

Methods of MR Fat Quantification and their Pros and Cons

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- No personal financial or other disclosures
- UCSD has had and has Lab Service Agreements with several CROs and pharmaceutical companies

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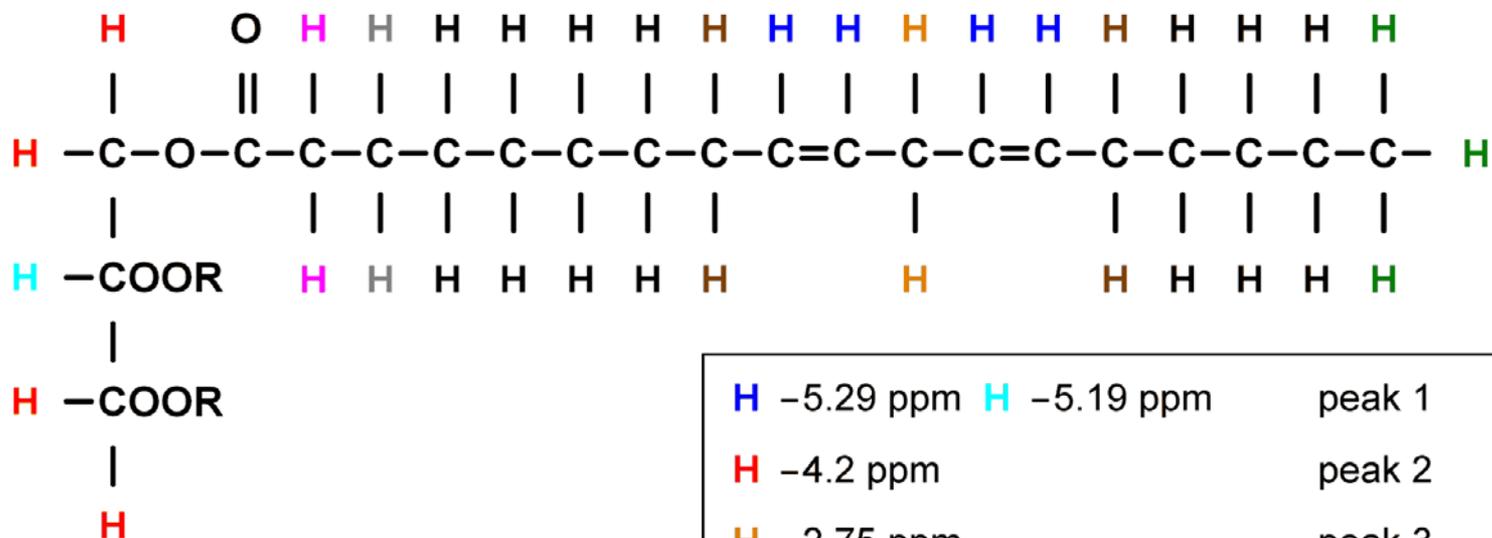
Aims of this talk

- Background on history and principles of MR assessment of liver fat, including description of proton density fat fraction (PDFF)
- Brief description of complex and magnitude MRI
- Pros and Cons of MR fat assessment methods
- PDFF vs. histologic steatosis grade
- Possible contexts of use of MRI PDFF
- Clinical trial considerations
- Closing remarks

Background

- Proton density fat fraction (PDFF) is an MR biomarker of hepatic steatosis
- Developed over the last 13 years
- 62 papers published since 2011 in PubMed
- MRI emerging as a method of consensus
- Newly formed QIBA PDFF Biomarker Committee
- Applies to both MR imaging and MR spectroscopy
- PDFF is the ratio of corrected observable fat signal, to sum of fat and water signals
- This, a ratio of signals, not a ratio of weights

