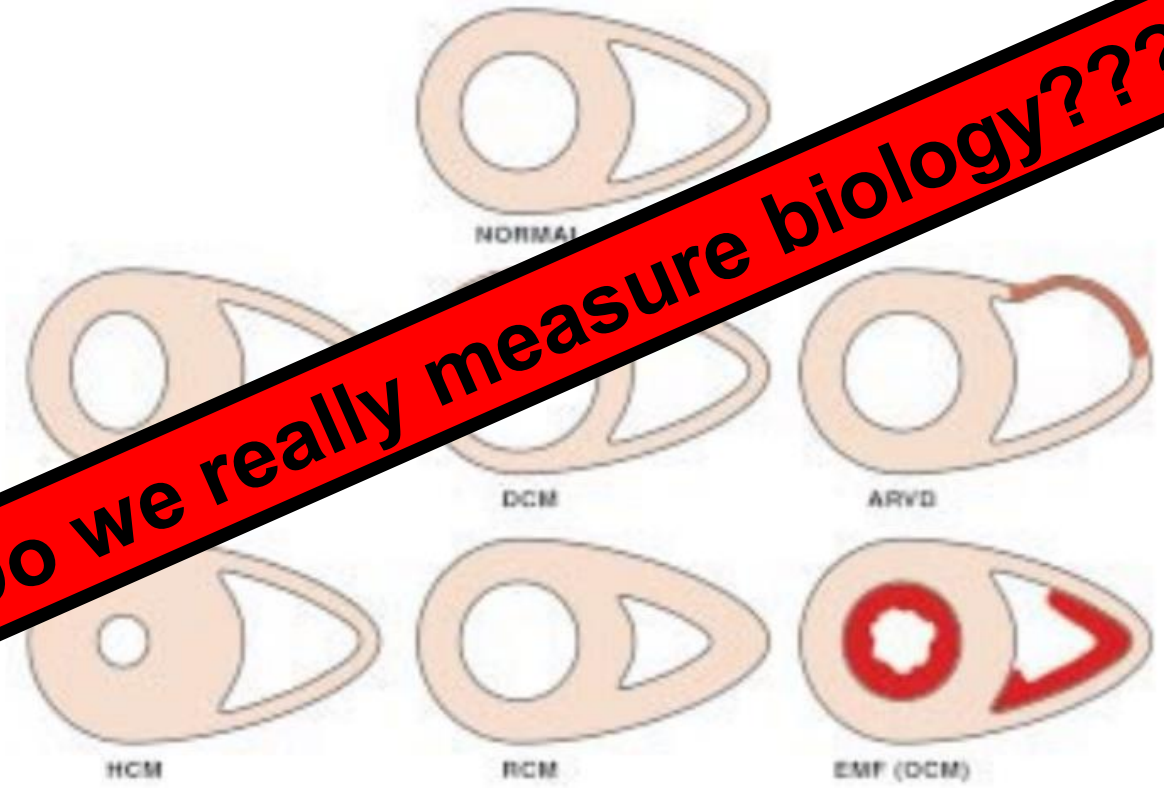
Heart Muscle and Hypertrophy



So where did you want to measure????

Images courtesy of Prof James Moon

Heart Muscle and Hypertrophy

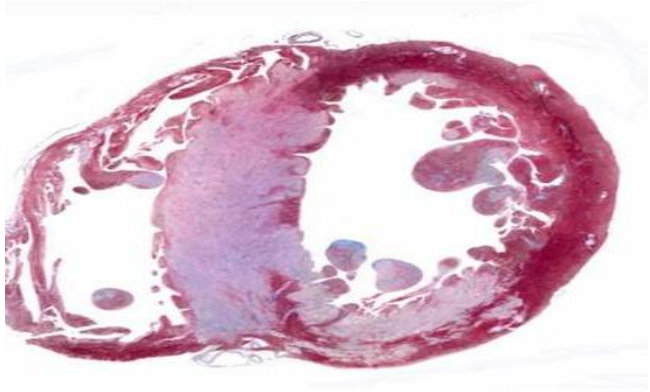


Do we really measure biology????

