MR Imaging of MASH

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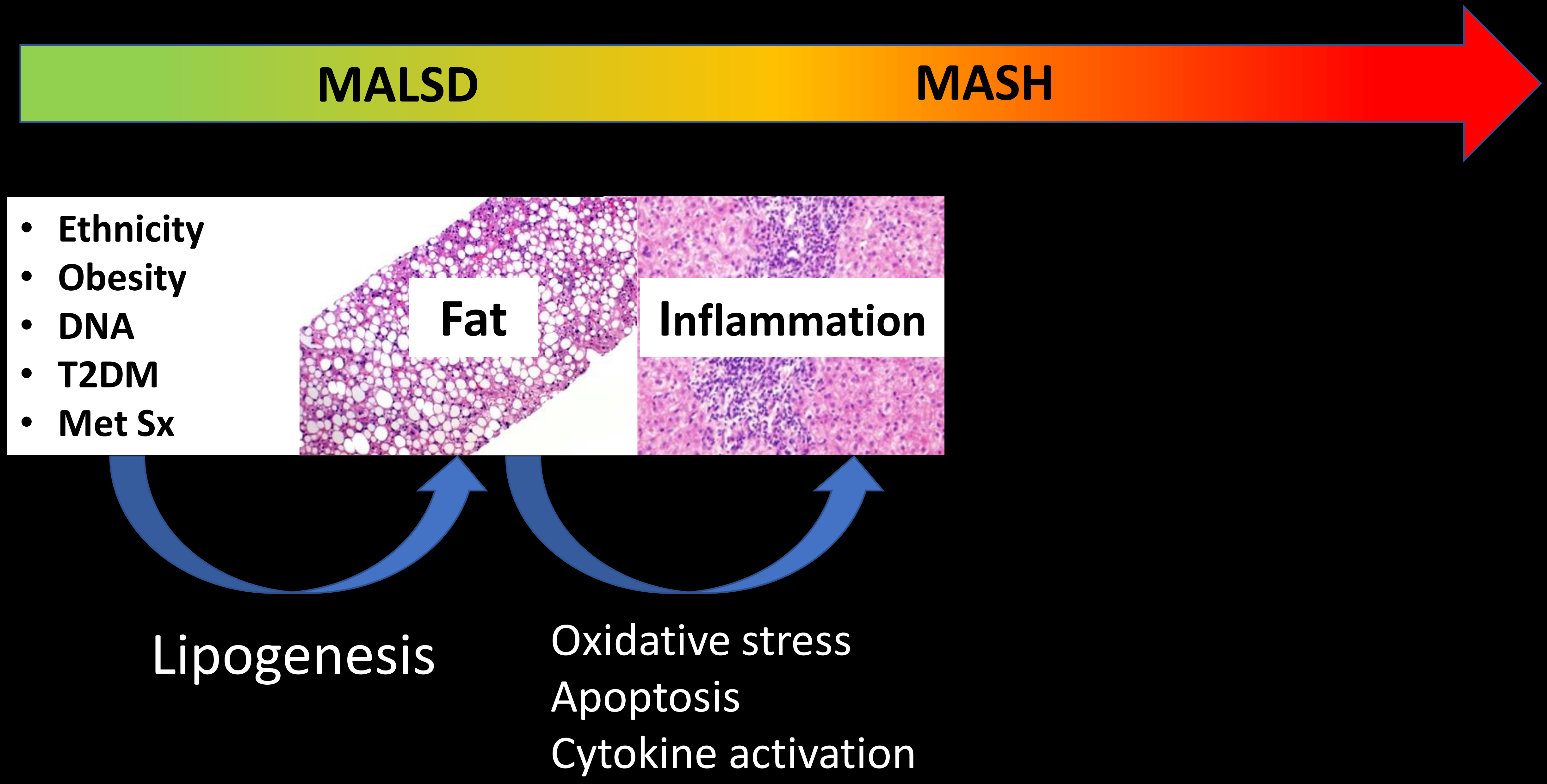
Disclosures

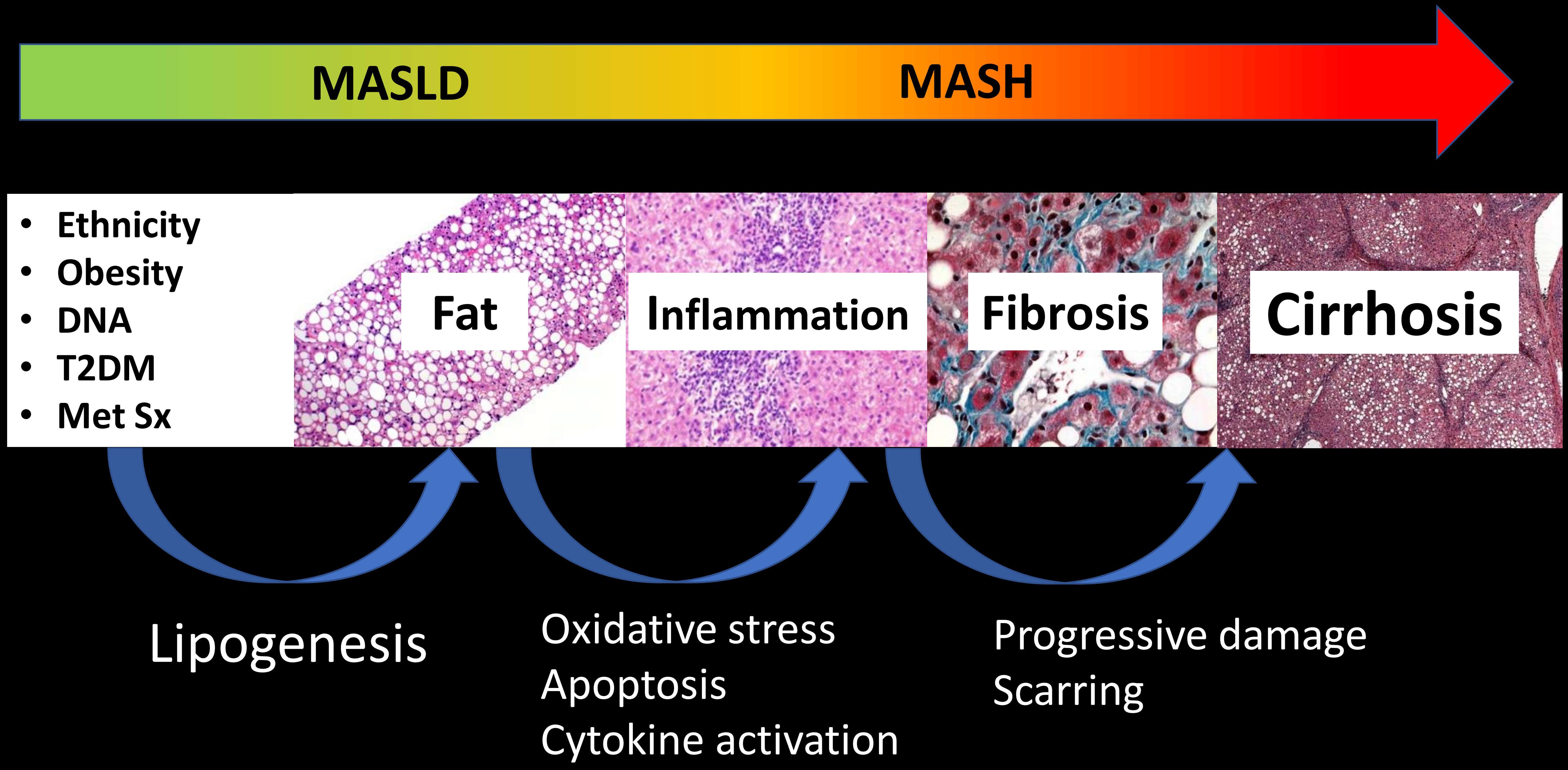
- Grant support-Bayer, Pfizer, Siemens, GE, Median
- Consulting-Bayer, epigenomics, GE