Triglyceride proton environments¹

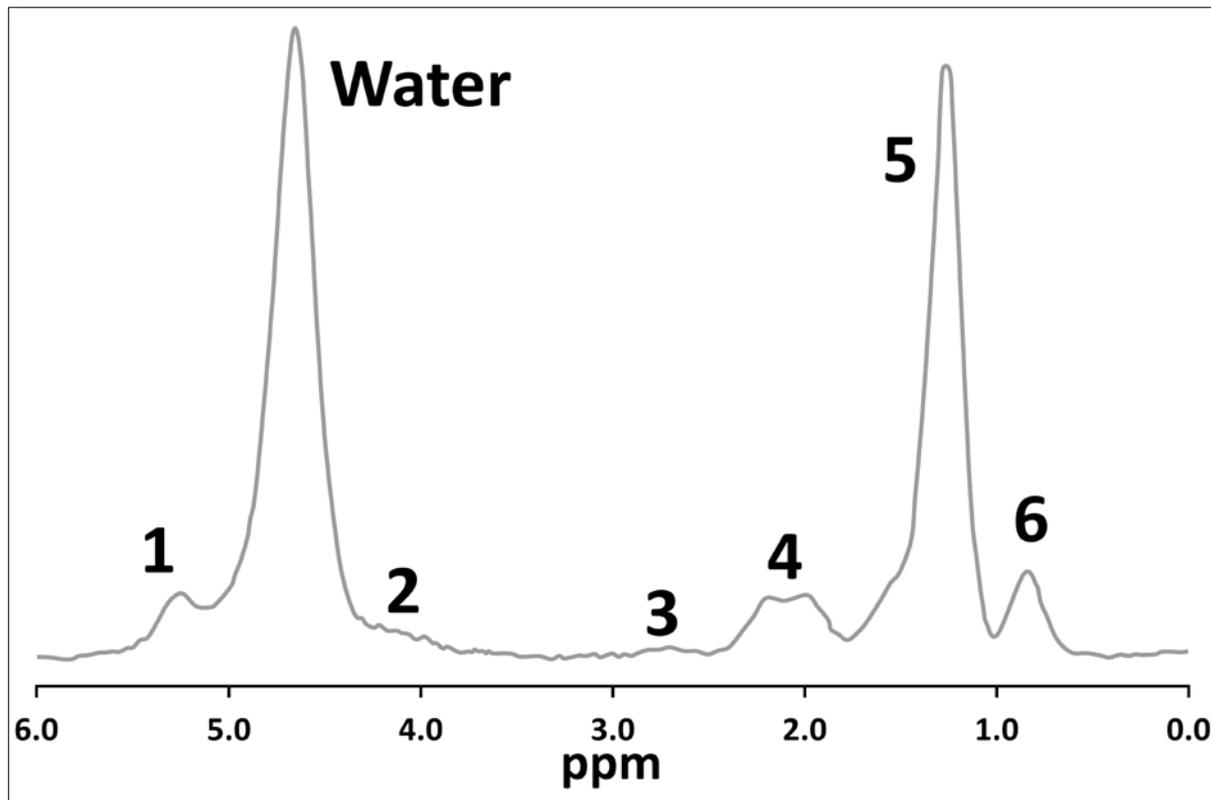


H -5.29 ppm	H -5.19 ppm	peak 1
H -4.2 ppm		peak 2
H -2.75 ppm		peak 3
H -2.20 ppm	H -2.02 ppm	peak 4
H -1.6 ppm	H -1.3 ppm	peak 5
H -0.9 ppm		peak 6

¹ - Hamilton et al, *NMR Biomed* **2011**; 24:784-790

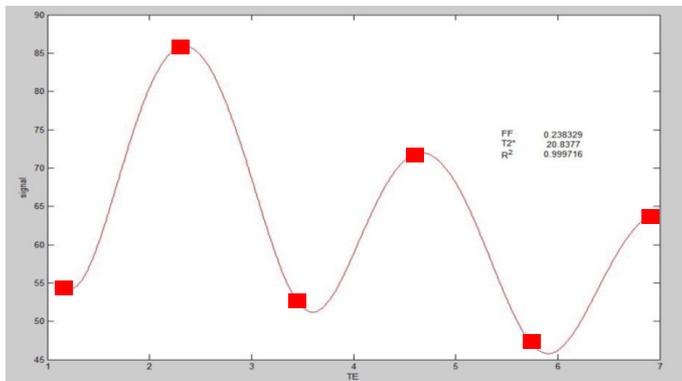
^1H Spectrum of Fat and Water

- One water peak, multiple fat peaks
- Can be acquired at 1.5T and 3T (STEAM sequence)