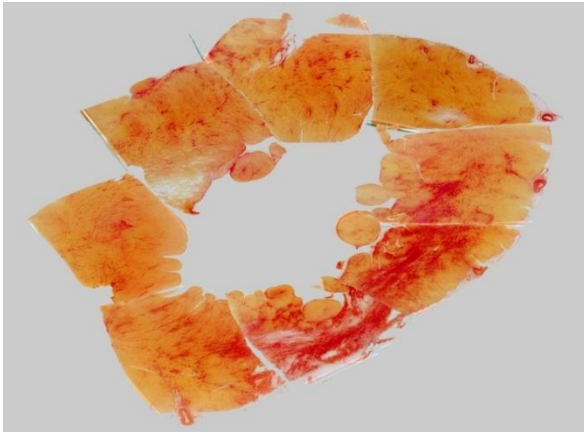
Heart Muscle and Hypertrophy: Histology

HCM

Amyloid*

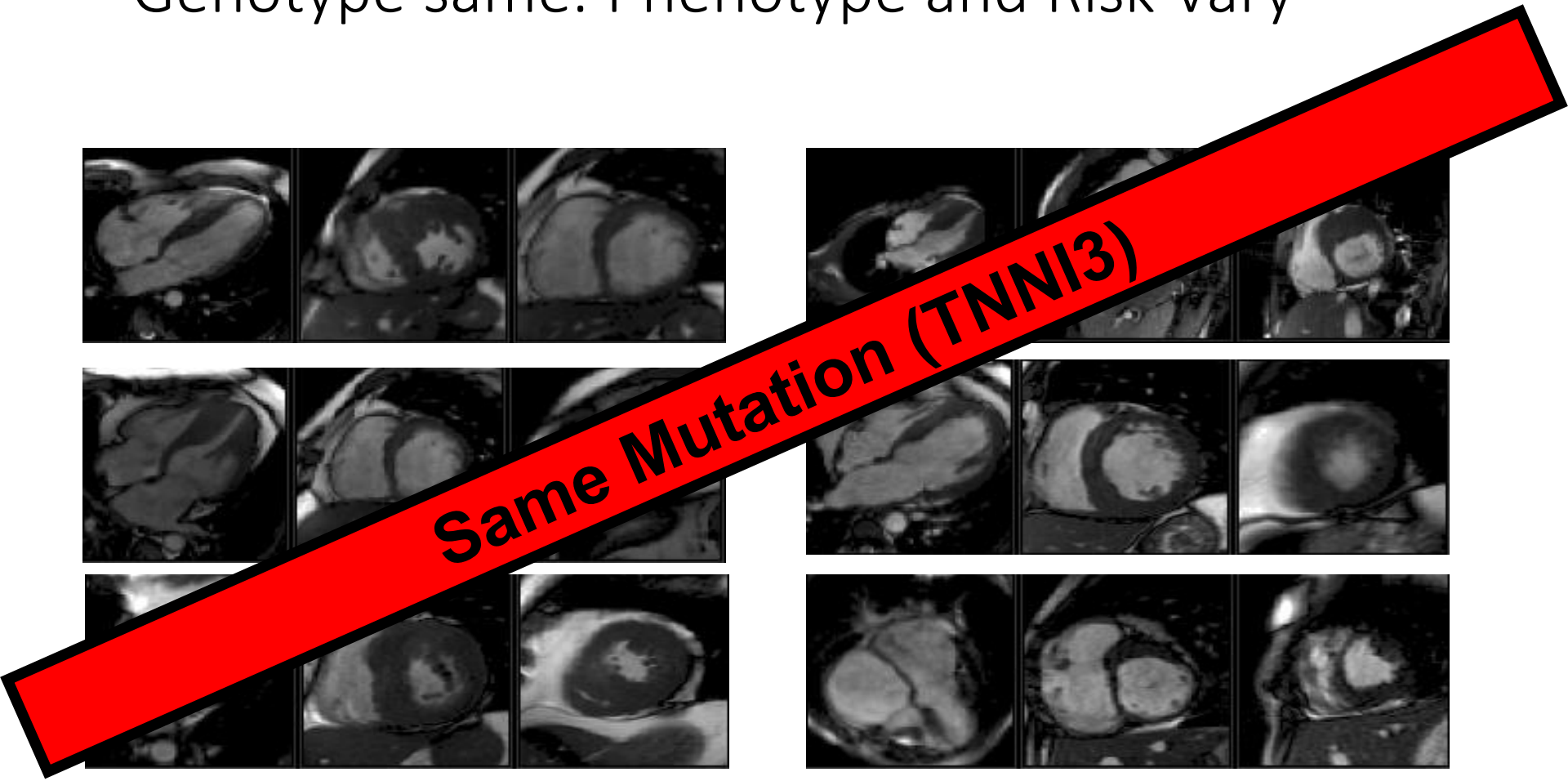


AFD

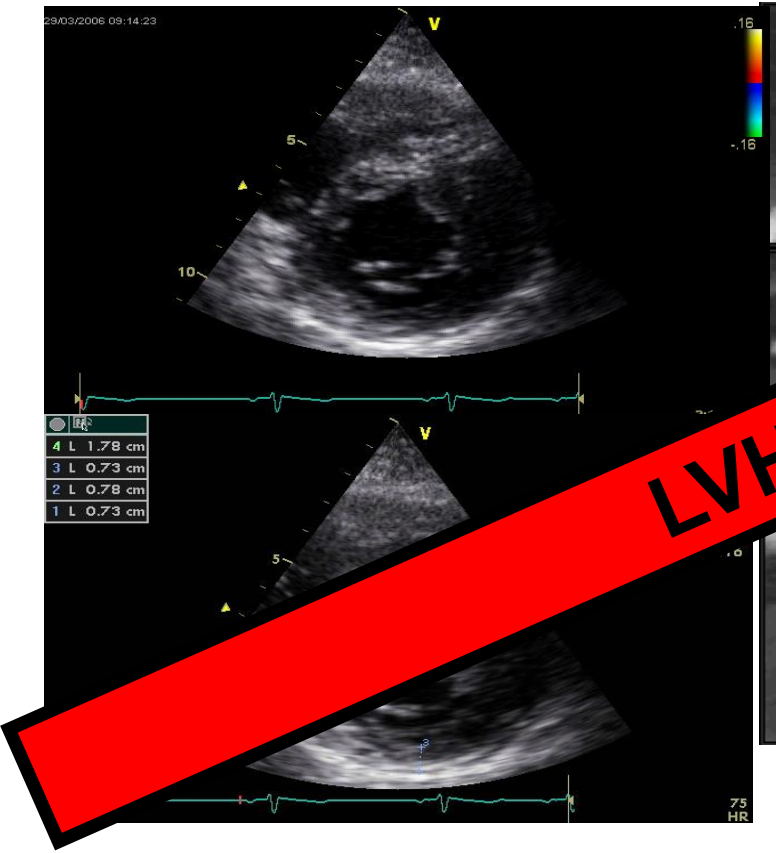


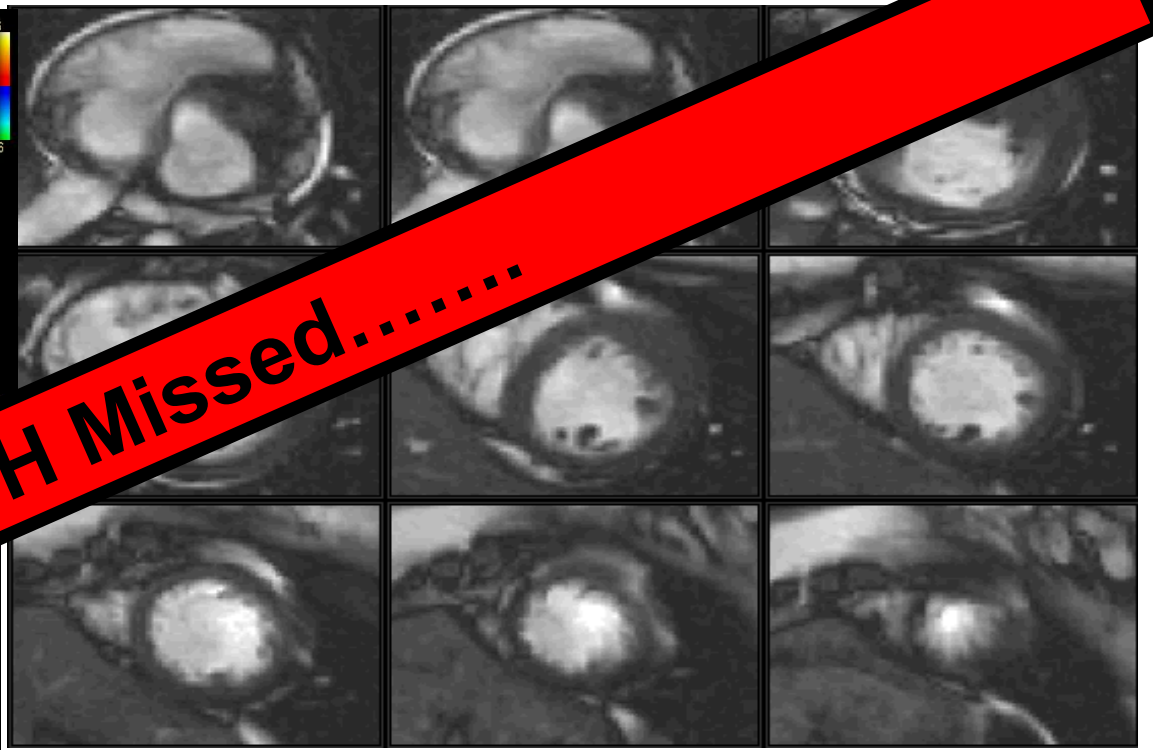
*acknowledgement Claudio Rapezzi

Genotype same. Phenotype and Risk Vary



Echo Isn't Everything……



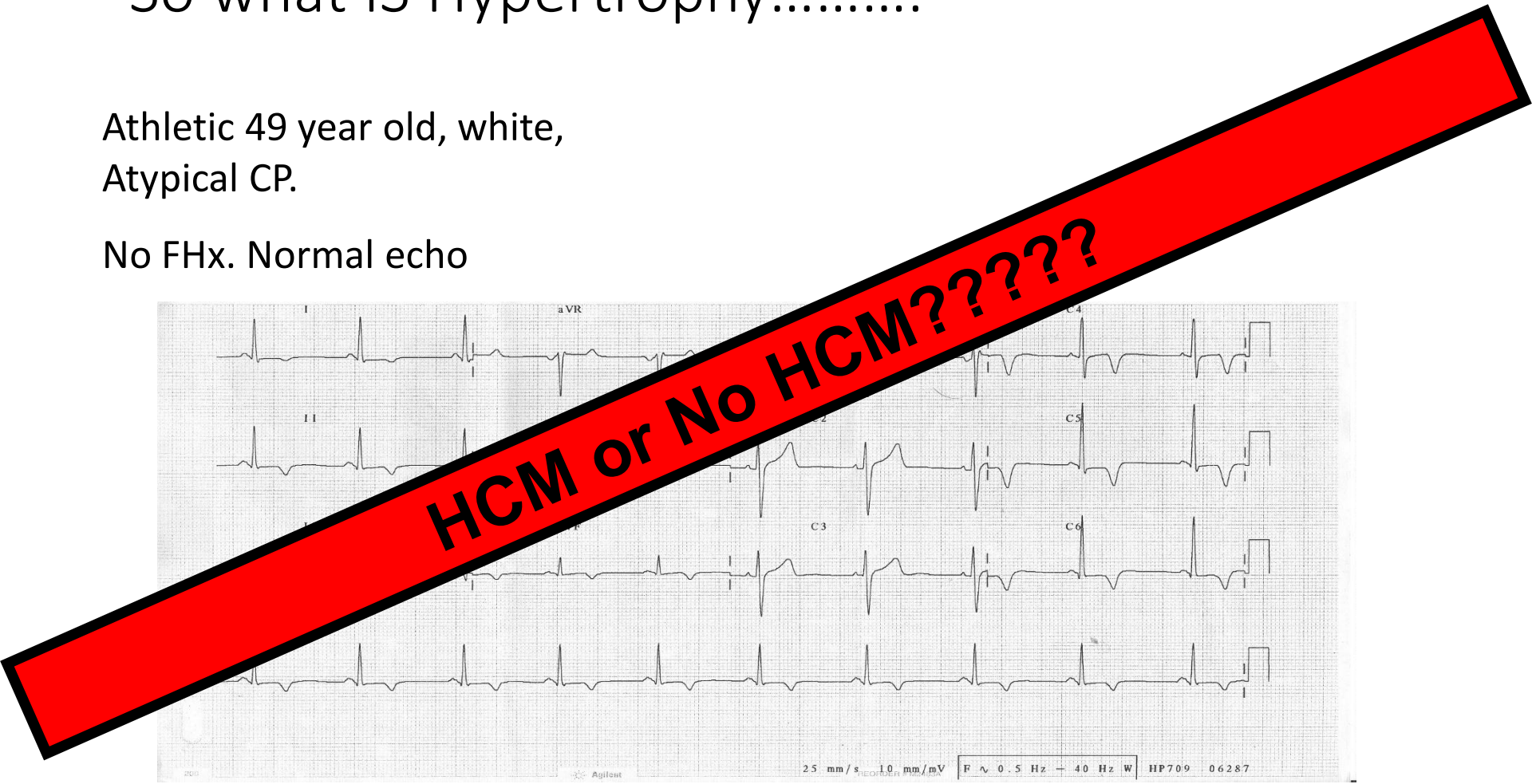


LVH Missed……

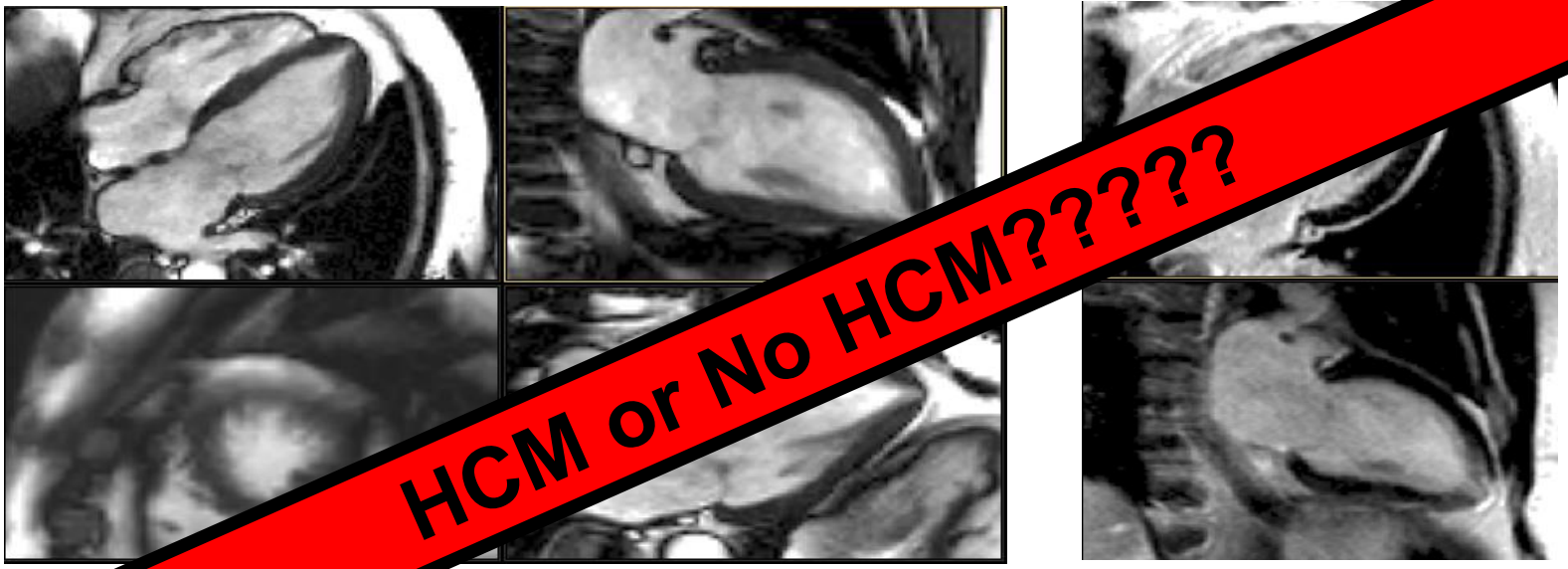
So what IS Hypertrophy…….

Athletic 49 year old, white,
Atypical CP.

No FHx. Normal echo

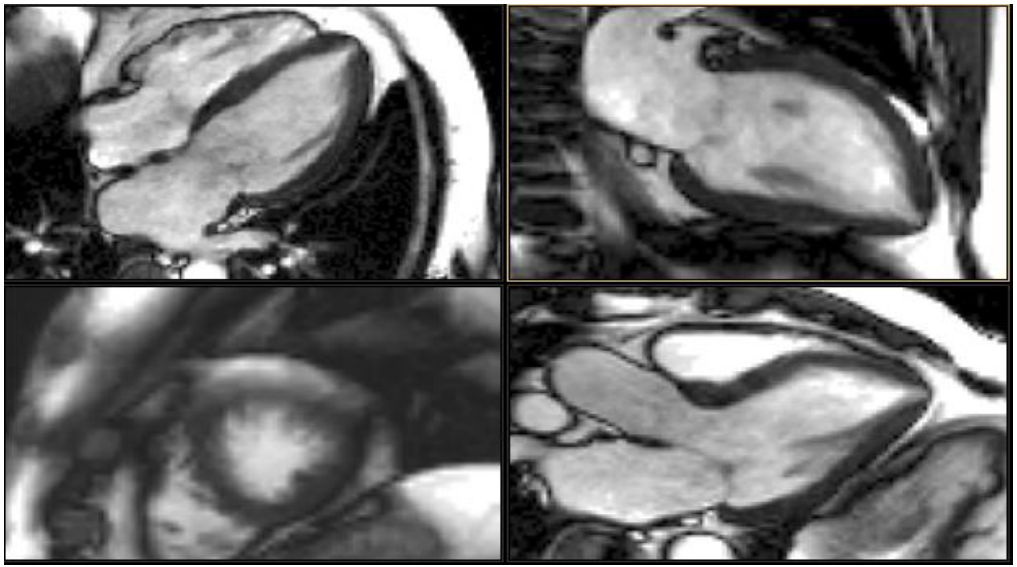


So what IS Hypertrophy…….



HCM or No HCM?????

Relative Apical HCM

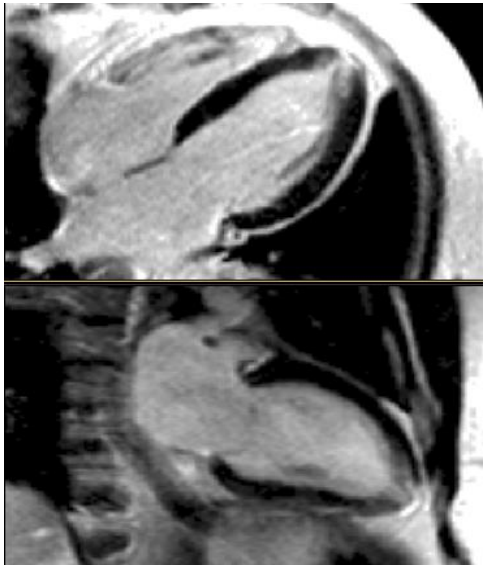


Relative apical hypertrophy (max 10mm)