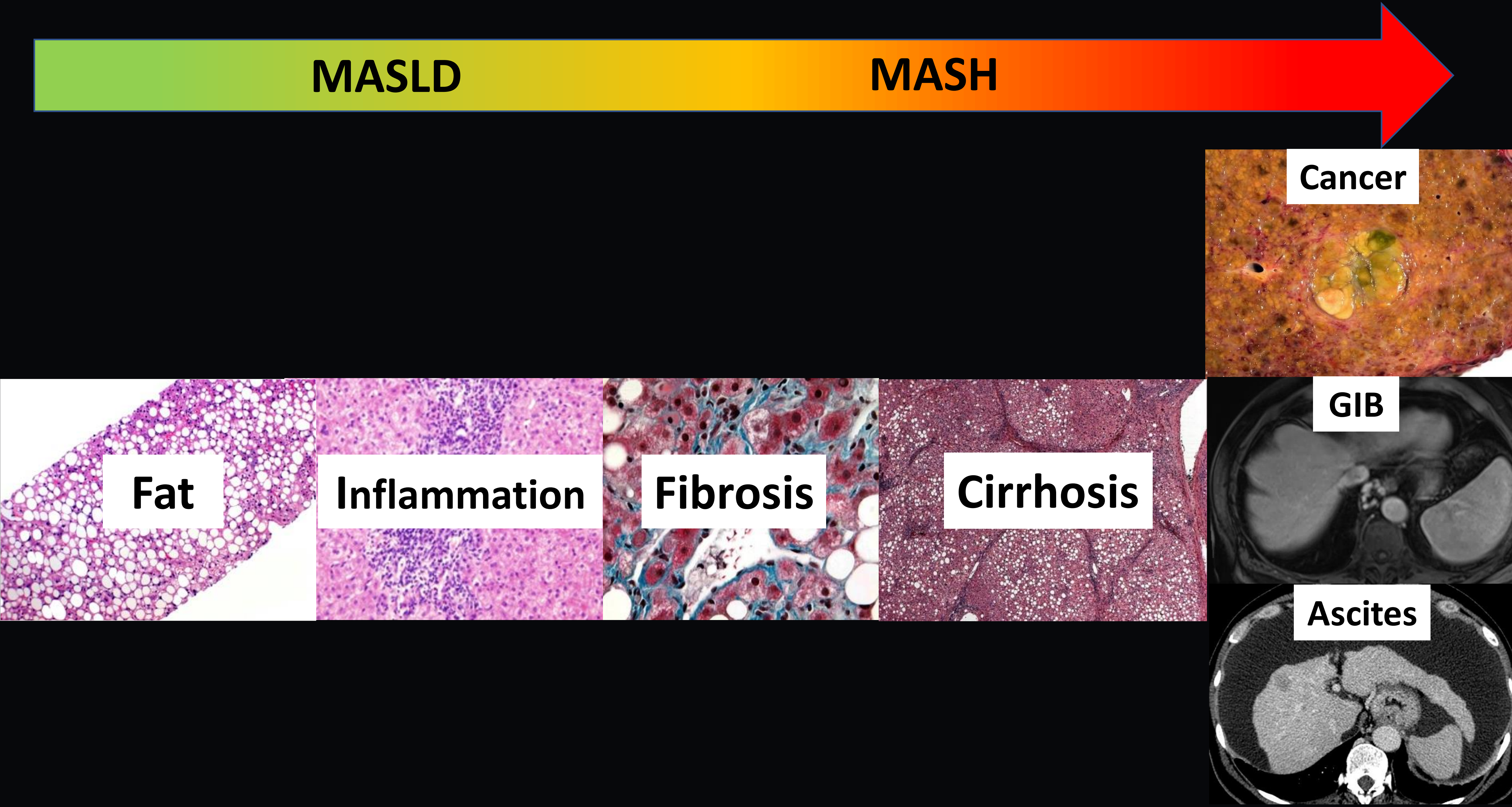
MASLD → **MASH**

- **Ethnicity**
- **Obesity**
- **DNA**
- **T2DM**
- **Met Sx**

Lipogenesis

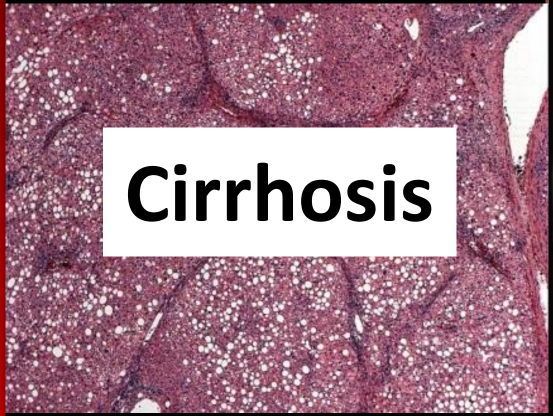

MALSD
MASH
• Ethnicity
• Obesity
• DNA
• T2DM
• Met Sx
Fat
Inflammation
Lipogenesis
Oxidative stress
Apoptosis
Cytokine activation

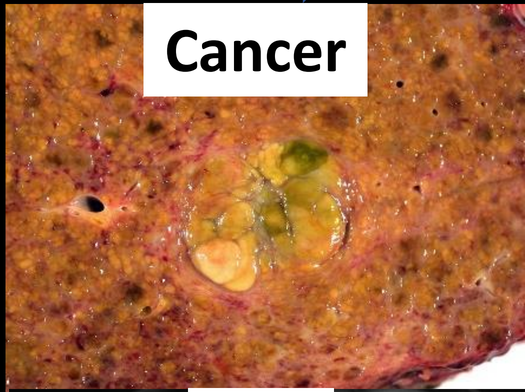

MASLD
MASH
• Ethnicity
• Obesity
• DNA
• T2DM
• Met Sx
Fat
Inflammation
Fibrosis
Cirrhosis
Lipogenesis
Oxidative stress
Apoptosis
Cytokine activation
Progressive damage
Scarring

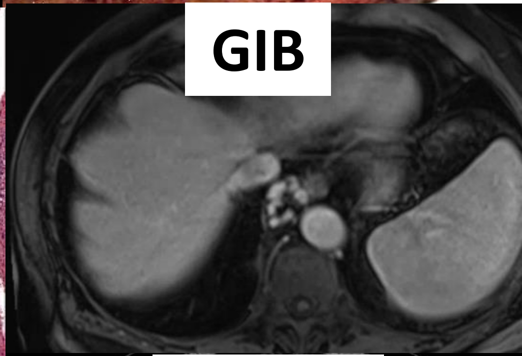


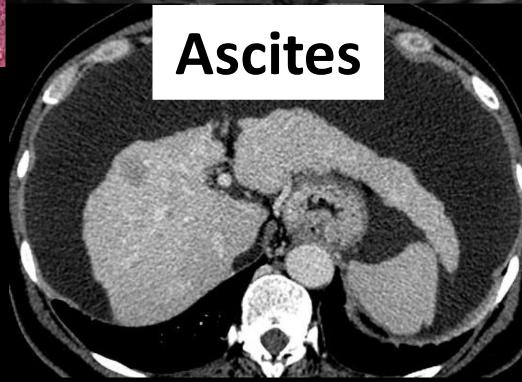
MASLD
MASH
Cancer
GIB
Ascites
Fat
Inflammation
Fibrosis
Cirrhosis