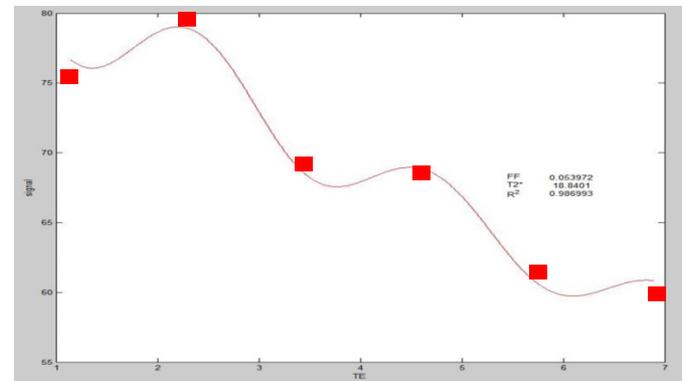


Main principles of MR fat imaging

- As TE increases, fat and water peaks go in and out of phase with each other
- When peaks are 'in phase', their signals add, and when they are out of phase, their signals cancel
- Additionally, there is overlying decay of all MR signals with time, described by the variable $T2^*$



High liver fat
(PDFF = 20.8%)



Low liver fat
(PDFF = 5.4%)

Methods of acquisition

- Two main methods to estimate PDFF:
 - Complex MRI (IDEAL-IQ)²
 - Magnitude MRI (LipoQuant)
- Similarities:
 - Both typically acquire 6 echoes
 - Both are acquired avoiding T1 weighting
 - Both correct for T2* decay
 - Both acquired in a single breath-hold

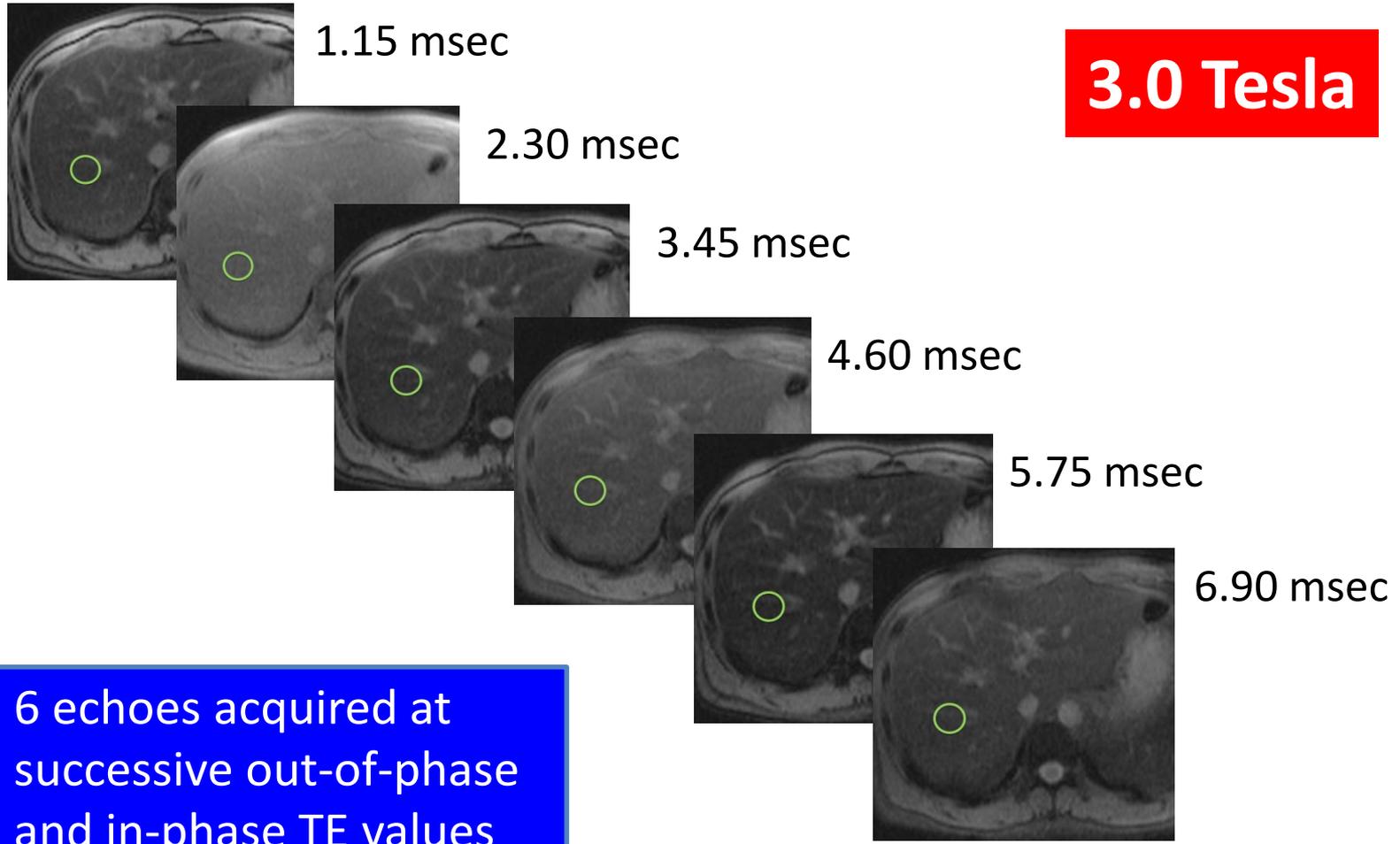
- Differences:

	Complex	Magnitude
Type of acquisition	3D	2D
Type of data acquired	Real and imaginary	Magnitude
Range	0 to 100%	0 to 50%

Confounder correction/avoidance

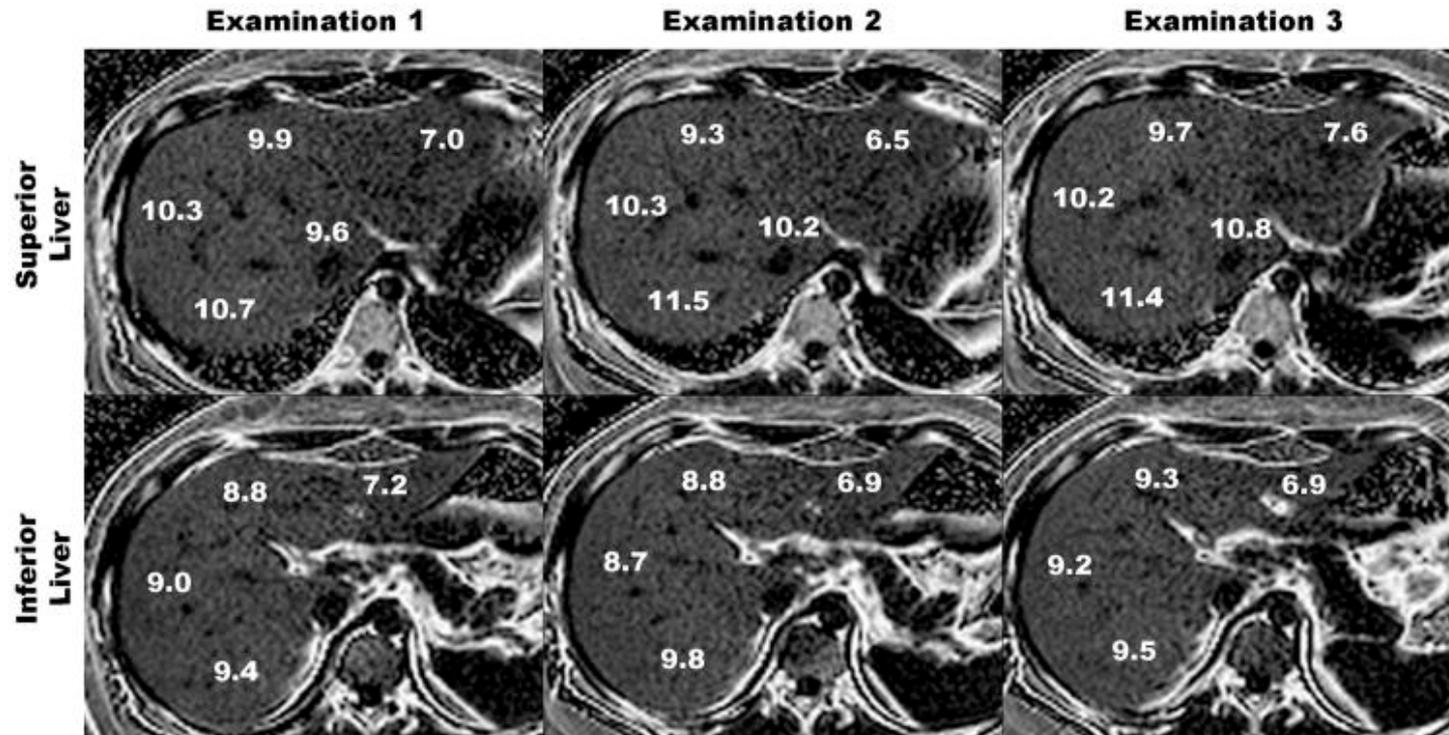
- T1 weighting avoided by using long TR values, and small flip angles
- T2* decay corrected for by collecting images at multiple TE values, and then solving for T2* and PDFF simultaneously using custom MatLab algorithm
- Multi-frequency interference amongst the water peak and the major fat peaks accounted for by 'including' the full, known spectrum of human liver fat in the analysis
- Images at all TEs acquired in a single breath-hold to:
 - provide good co-localization between images
 - avoid possible differences in transmit and receive gain