2cm apical cavity obliteration

Micro-aneurysm

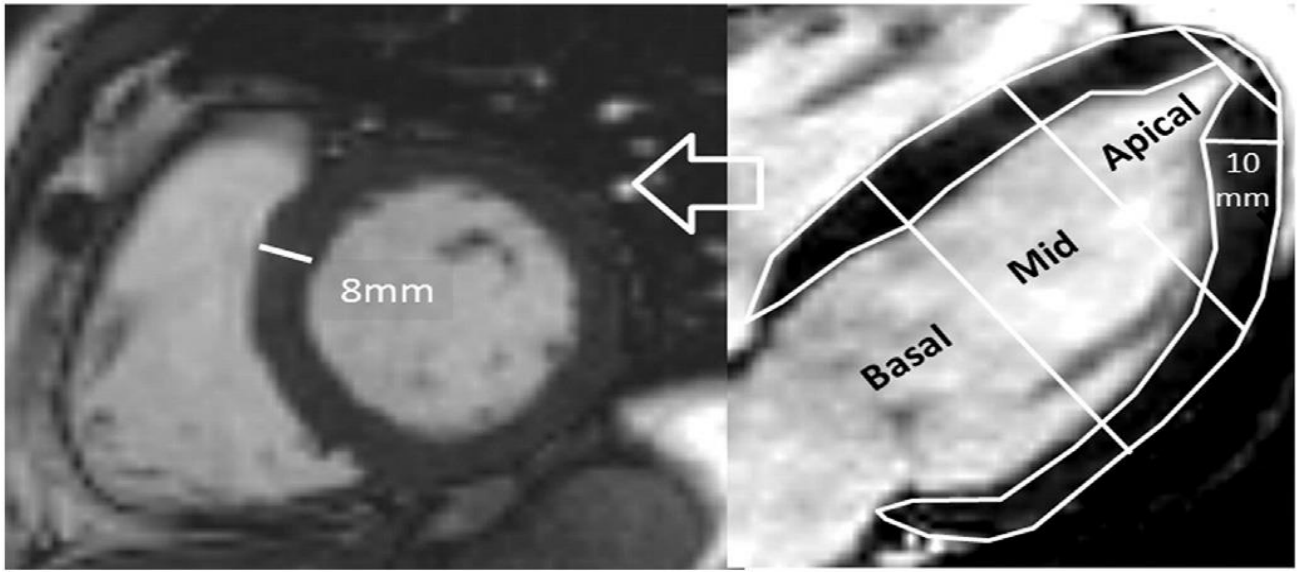
LA dilation



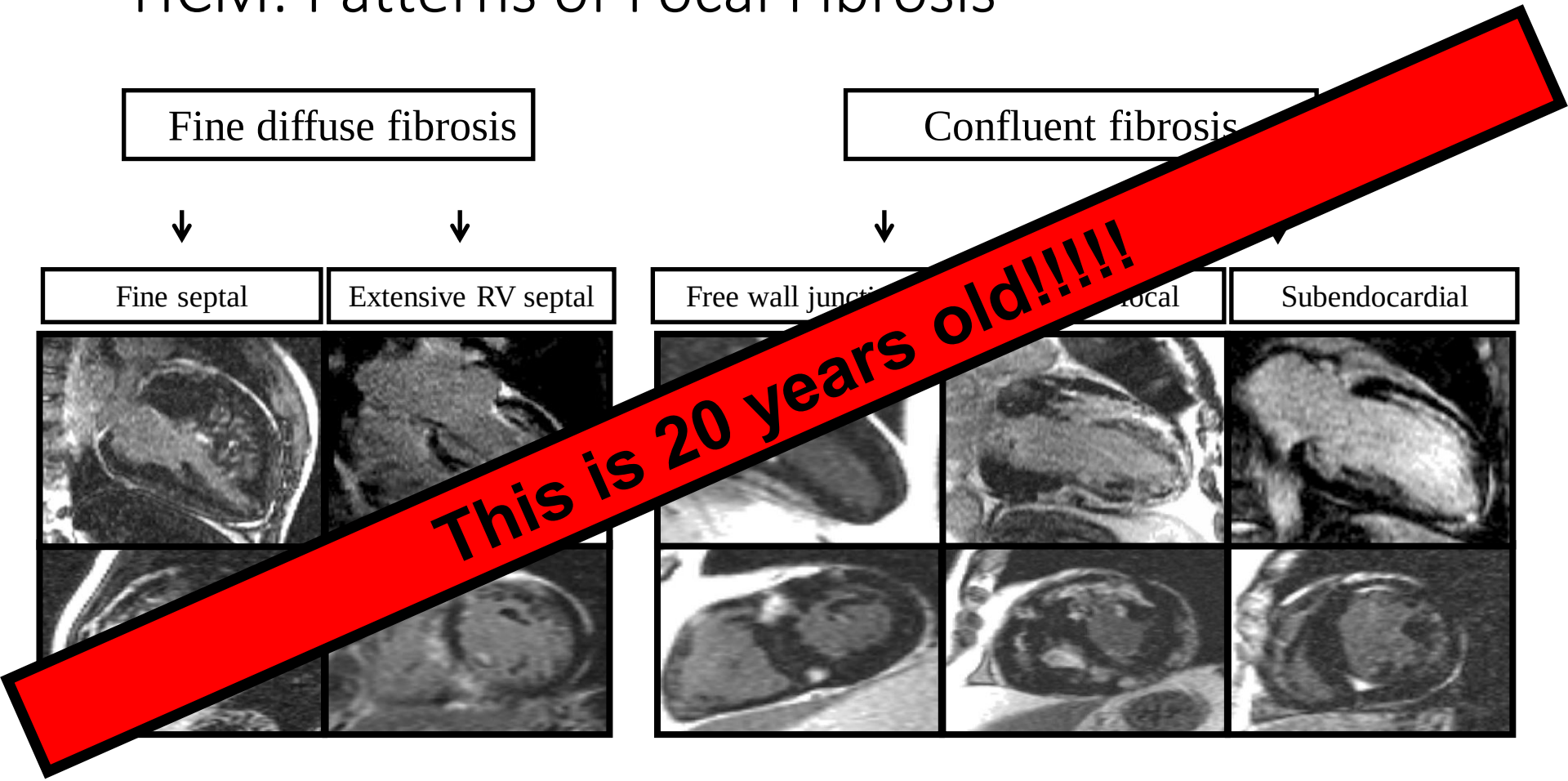
Apical LGE

(LA dilatation, perfusion defect)

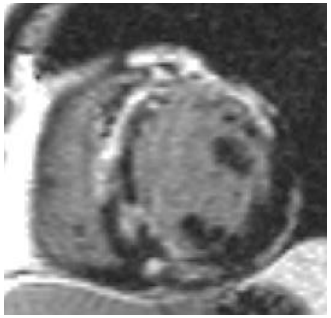
Relative Apical HCM



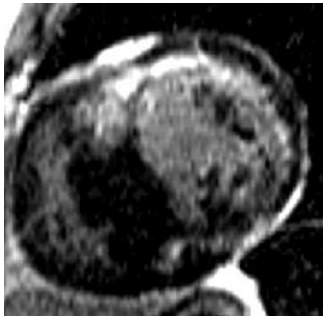
HCM: Patterns of Focal Fibrosis



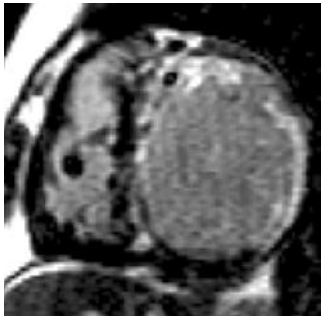
Fibrosis is always the final common pathway



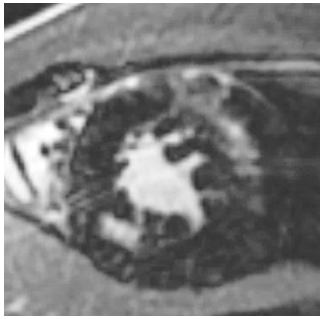
Sarcomeric



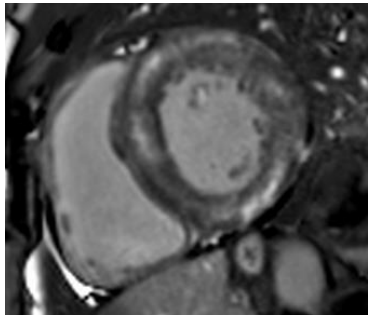
Fabry



GSDIIIa



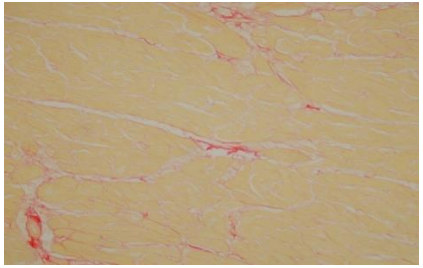
Danon



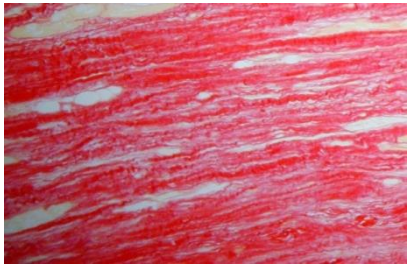
Mitochondrial

Danon’s case courtesy, Michael Arad

But the Pathology is NOT the same…..

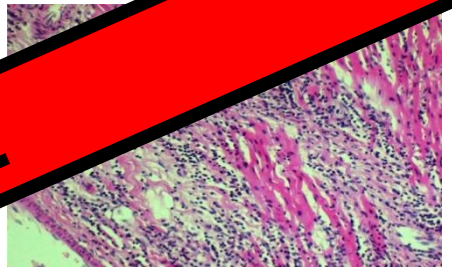


Normal

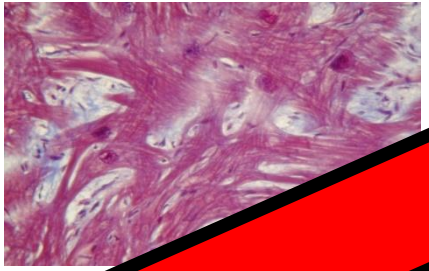


Infarction

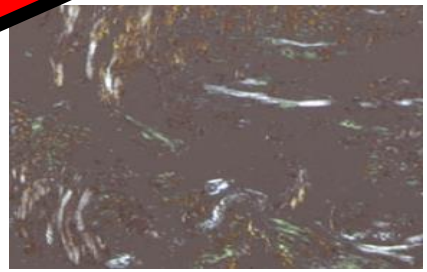
fibrosis



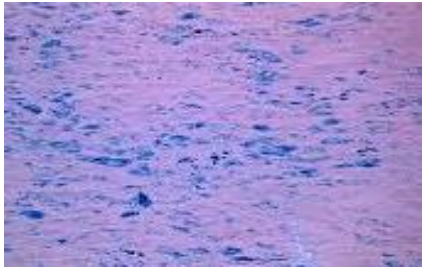
Myocarditis



Fabrys

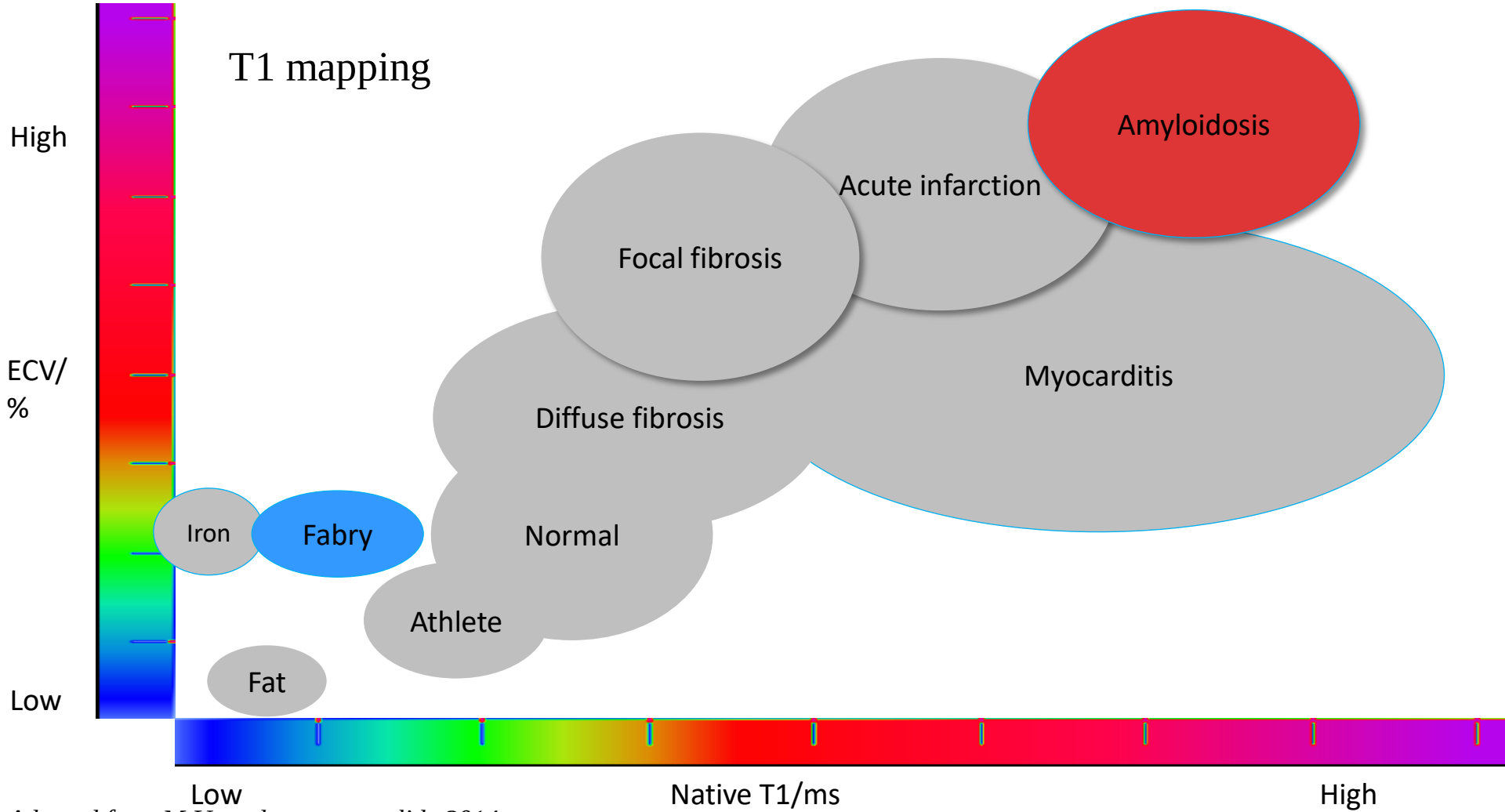


Amyloid



Iron

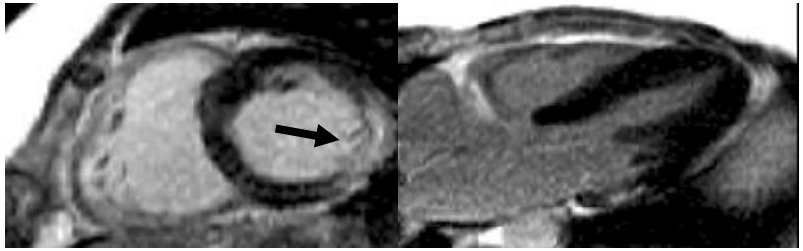
Use T1 Mapping to Split…..



Adapted from M Ugander concept slide 2014:

Fabrys vs HCM – which is it?