MASLD MASH



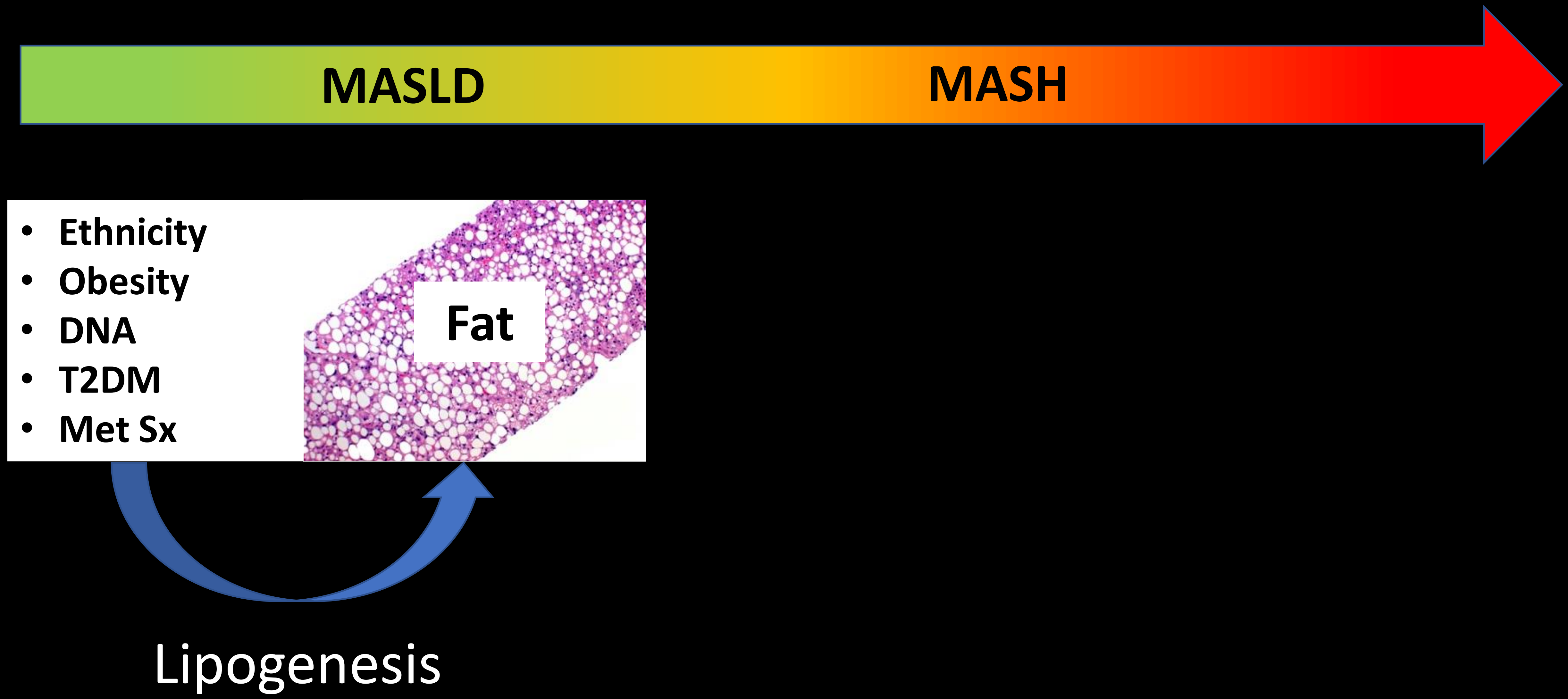






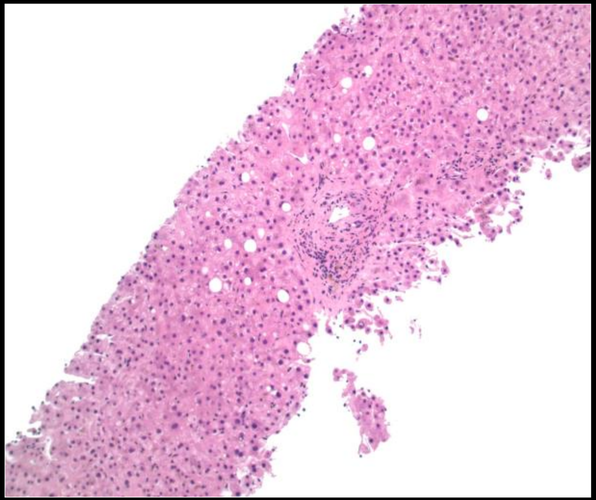
“horse left barn” Paul murphy @ Pinterest.com

Whats-thesayinganswers.com

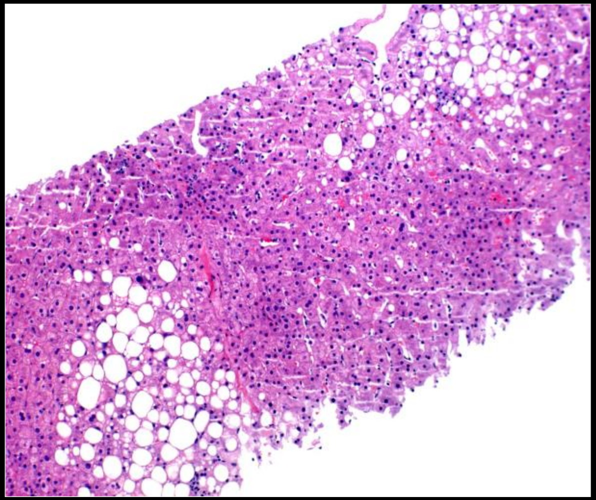

MASLD
MASH
Ethnicity
Obesity
DNA
T2DM
Met Sx
Fat
Lipogenesis

Range of fat in liver

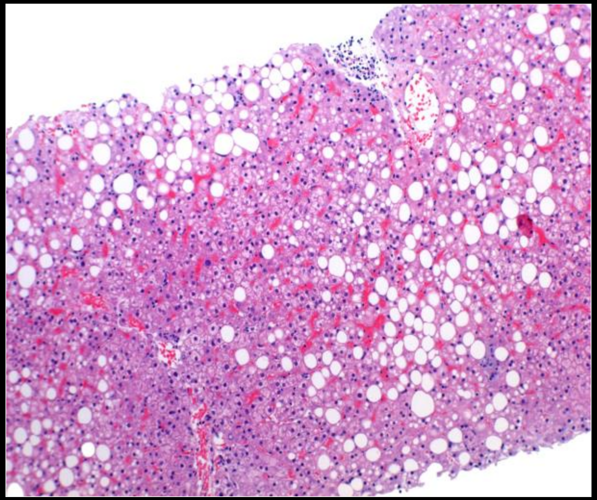
Steatosis



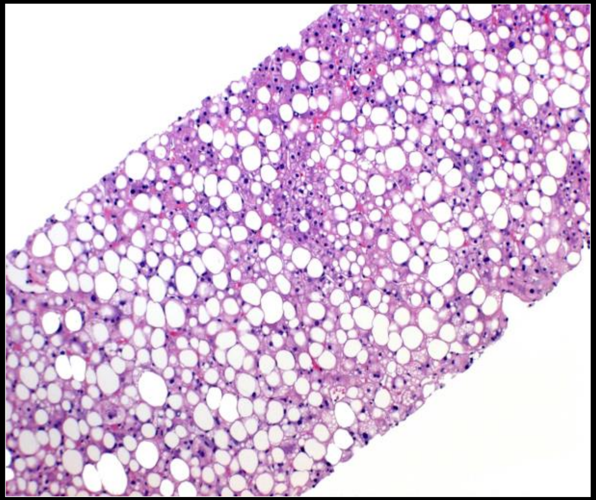
Minimal



Mild



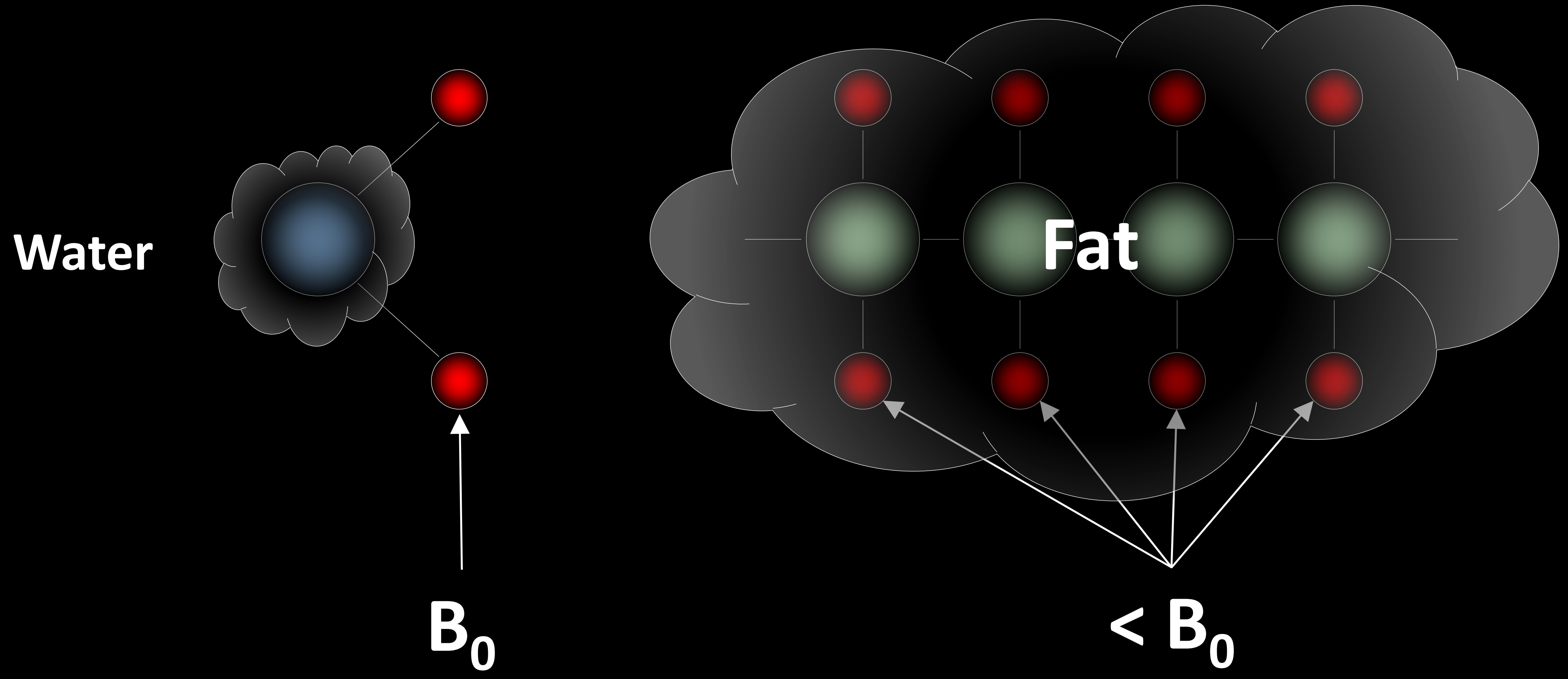
Moderate



Severe

How do we image Fat?