Typical magnitude MRI acquisition



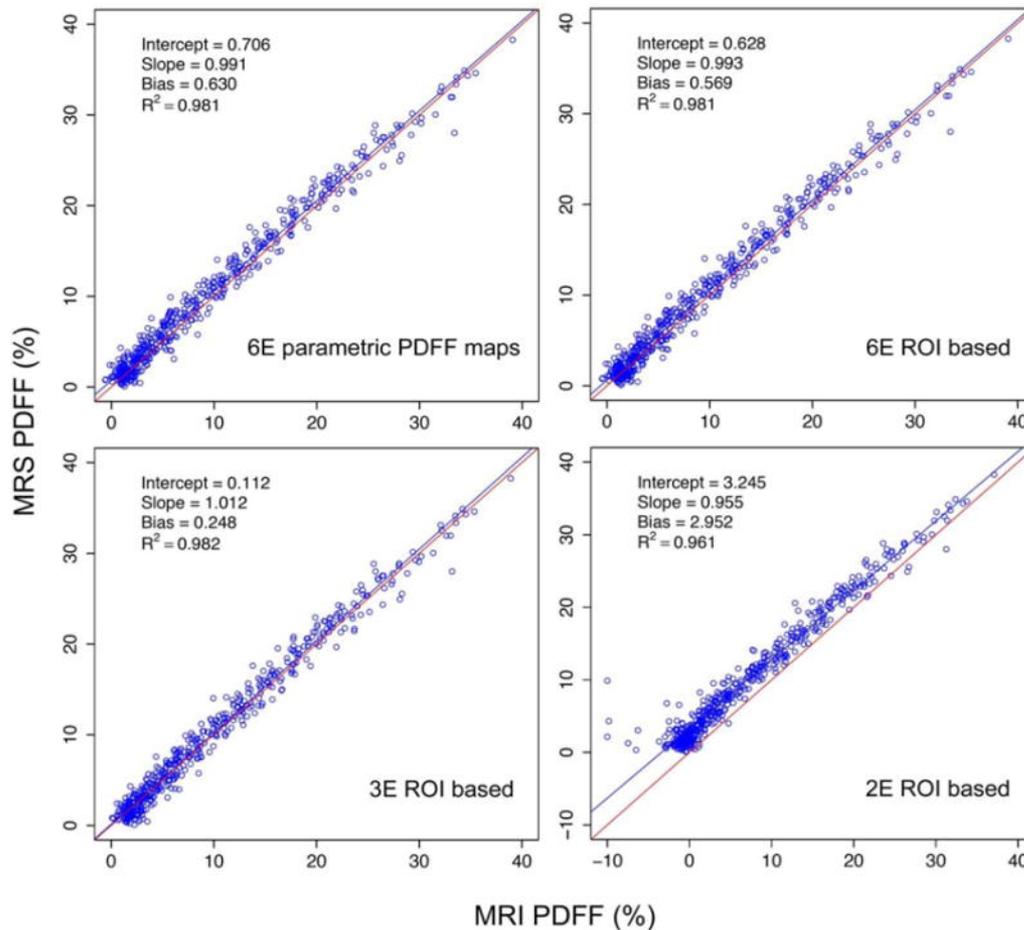
Precision

- Magnitude MRI is precise (3 separate exams, same day)³
- Inter-examination ICC for whole liver was 0.999 (95% CI: 0.998, 1.000)