1



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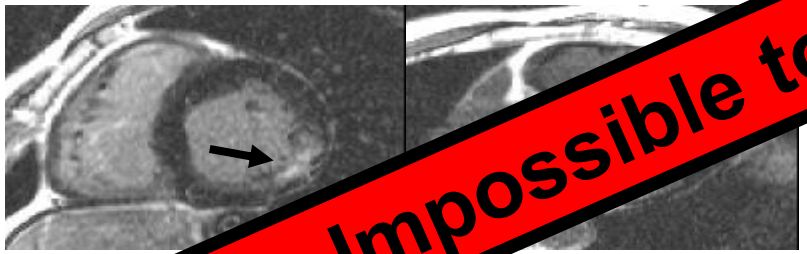
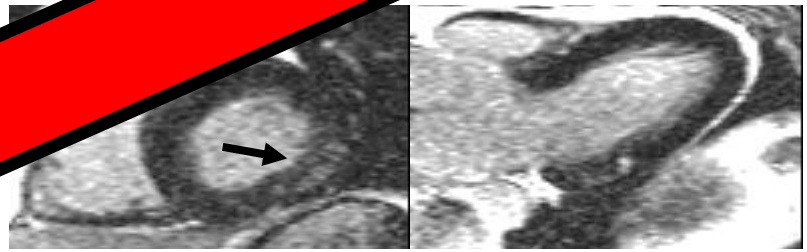
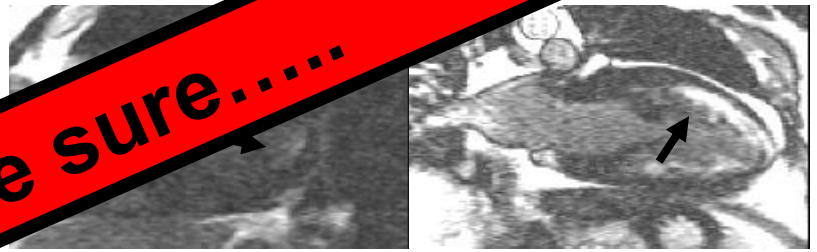
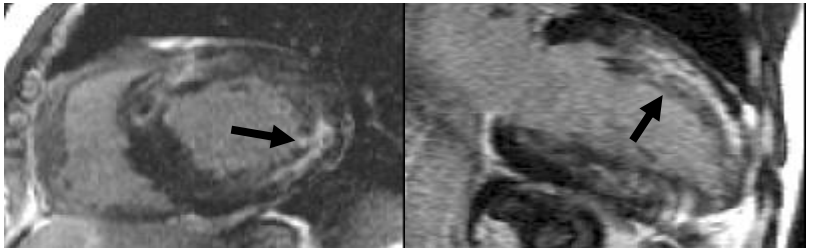




Impossible to be sure……



5



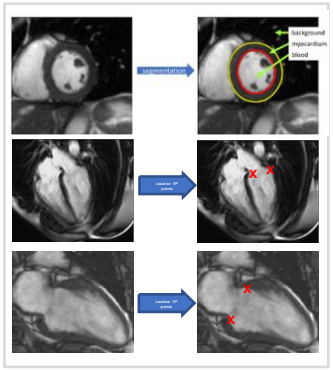
Wall Thickness

The ‘Right’ AI……

Training data
Consented medical imaging
Representative

Disease	Manufacturer	Field
Normal	Siemens	1.5T
Dilated	Philips	3.0T
	Hypertrophied	GE
		Impaired
		Global/Regional

Trustworthy research environment
1923 patients
⇒14 institutions
⇒3,000,000 images
⇒900,000 cine images

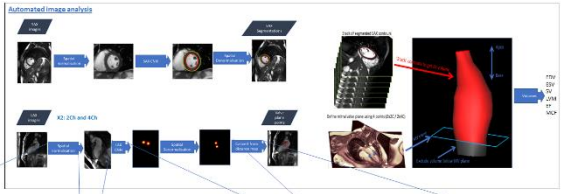


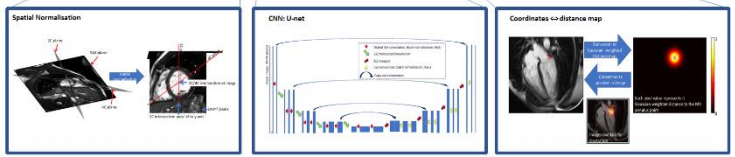
Expert
Trainee 1/Trainee 2/Trainee

65,000 contours

Identify cause Resegment

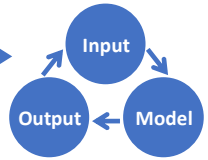
Why?
Bug?
Inadequate model?
Inaccurate training data?





Aiming for superhuman
If output > human / Then output > input

Interrogate understand



No

“Turing Test”
Would a human do that?

Review tools

Sample (fold) eg n=400

Superhuman test

Hold-out data, independent teams

Precision dataset: Test:retest
N = 110, 5 centres, any disease
Anonymised
Contoured by trainee and expert
Scan A, Scan B, Scan A
23,000 contours

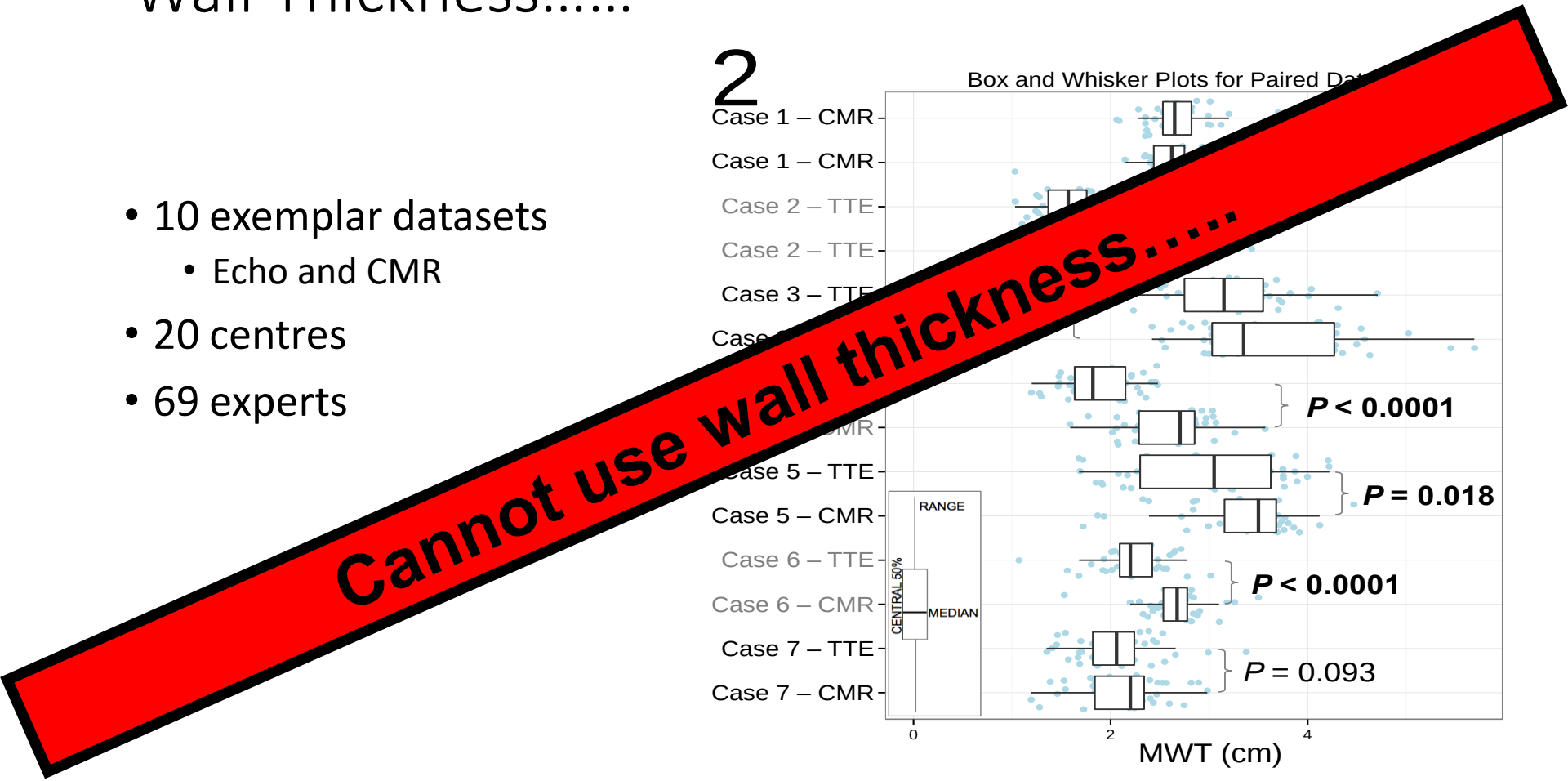
Outcome dataset
N = 1500
Single centre, USA
Anonymised
Alive/dead/MACE known
(n = 295 outcomes)

Error classification
Precision (CoV, trial size) vs human
Predictive power vs human

Precision: 50% better than human
Prediction: better than human
New biology: EF beaten by MCF

Wall Thickness……

- 10 exemplar datasets
  - Echo and CMR
- 20 centres
- 69 experts



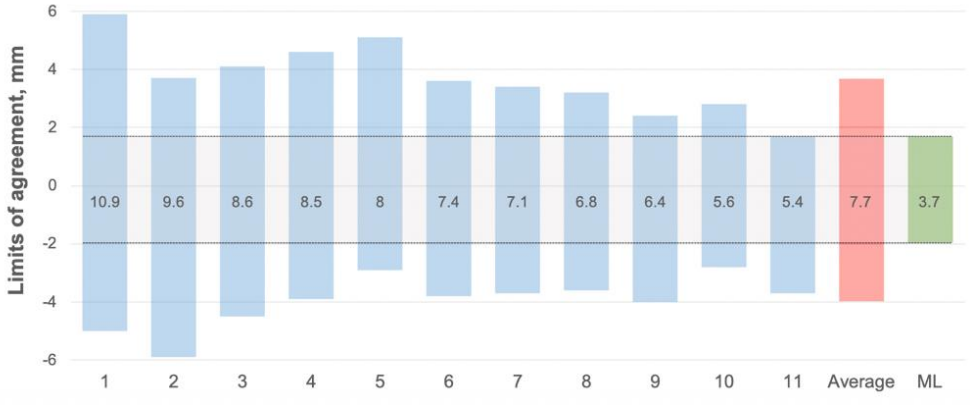
Captur G, JACC imaging 2021

Wall Thickness……

Measuring heart maximum wall thickness
12 credible international experts
- 4 continents
60 HCM patients
- scanned twice
- 5 different scanners
- multiple institutions

AI beats not just one human, but all humans

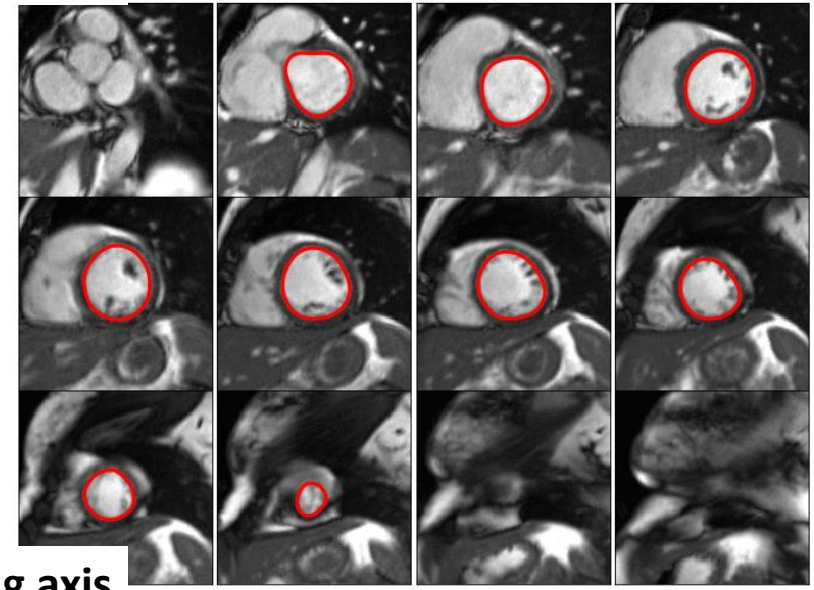
Figure 4. Test:retest Bland-Altman limits of agreement (LOA, mean bias ± 1.96 SD) for each expert (1 – 11, blue) and machine learning (ML, green). The average LOA for all experts is shown in red. The difference between the upper and lower LOAs is displayed in each bar. The LOA for ML was less than half of the average expert LOA.