Chemical Shift



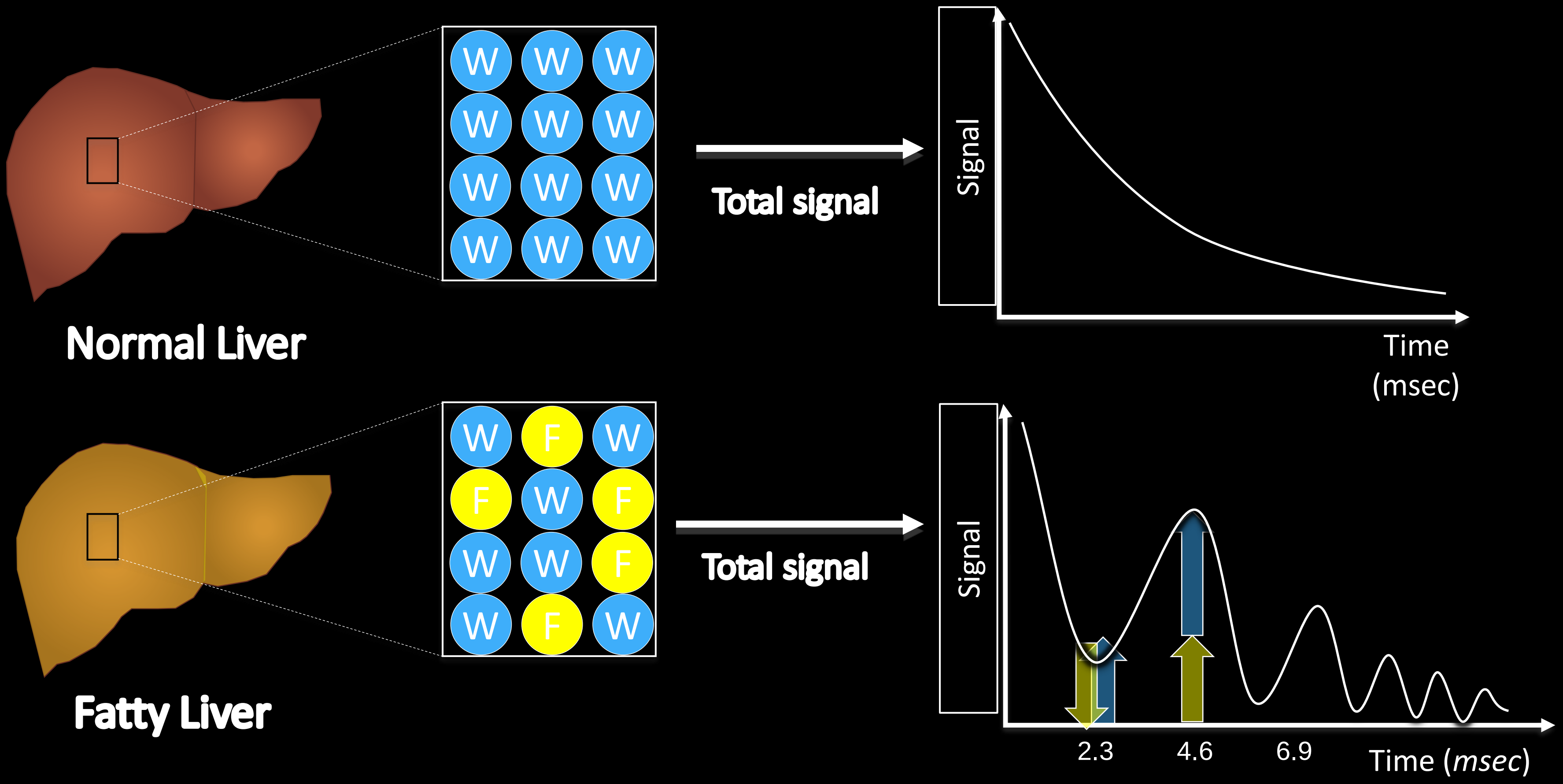
Precess fast

Precess a bit slower

Larmor Frequency differences

Chemical Shift

at B_0 = 1.5T



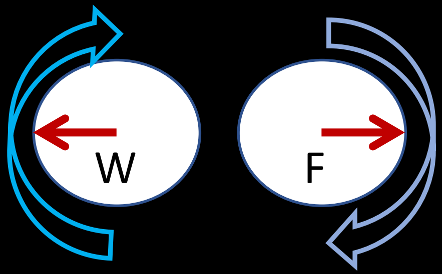
If Opposed → [Water – Fat]

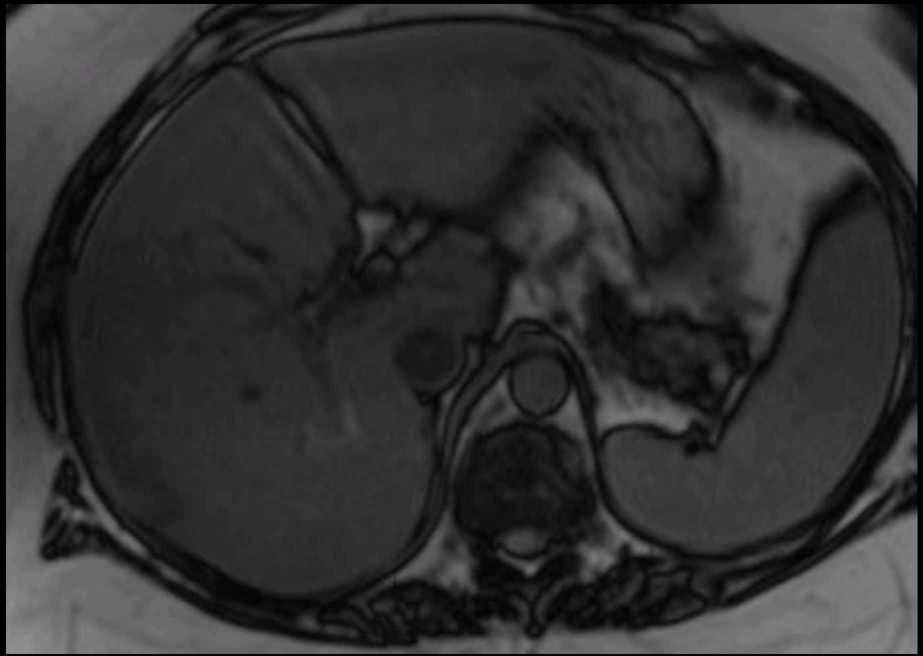
If In-phase → [Water + Fat]

Hood et al, RG 1999; Hashemi et al. MRI: the basics. Philadelphia, PA: Lippincott Williams & Wilkins,2004 : 190-199