Accuracy: Regression

- Magnitude MRI is accurate compared to MR spectroscopy as gold-standard



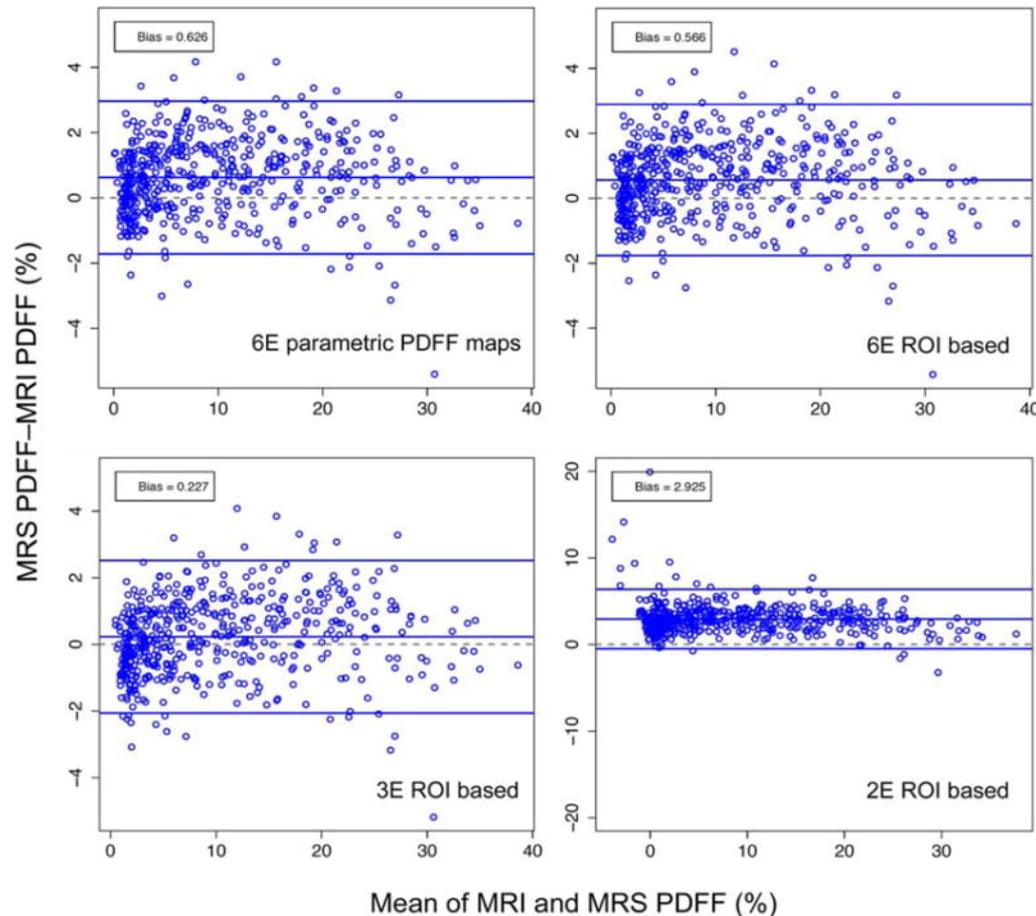
from:

Heba et al, *JMRI*
2016: 43:398-406

- 506 adults subjects
- all had MRI and MRS

Accuracy: Bland-Altman

- Magnitude MRI is accurate, compared to MR spectroscopy as reference standard



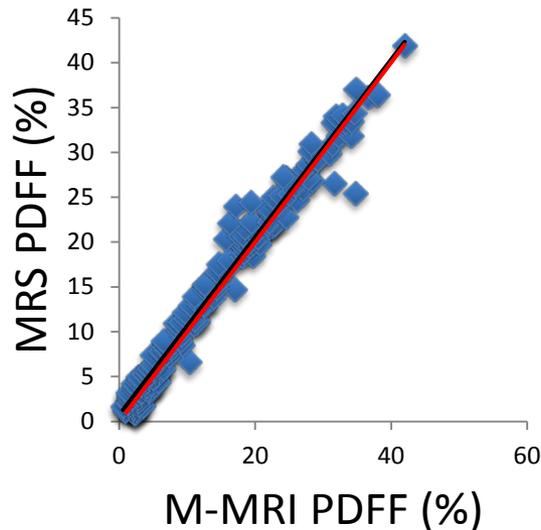
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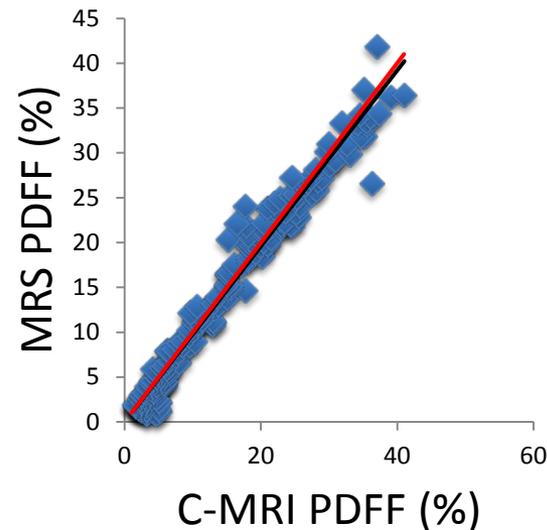
- 506 adults subjects
- all had MRI and MRS