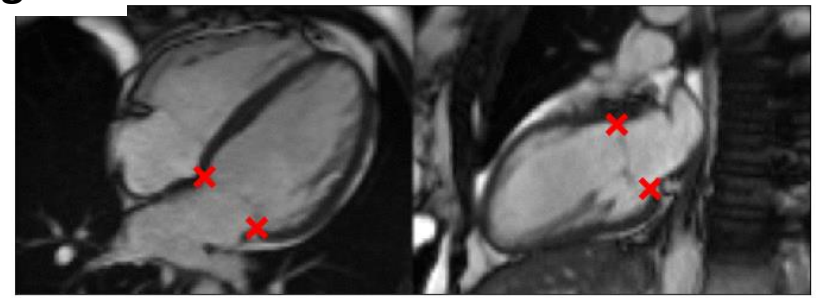
Joao Augusto et al Diagnosis and risk stratification in hypertrophic cardiomyopathy using machine learning wall thickness measurement: a comparison with human test-retest performance. Lancet digital health 2020

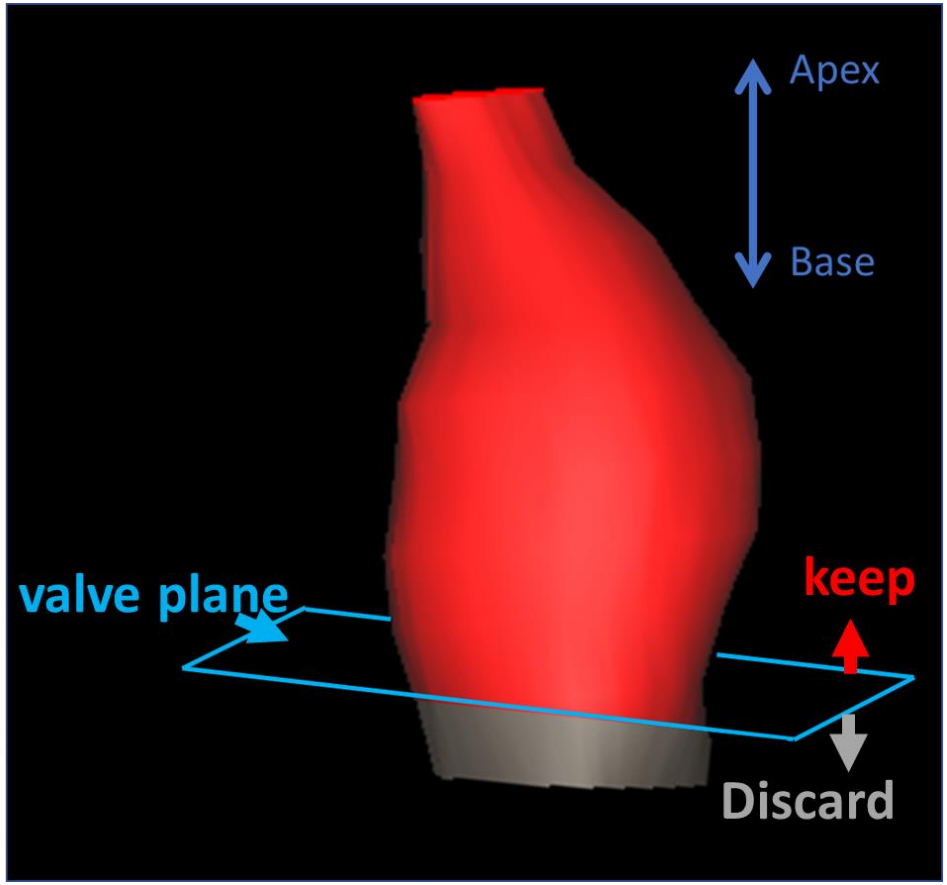
AI – Superhuman Segmentation….

Short axis

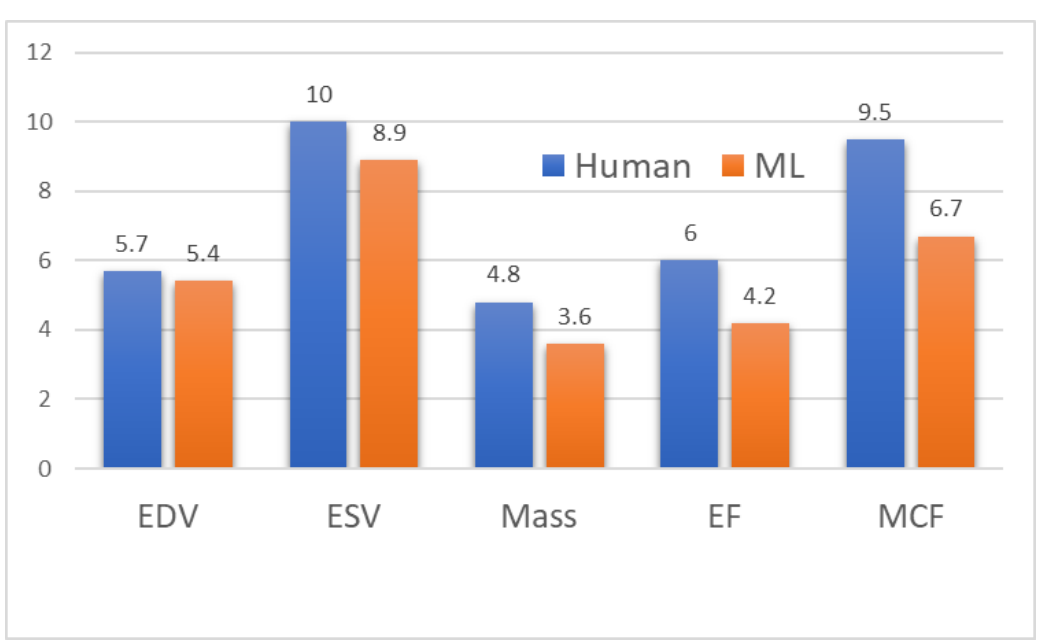


Long axis





AI – Superhuman Repeatability….



Translates to clinical trials:

- to detect 3% change in EF

⇒ need 40% fewer subjects

Early change detection

Fewer scans needed for a patient

$$\textbf{m}yocardial\ contraction\ fraction\ (MCF) = \frac{stroke\ volume}{myocardial\ volume}$$

Bhuva; Circ CVI; 2019

https://thevolumesresource.com

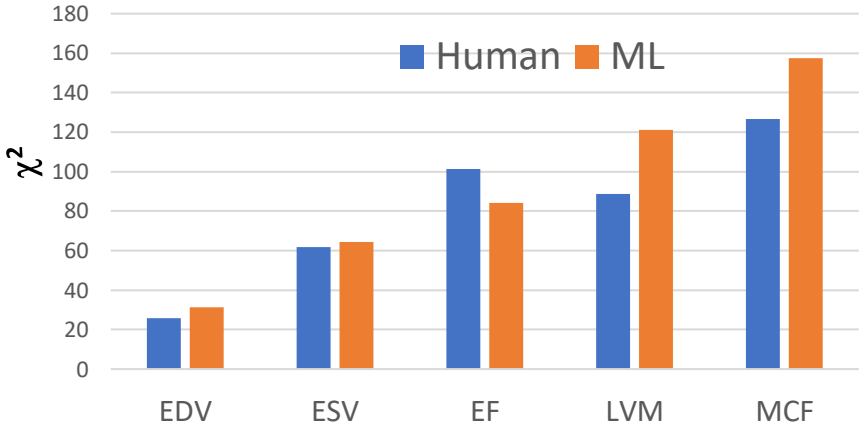
Predicting Clinical Outcome

- Cox regression analysis
  - LV metrics *vs* outcome
  - $\chi^2 \propto$ strength of association

Multivariate

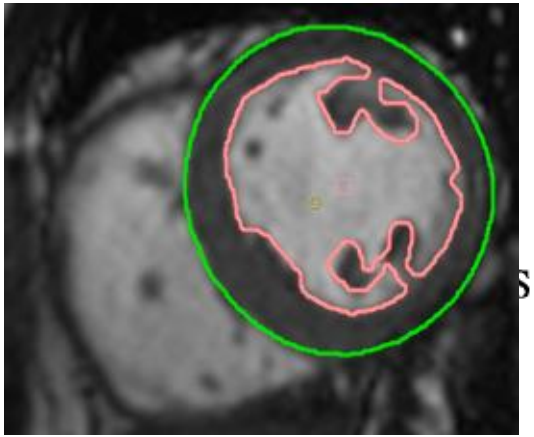
Human expert	ML algorithm	
χ^2 = 167	χ^2 = 191	p<0.01

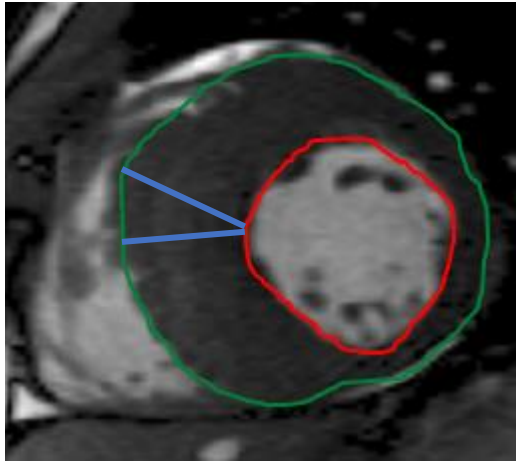
Univariate

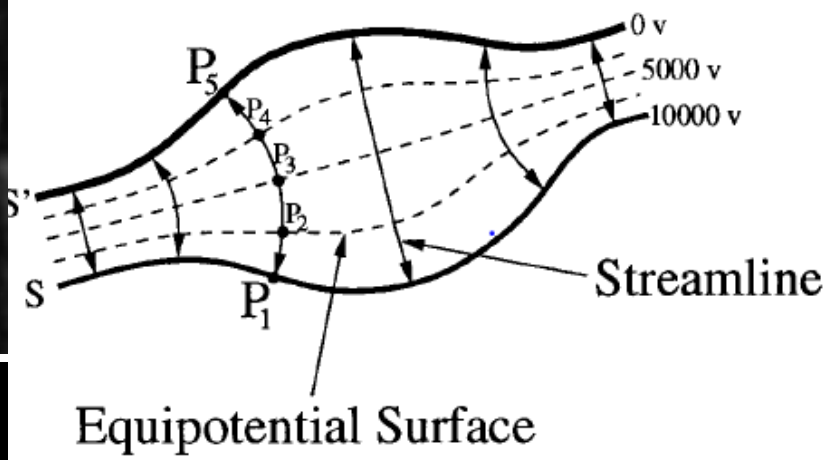


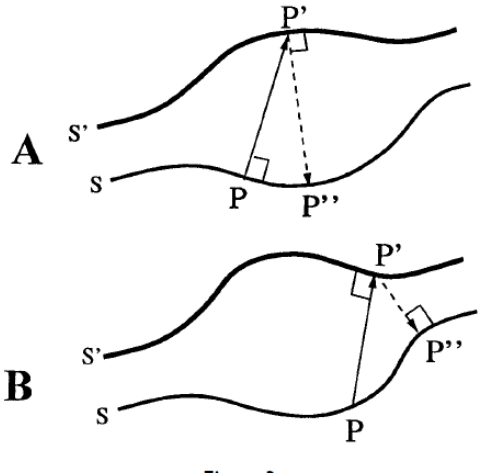
$$\textbf{m}yocardial\ contraction\ fraction\ (MCF) = \frac{stroke\ volume}{myocardial\ volume}$$

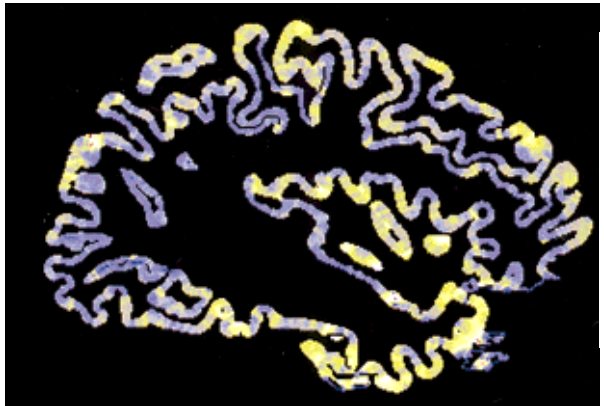
AI – A New Way of Wall Thickness….











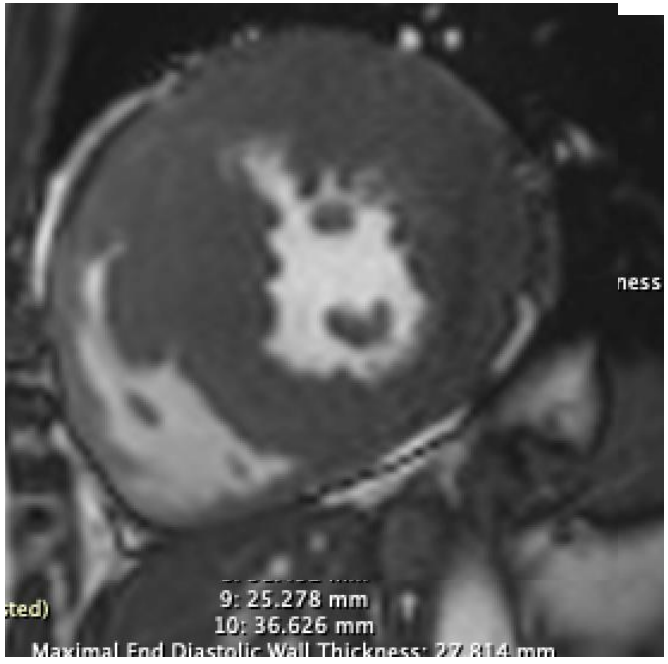
Three-Dimensional Mapping of Cortical Thickness Using Laplace's Equation