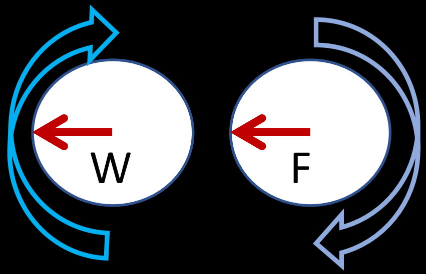
Dual Echo MRI

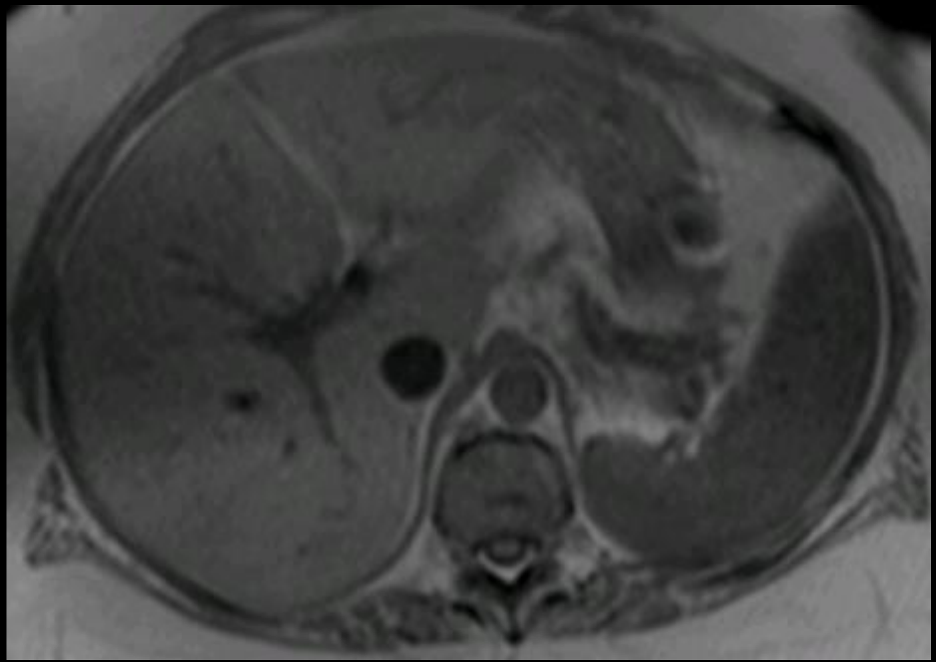
Out of phase



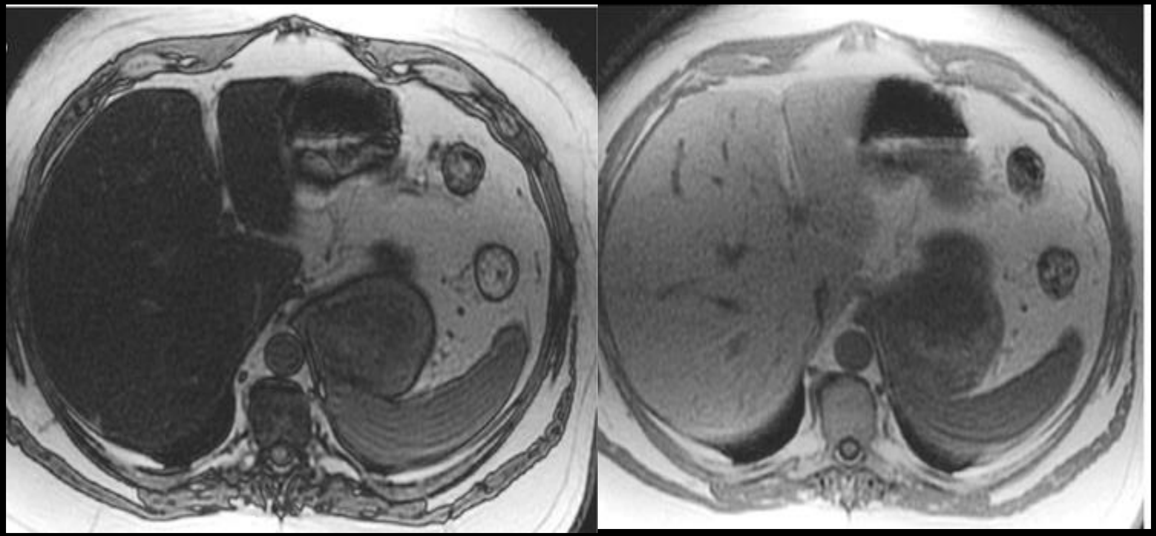


In phase

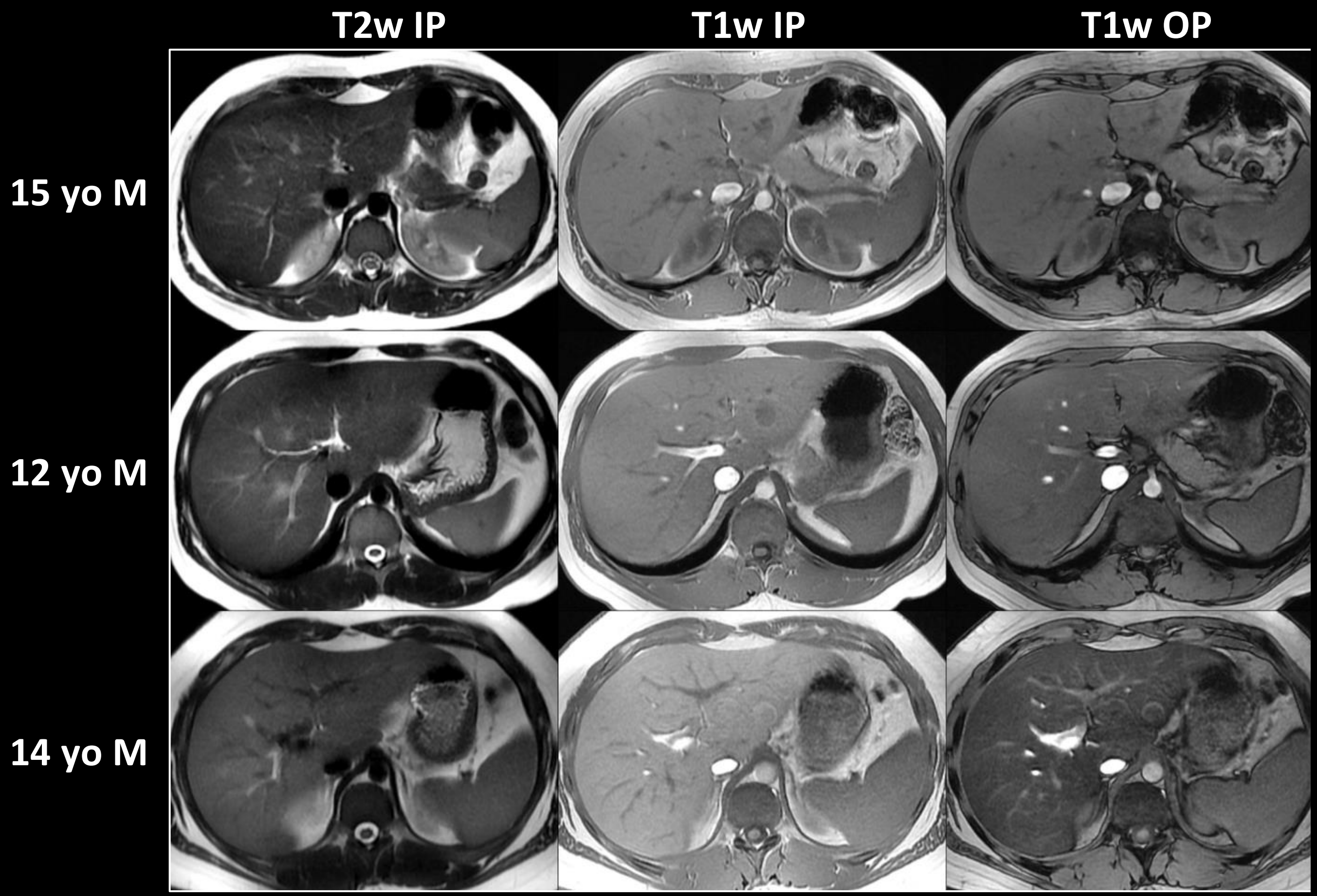




Loss of signal on out of phase due to fat

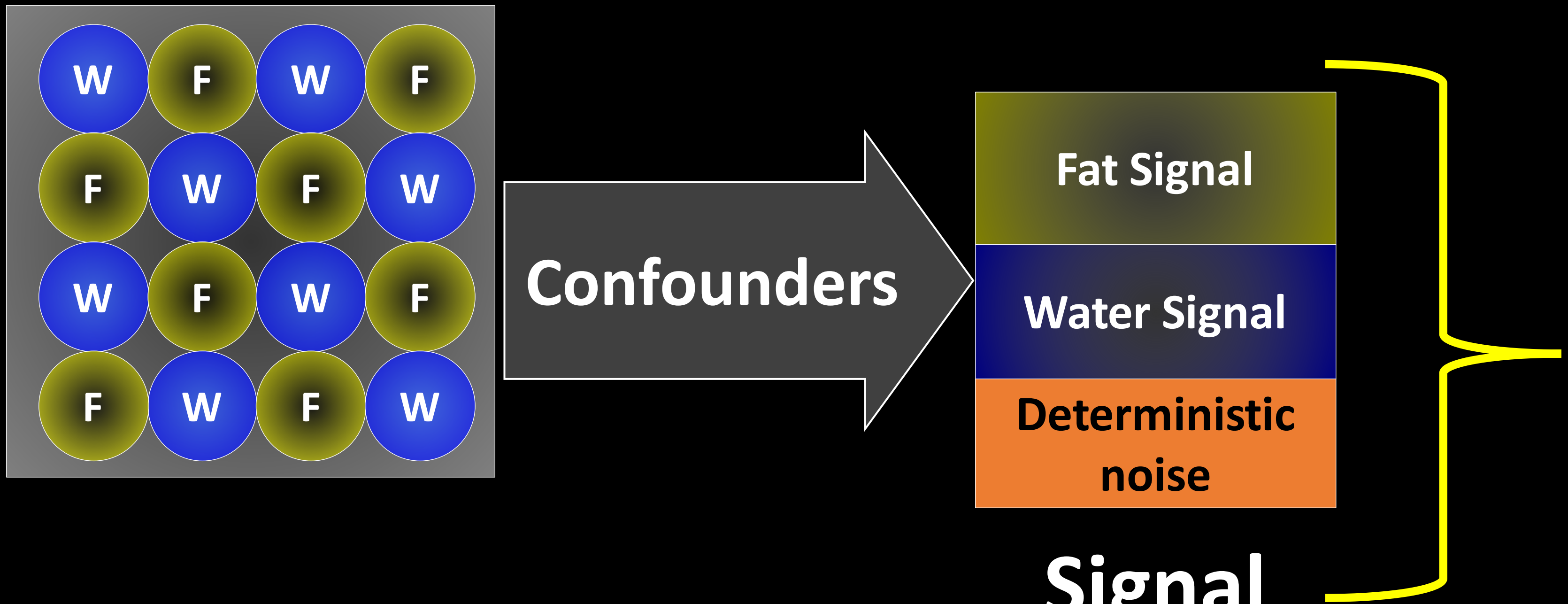


Conventional dual echo MRI



How much fat?

Not good for Quantification



True Tissue Fat Content

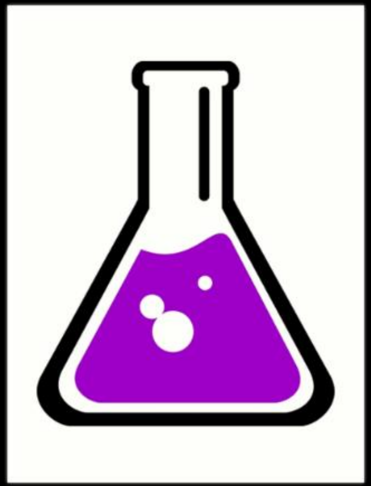
Signal Fat Fraction

Results are not pure

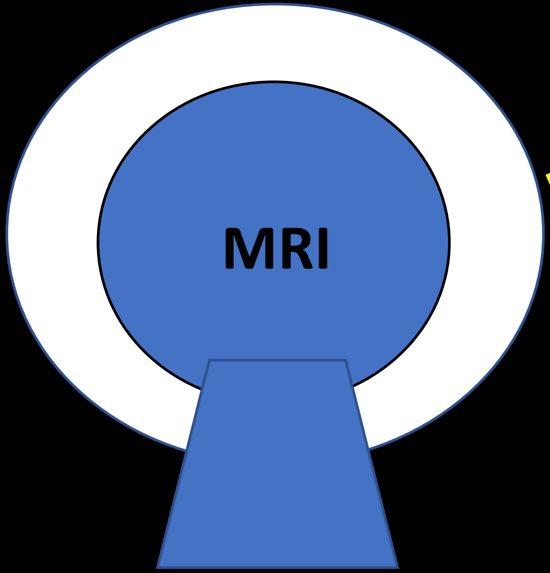