Complex MRI

- Implemented now by GE, Siemens, and Philips as supported sequences
- Comparable to magnitude MRI (200 children)⁴



slope = 0.991 (0.934, 1.021)
intercept = 0.729% (0.340, 1.237%)



slope = 0.981 (0.936, 1.022)
intercept = -0.017% (-0.515, 0.510%)

Pros and Cons

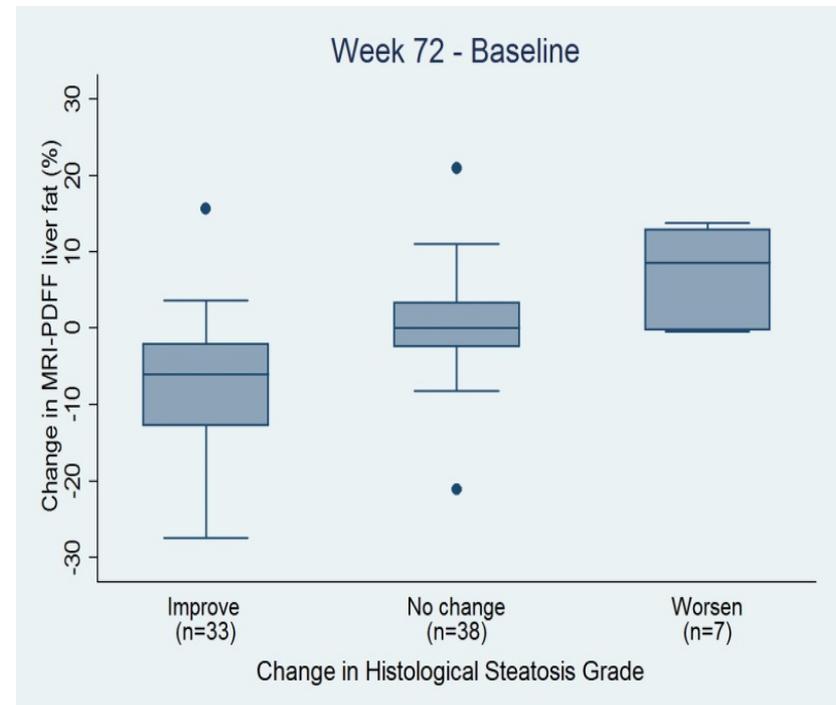
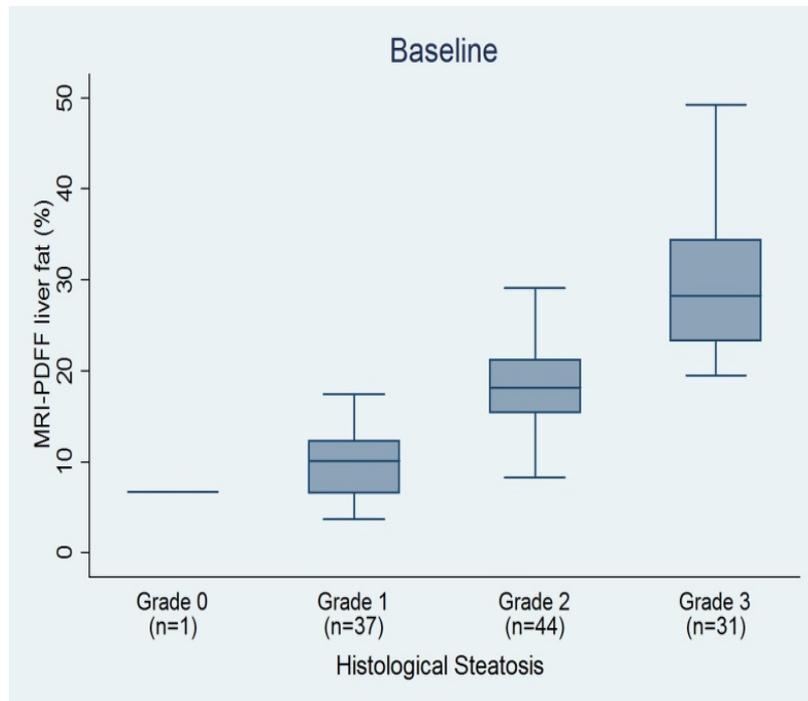
	Complex MRI	Magnitude MRI	MR Spectroscopy
Pros	<ul style="list-style-type: none"> Supported by MR scanner manufacturers Accurate and precise; requires no additional analysis for parametric maps Range 0 to 100% PDFF 	<ul style="list-style-type: none"> Sequences themselves available on nearly all scanners as standard product Validated as accurate and precise in many studies 	<ul style="list-style-type: none"> Currently considered reference standard for PDFF Offers additional capabilities over MRI
Cons	<ul style="list-style-type: none"> Requires purchase of a software package Not as widely available as magnitude MRI Reproducibility across scanner types not yet fully validated for on-site results 	<ul style="list-style-type: none"> Not supported per se by MR scanner manufacturers Requires additional post-processing to produce parametric maps and/or to analyze by ROIs Range 0 to 50% PDFF 	<ul style="list-style-type: none"> Requires on-site acquisition and analysis expertise Voxel placement only approximate Typically only single-voxel Most often only right lobe