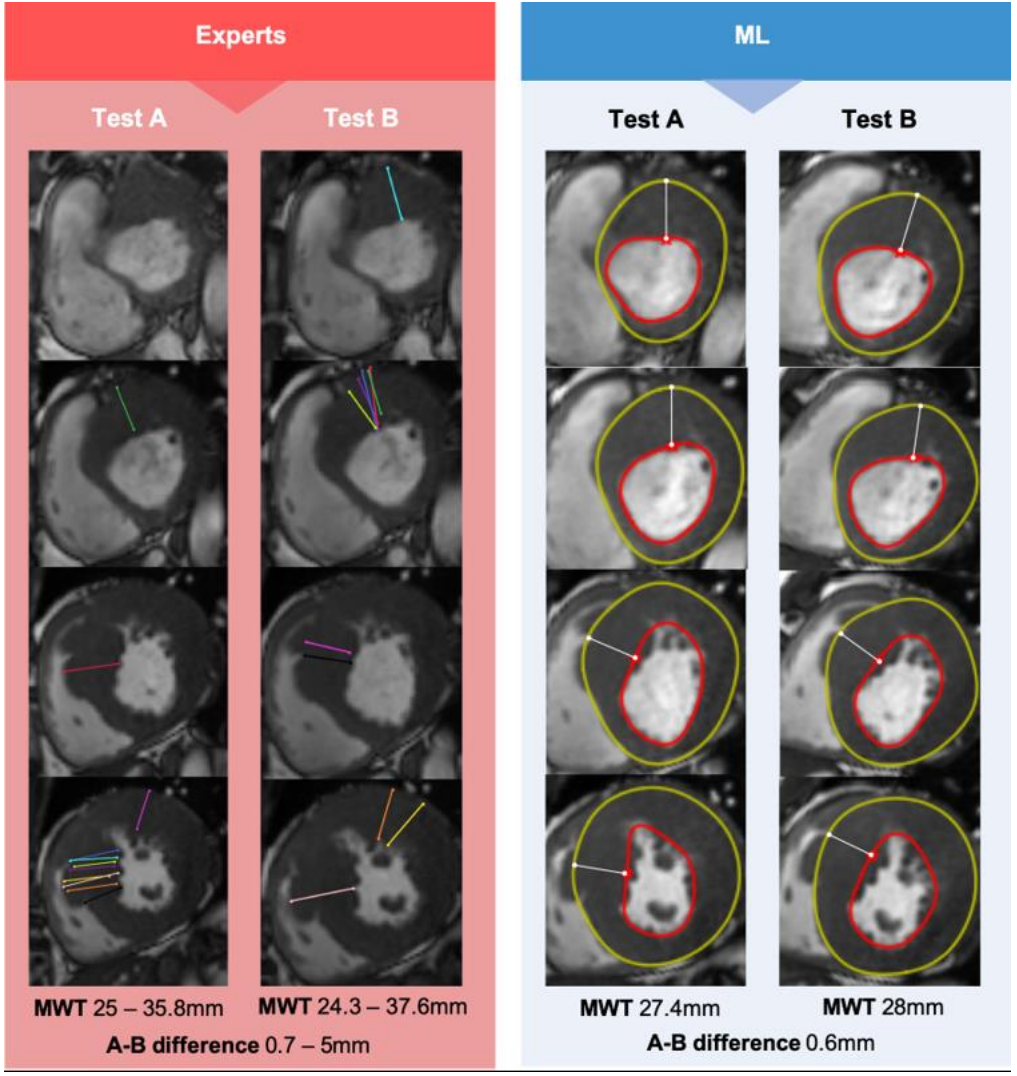
Stephen E. Jones,[1*] Bradley R. Buchbinder,[2] and Itzhak Aharon[3]

[1]*Tufts University School of Medicine*
[2]*Division of Neuroradiology, Department of Radiology, Massachusetts General Hospital*
[3]*Department of Neuroradiology, Massachusetts General Hospital*

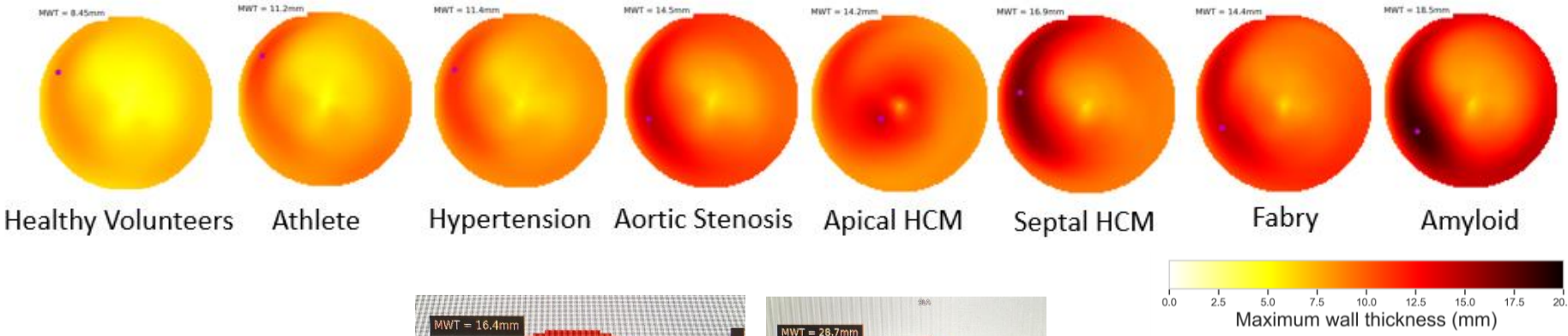
Human Brain Mapping 11:12–32(2000)

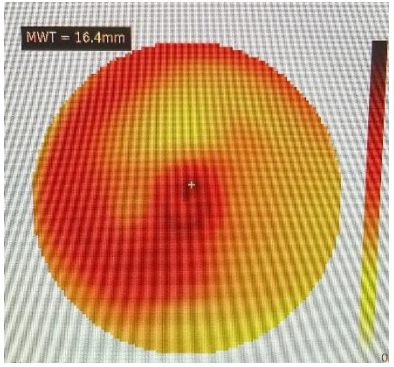
AI – Wall Thickness….

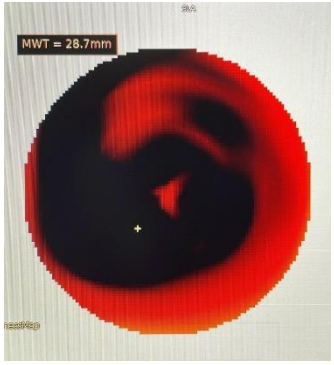




AI – New Visualisation Tools….



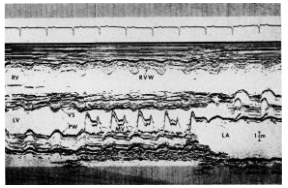




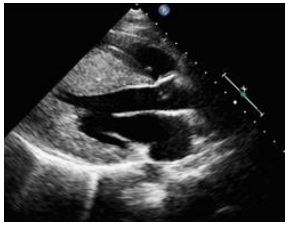
AI – What actually *is* HCM….

- Diagnosis = max wall thickness > 15 mm[1]
  - Unchanged for 50 years
  - Despite age, sex, body size, ethnicity…
- Disproportionate male skew
  - 3:1 M:F in HCMR registry[2] (N = 2755)
  - Females present at a more advanced stage of disease[3]

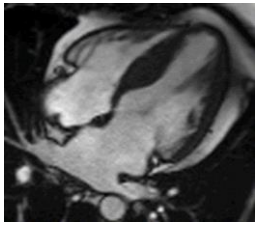
M-Mode
1954



2D-Echo
1970



CMR
1984



AI – What actually *is* HCM….

HCMcalculator.com

* Rounded to nearest 1 mm

Example Pseudo-patients		Predicted normal MWT adjusted for age, sex and BSA	Current MWT Upper Threshold	Adjusted MWT Upper Threshold
Patient #1	♀ Age 74y BSA 2.3m²	12.4mm	15mm	16mm
Patient #2	♂ Age 62y BSA 1.5m²	10.0mm	15mm	13mm
Patient #3	♂ Age 50y BSA 2.3m²	12.7mm	15mm	17mm
Patient #4	♀ Age 40y BSA 1.5m²	7.4mm	15mm	9mm

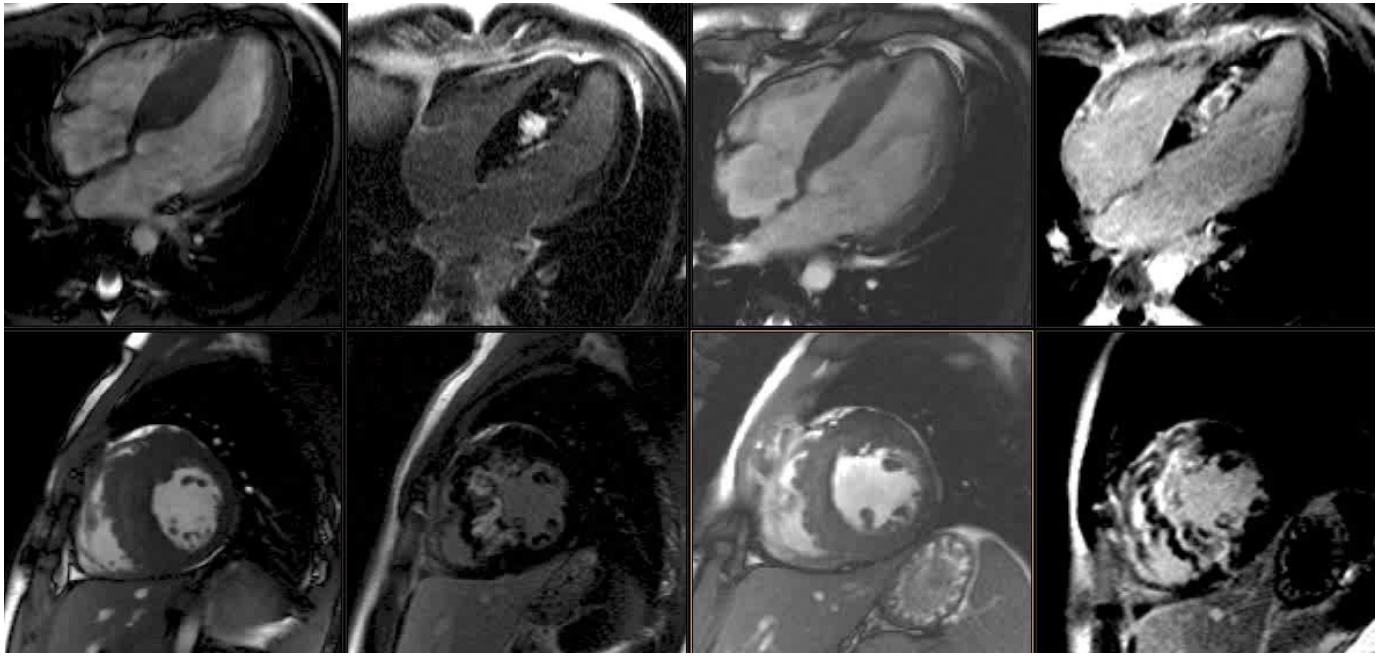
Upper limit maximum wall thickness formula

Males = 1.3* (3.90*BSA + 0.03*Age + 2.06)

Females = 1.3* (3.20*BSA + 0.07*Age - 0.34)

LGE/ Fibrosis

Fibrosis – Predicts Heart Failure…..



Baseline **6 years later**

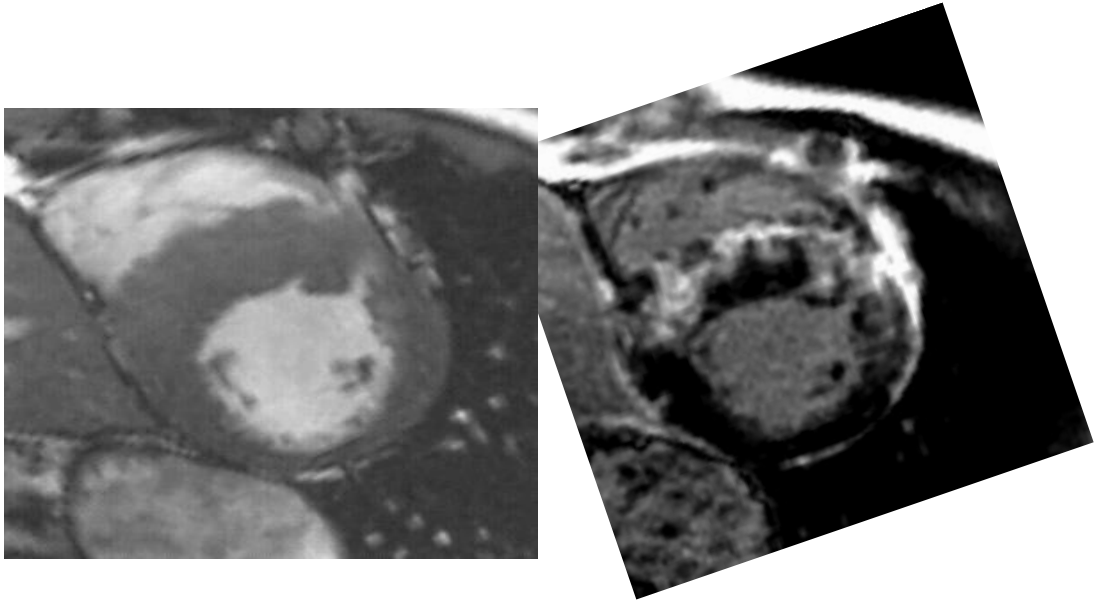
Fibrosis – Predicts Arrhythmia….

31♂ HCM

Asymptomatic

FHx SD

1x3 beat NSVT 7 years ago



Fibrosis – Quantification is Difficult…..

So Which IS Correct?????