impacted by confounders

How to Quantify

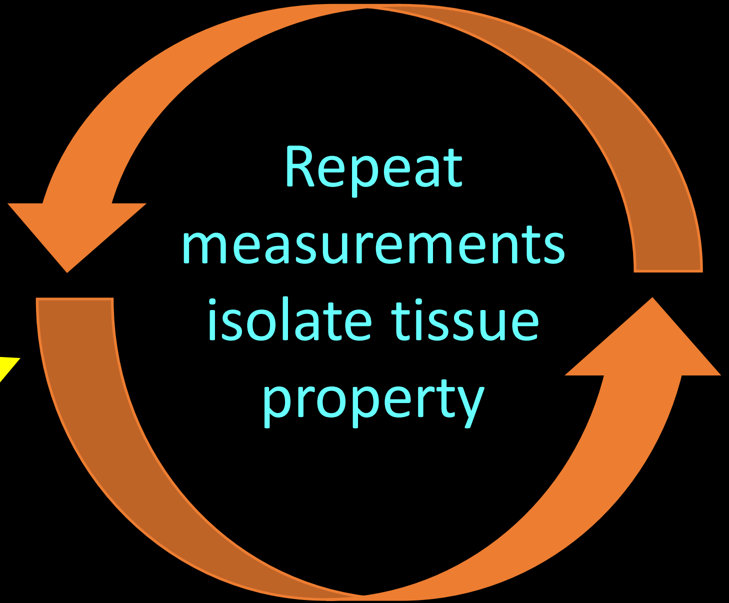
- MRI=signal intensity



Unknown parameter
-tissue property
-confounders



Known
parameters
(adjust TE)

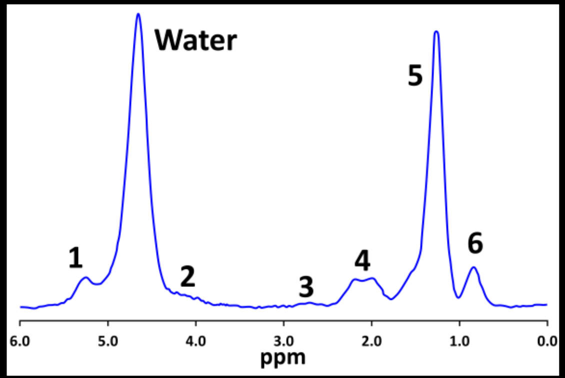


Quantitative data=
deterministic noise
+ tissue property

Overview of MR biomarkers-Curtis W, Radiology 2019

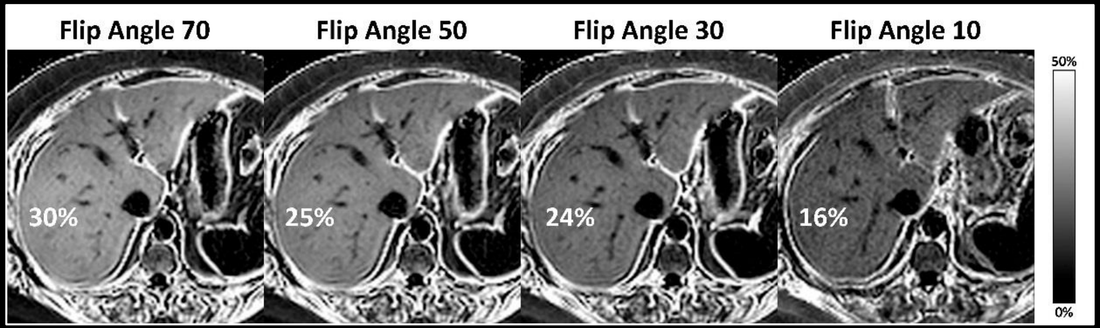
Confounders

- **Complicated interference pattern,**
  Different fat protons experience different magnetic fields