PDFF vs. histologic steatosis grade

- Not quantitatively the same
- Steatosis grade is percentage of hepatocytes showing fat globules by visual inspection on H&E stained slides
- PDFF is ratio of MRI signals from fat, compared to that from sum of fat and water
- Consider case when all hepatocytes filled to about 50% of their volume with fat globules:
 - Histologic steatosis percentage would be 100%
 - PDFF (ignoring details) would be about 50%
- Rule of thumb thus is that histologic steatosis percentage is about double PDFF

NASH CRN FLINT Trial Results⁵

- Cross-sectional and longitudinal relationships between PDFF and histologic steatosis grade (113 subjects, 8 sites)



Diagnostic accuracy of PDFF⁵

- MRI PDFF thresholds and accuracy to classify histologic steatosis grades, and histologic steatosis grade change

Cross-sectional steatosis classification (n = 113)	MRI PDFF threshold (%)		Sens (%)	Spec (%)	PPV (%)	NPV (%)
0-1 vs. 2-3	16.3		83	90	95	73
0-2 vs. 3	21.7		84	90	76	73
Longitudinal steatosis change classification (n = 78)	Δ PDFF Mean (SD) (%)	MRI PDFF cutoff at 90% specificity	Sens (%)	Spec (%)	PPV (%)	NPV (%)
Improvement (n = 42)	-7.4 ± 8.7	- 5.1%	58	90	83	75
No change (n = 49)	0.3 ± 6.3	-	-	-	-	-
Worsening (n = 9)	7.7 ± 6.0	5.6%	57	90	36	96

Possible PDFF contexts of use

- Safety assessment in drug development related to hepatic steatosis, for any study where elevated hepatic steatosis is a concern
- Accurate population enrichment to avoid unnecessary biopsies and reduce study costs
- As a replacement for histologic steatosis grade (primary, secondary, and exploratory aims), whenever histologic steatosis grade is a biomarker of a clinical endpoint
- Add-on to any liver MRI already being done (potentially high incremental value for relatively low additional incremental time and cost)

Clinical trial considerations

- Magnitude MRI implemented at over 300 sites in over 3,000 subjects in pharmaceutical company studies
- UCSD acted as Central Radiology Coordinating Center (RCC) for those studies
- For PDFF, and by inference for any quantitative imaging biomarker:
 - Acquisition and intake QC is essential to study success
 - QC and analysis supervision by an expert is necessary until validation and responsibility is assumed by MR manufacturers or others
- MRI is strongly preferable to MRS if only estimation of hepatic PDFF is required

Closing remarks

- MRI-estimated PDFF is a validated, accurate, and precise biomarker of hepatic steatosis
- Magnitude MRI supported by a central expert currently allows more flexibility in site selection, but complex MRI will eventually take over that role when it is more widely available, and acquisition methods and results are fully harmonized across MR scanner types
- For clinical trials where there is a need to evaluate hepatic steatosis:
 - central analysis is recommended with special attention to site training and intake QC
 - MR imaging is strongly recommended over MR spectroscopy