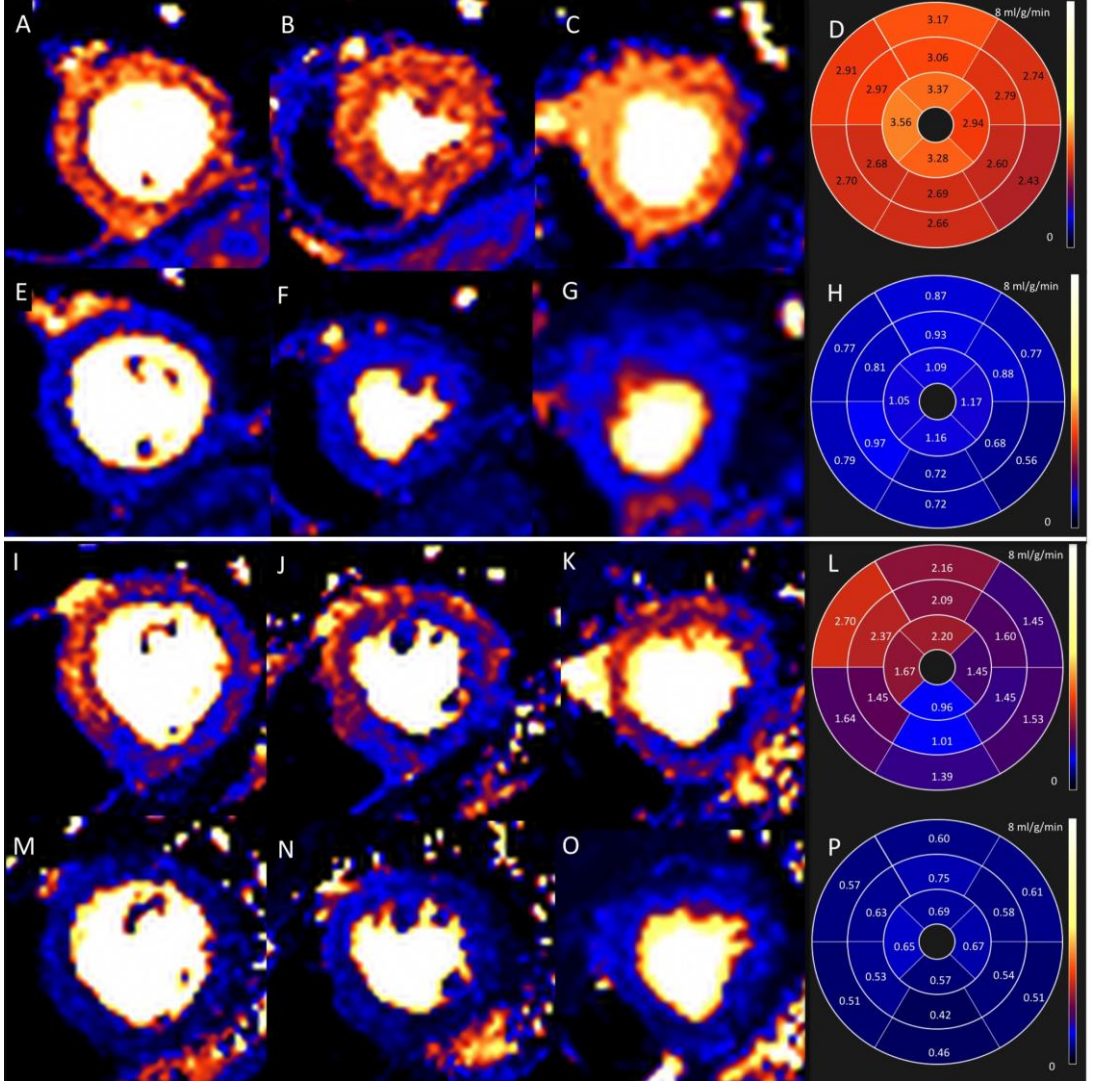
Fibrosis – The Challenges….

- Age and Time Since Hypertrophy Dependent
- Rate of Change, how to assess???
- LGE has challenges
  - How to Quantify (especially Absolute)
  - What About Diffuse Fibrosis

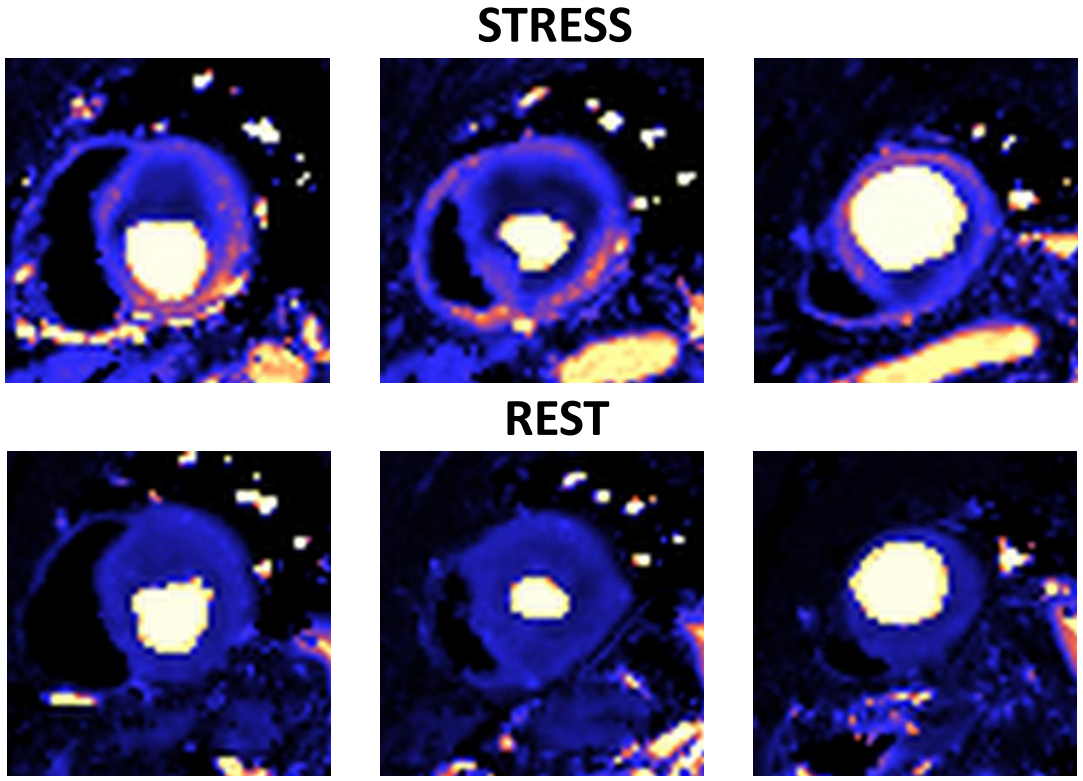
Other Techniques….

Perfusion…..

Perfusion – CAD

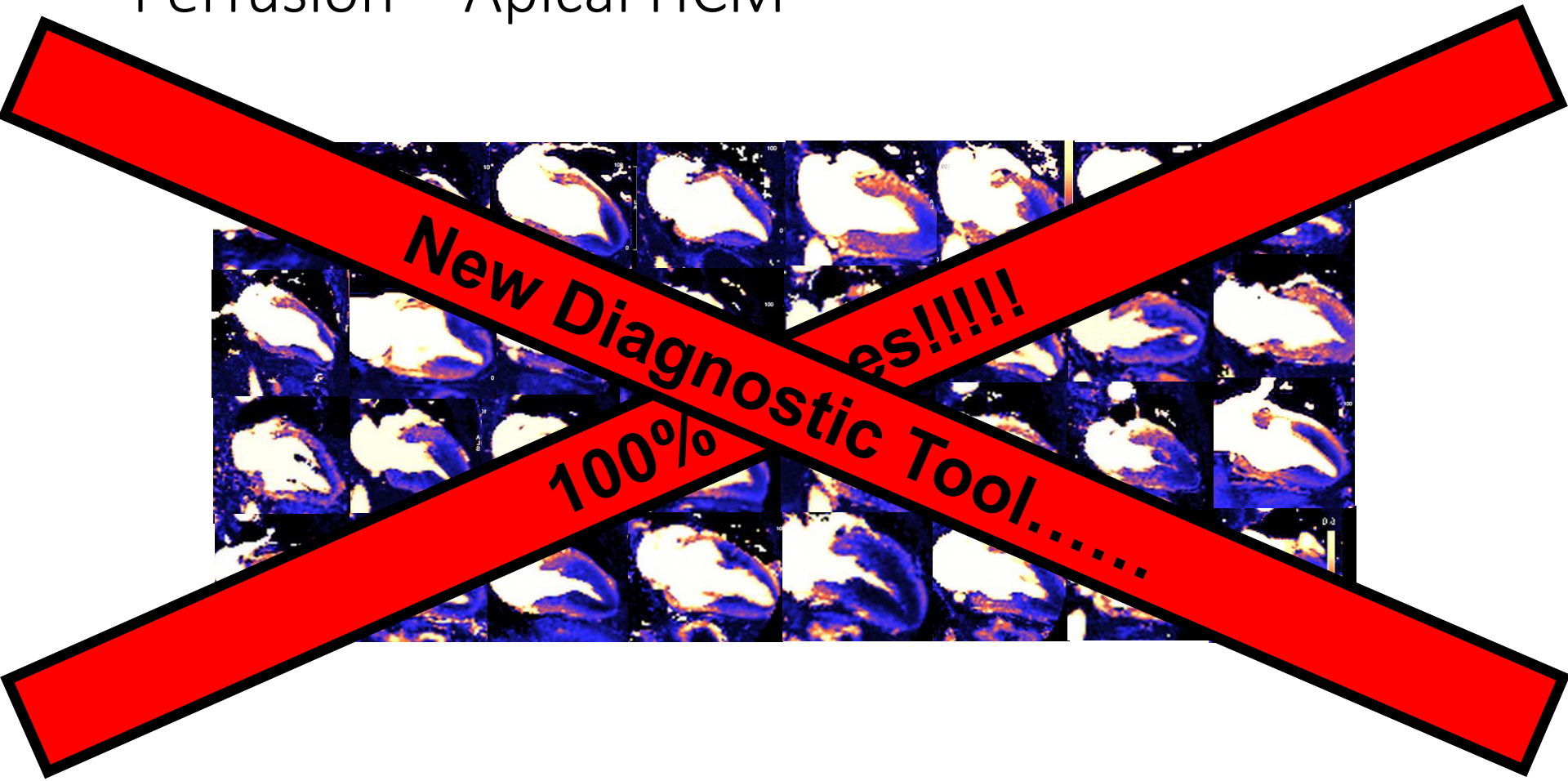


Perfusion – HCM



Images courtesy of C. Camaioni - BSCMR 2017

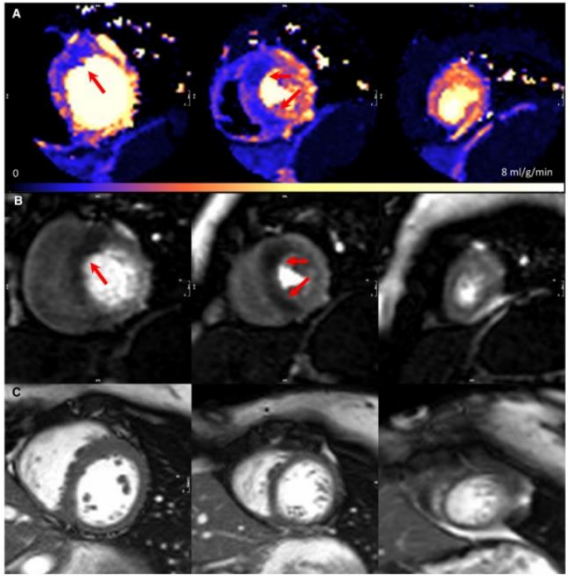
Perfusion – Apical HCM

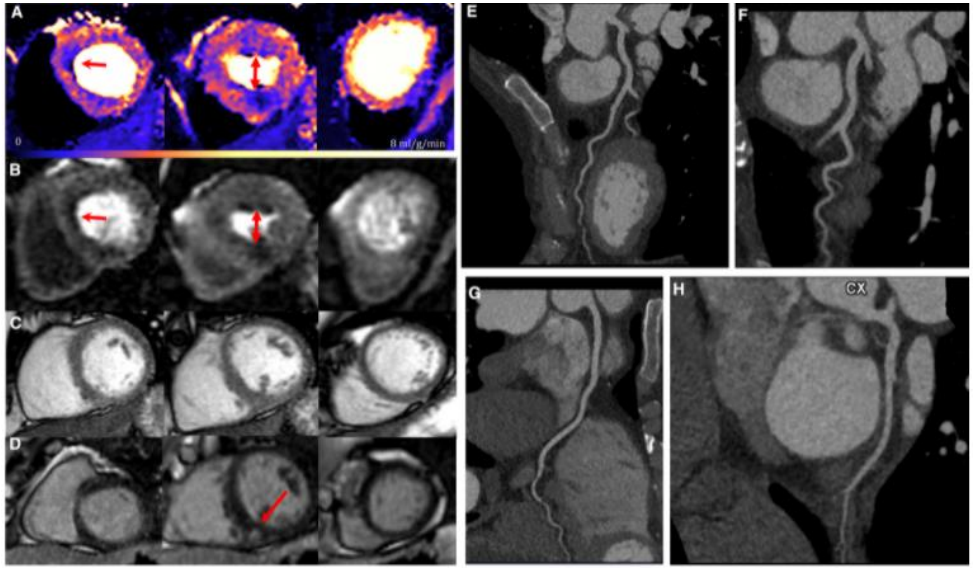


Rebecca Hughes, BSCMR 2021 YIA

Perfusion – May Precede LVH….