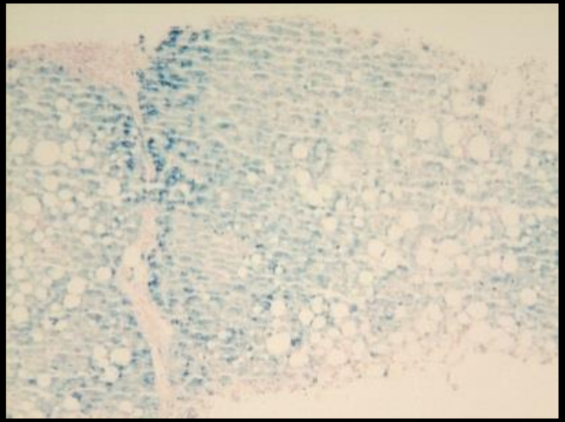


The solution: incorporate a typical fat spectrum

T_1 bias—fat has shorter T1 than water, T1-weighting amplifies fat signal



Solution: minimize T_1 bias via low FA or long TR



Iron causes T_2* decay

Solution: correct for decay by acquiring multiple echoes

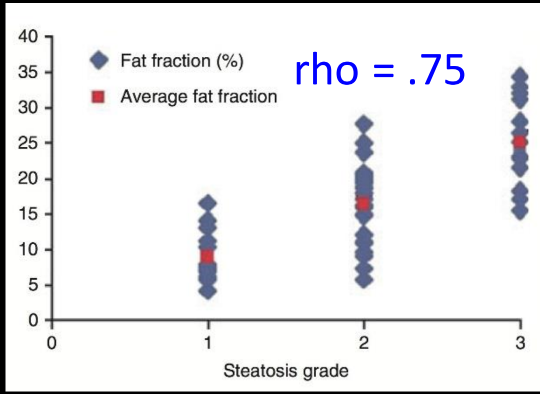
MRI-PDFF --- Quantitative Imaging Biomarker

- T_1 bias
- T_2 or T_2^* decay
- Multiple fat peaks
- Noise bias
- Eddy currents

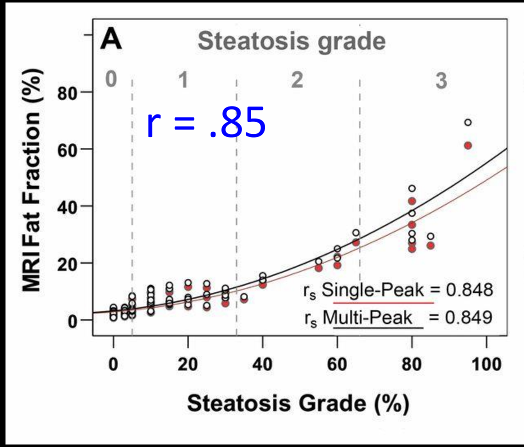
Magnitude MRI (first four items)

Complex MRI (all five items)

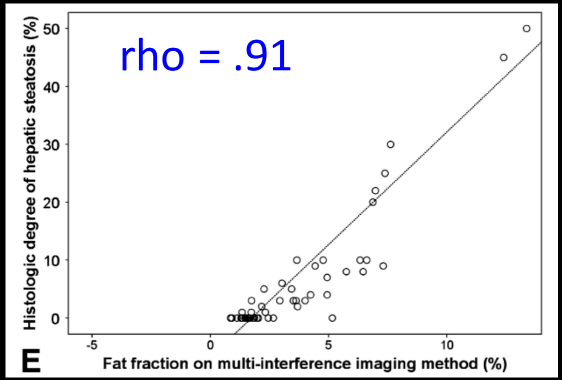
MRI-PDFF --- Correlates well with Histology



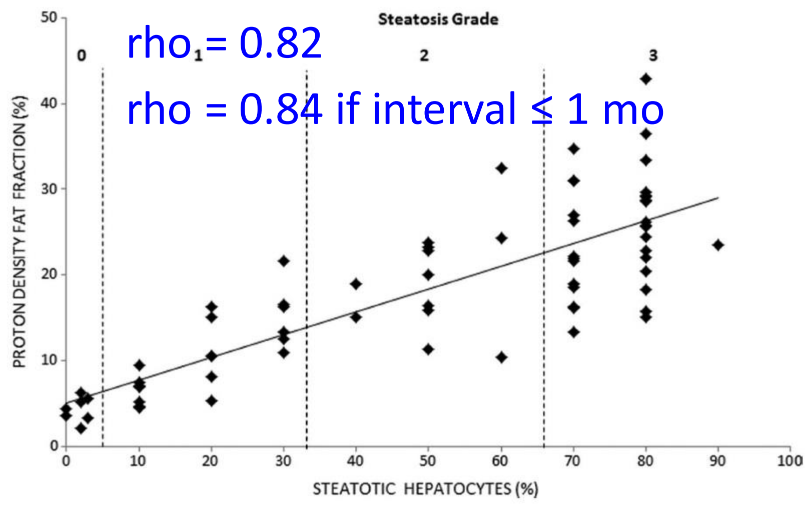
Permutt AP&T 2012
(NAFLD)



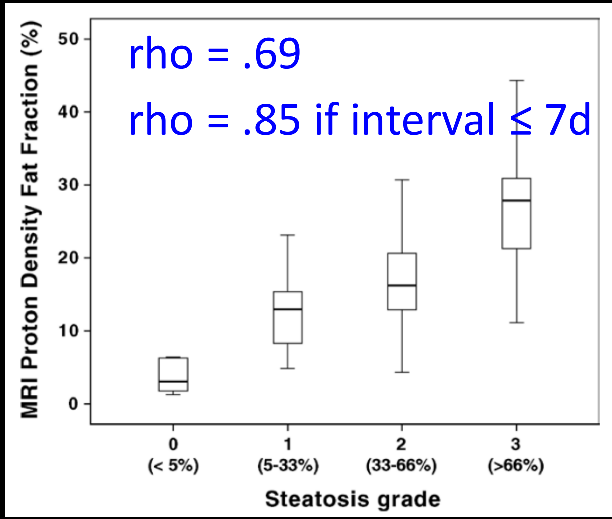
Kuhn et al Radiology 2012
(Mixed Liver Disease)



Kang et al Invest Radiology 2012
(Mixed Liver Disease)

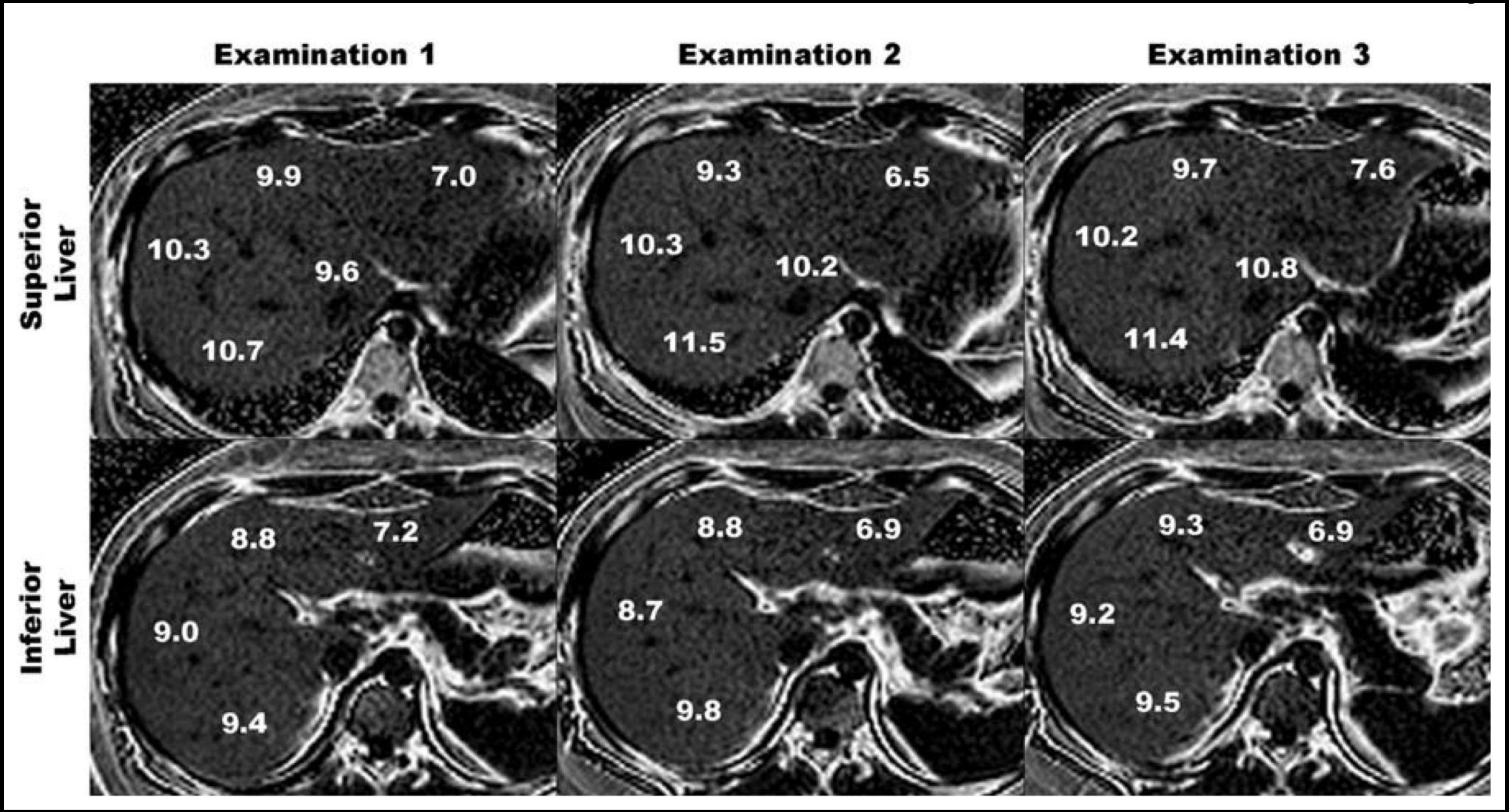


Idilman et al Radiology 2013
(NAFLD)