2 different Gene Positive LVH- HCM pathogenic mutation carriers



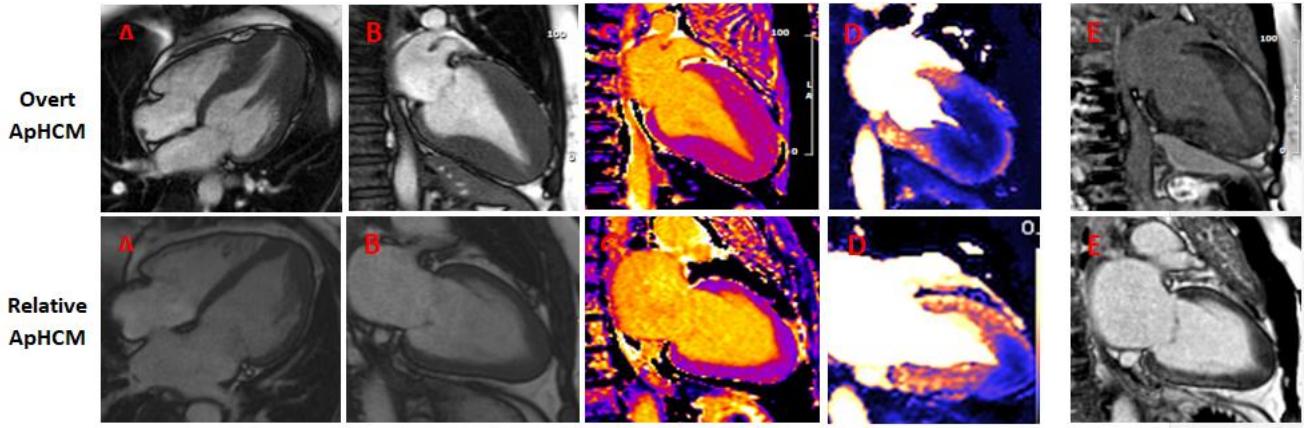


Myocardial Perfusion Defects in Hypertrophic Cardiomyopathy Mutation Carriers

Rebecca K. Hughes, Claudia Camaioni, João B. Augusto, Kristopher Knott, Ellie Quinn, Gabriella Captur, Andreas Seraphim, George Joy, Petros Syrris, Perry M. Elliott, Saidi Mohiddin, Peter Kellman, Hui Xue, Luis R. Lopes ✉, and James C. Moon

Originally published 27 Jul 2021 | https://doi.org/10.1161/JAHA.120.020227 | Journal of the American Heart Association. 2021;10:e020227

HCM – Early and Advanced Disease

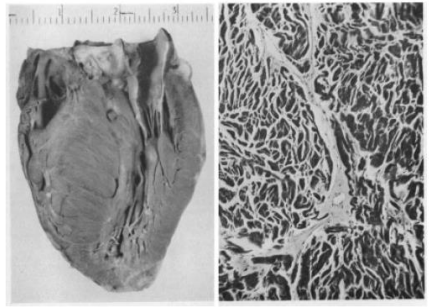


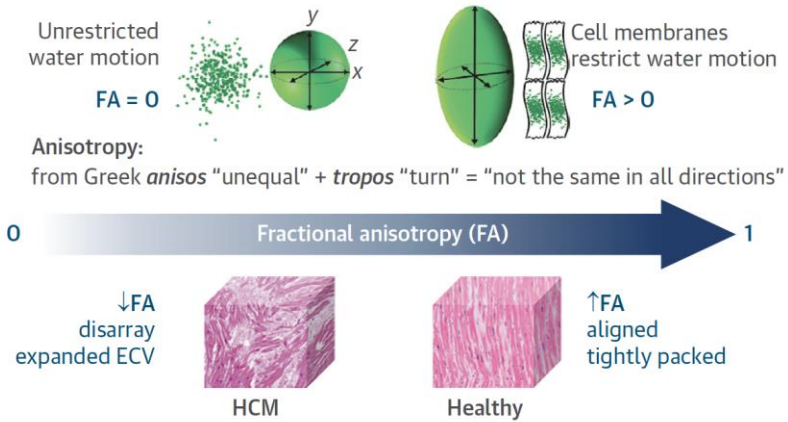
Diffusion Tensor Imaging….

DTI – Disarray…..

- Disarray
- A scale we do not use clinically
- DT CMR maps the diffusion of water in 3 dimensions
- Fractional anisotropy measures the directionality of water diffusion
- When diffusion of water is unrestricted (perfect isotropy) – FA = 0
- FA Therefore low in disorganized myocytes with expanded ECV (HCM)

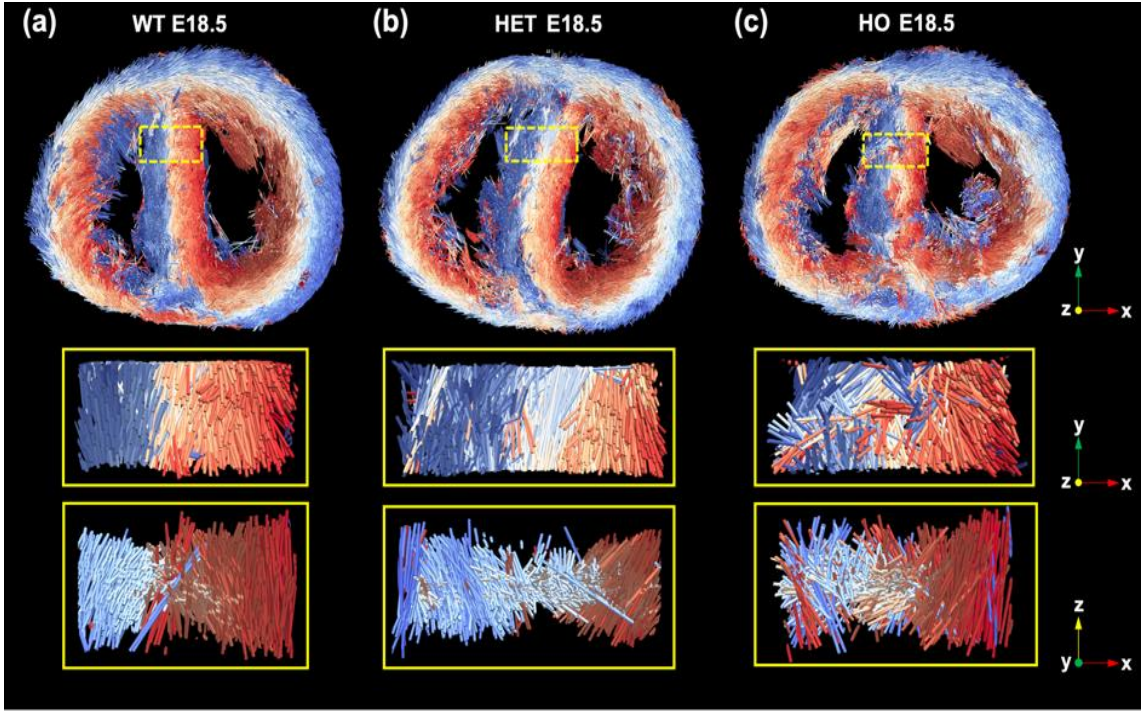
Donald Teare 1958

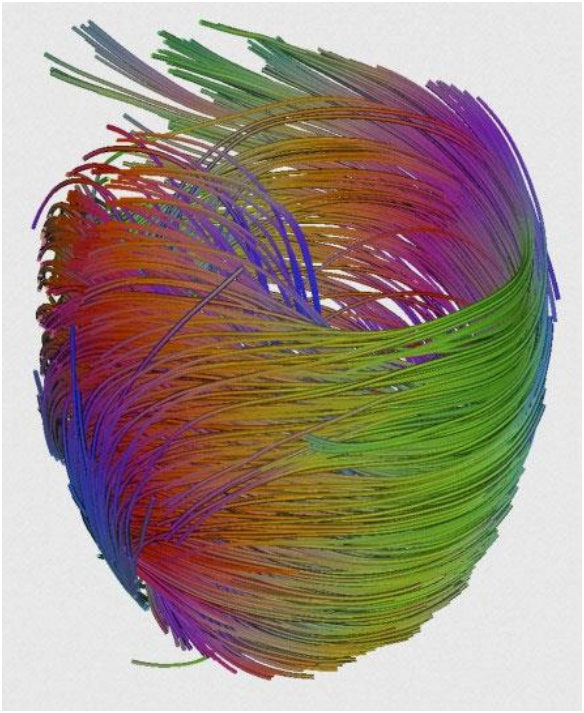




Ariga et al, JACC 2019

DTI – Myocytes for fibrils…..

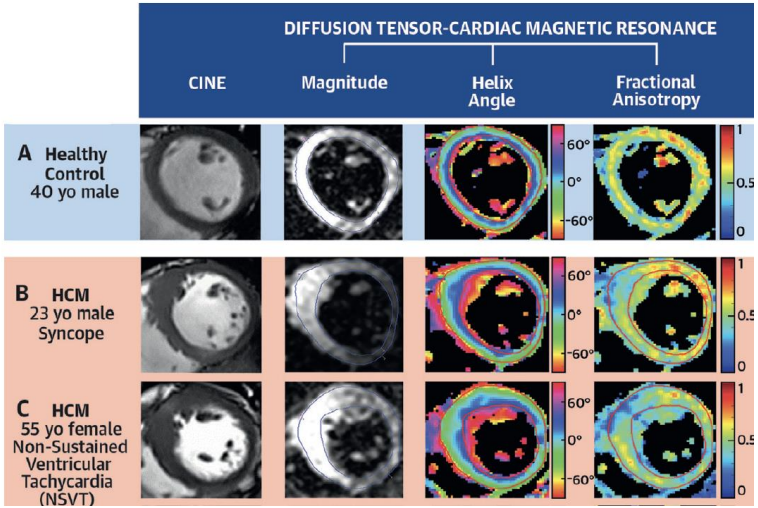




DTI – HCM…..

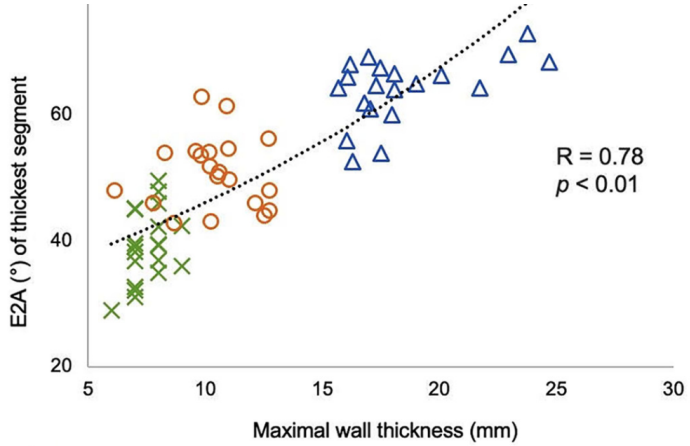
Ariga et al (JACC 2019):

50 HCM vs 30 Healthy volunteers
FA in the hypertrophy and NSVT



Das et al (JCMR 2020):

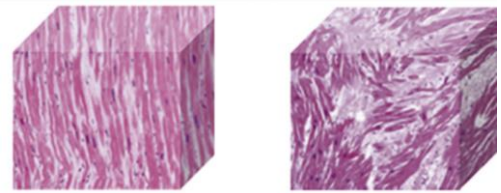
20 HCM vs 20 Athletes vs 20 Volunteers
HCM lower FA
-Secondary Eigenvectors Angles (E2A) measure directionality of laminar sheetlets depicting local contraction.
-Athletes and HCM adopted steeper configuration of sheetlets than HCM (in the thickest segment).
(parallels ECV in Athletes (Swoboda et al JACC 2016)



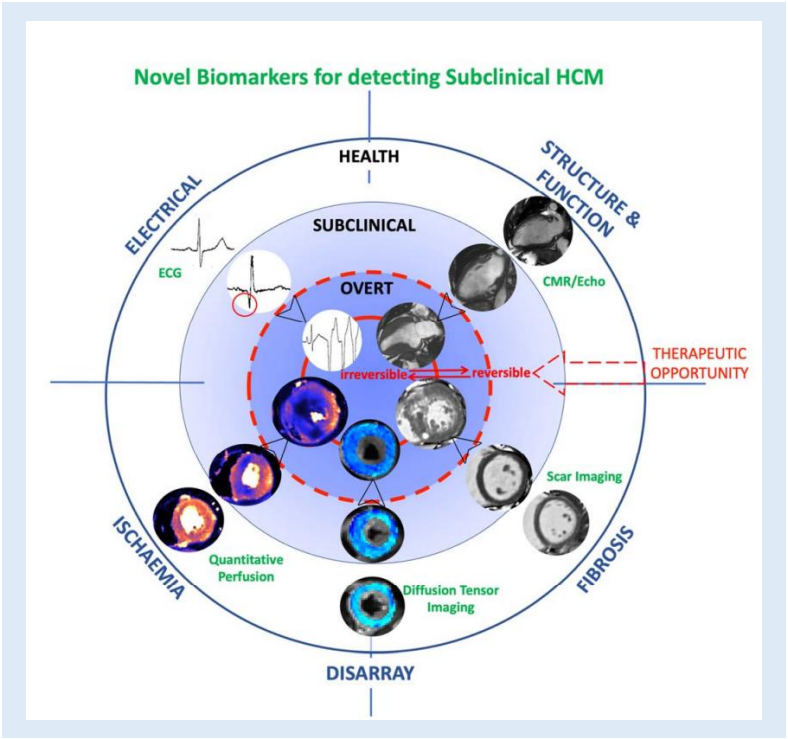
Personalised Imaging

Personalised imaging, layering techniques…..

- Personalised wall thickness
- Perfusion
- ECG (ECG imaging?)
- Diffusion tensor imaging: early disease?



Healthy HCM



Ariga et al, JACC 2019

‘Genetic Cardiomyopathy’

- Genetics
- Based on genes
- Cardiomyopathy
- Anything wrong bu tery disease

But this isn’t what we currently do…..