Tang et al Radiology 2013
(NAFLD: children & adults)

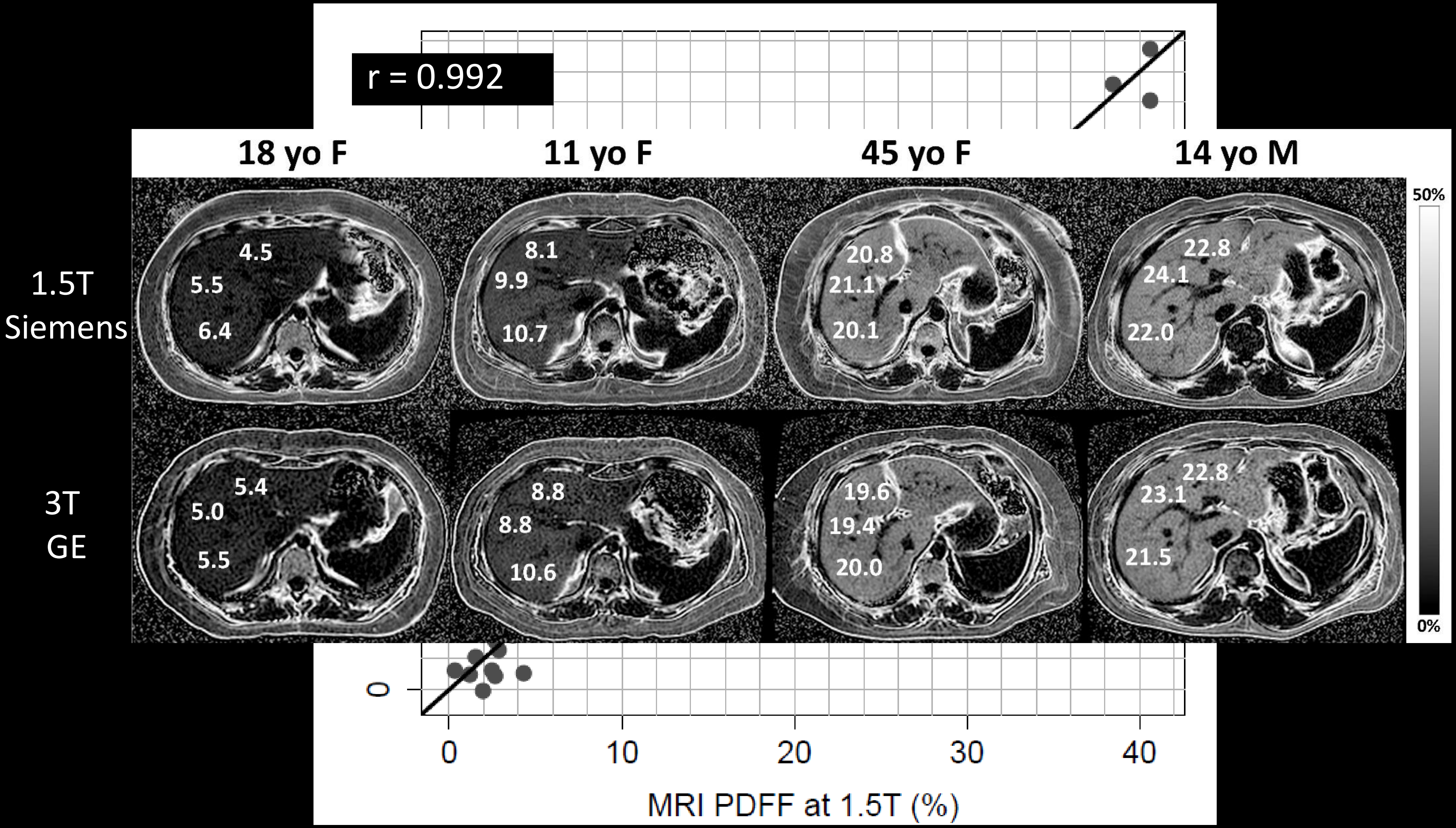
MRI-PDFF --- Repeatable



Negrette et al. JMRI 2013
Children & Adults with NAFLD

SD of repeated examinations = **0.24 to 0.62 % points**
ICC of repeated examinations = **0.992 to 0.999**

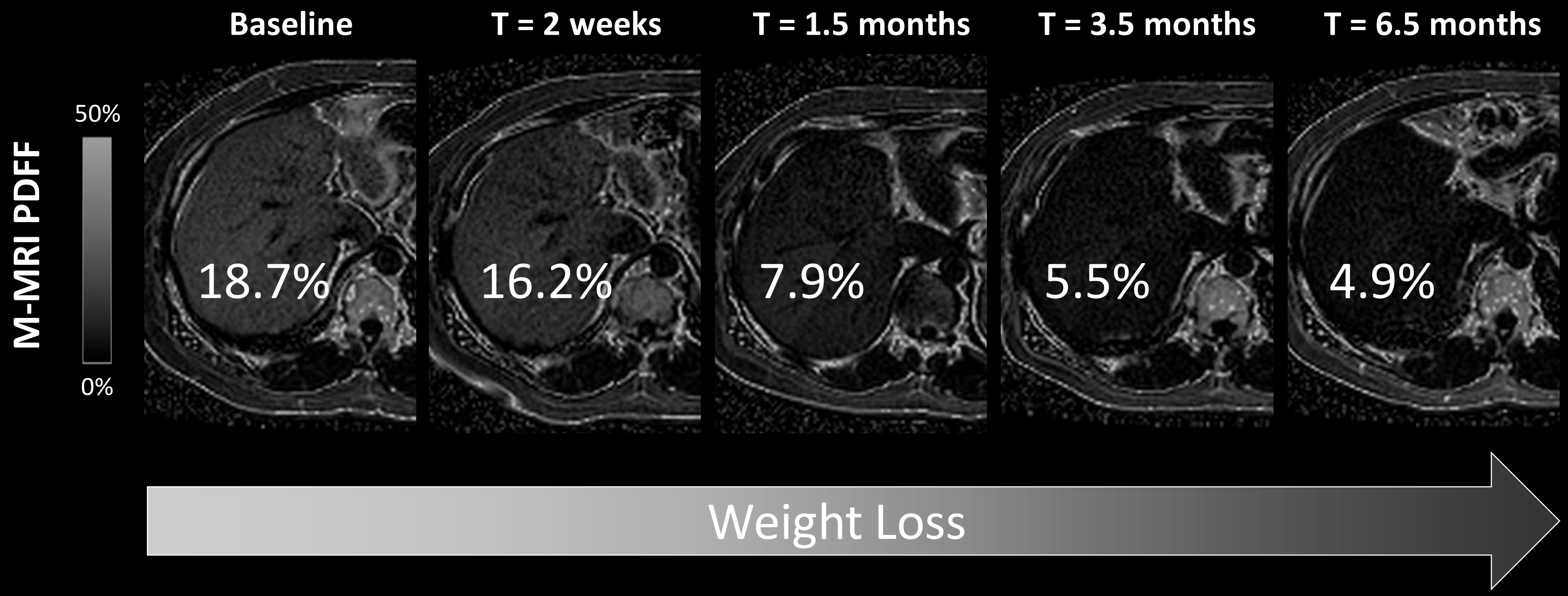
MRI-PDFF --- Reproducible across field strength



Kang et al. JMRI 2011
Children & Adults with NAFLD

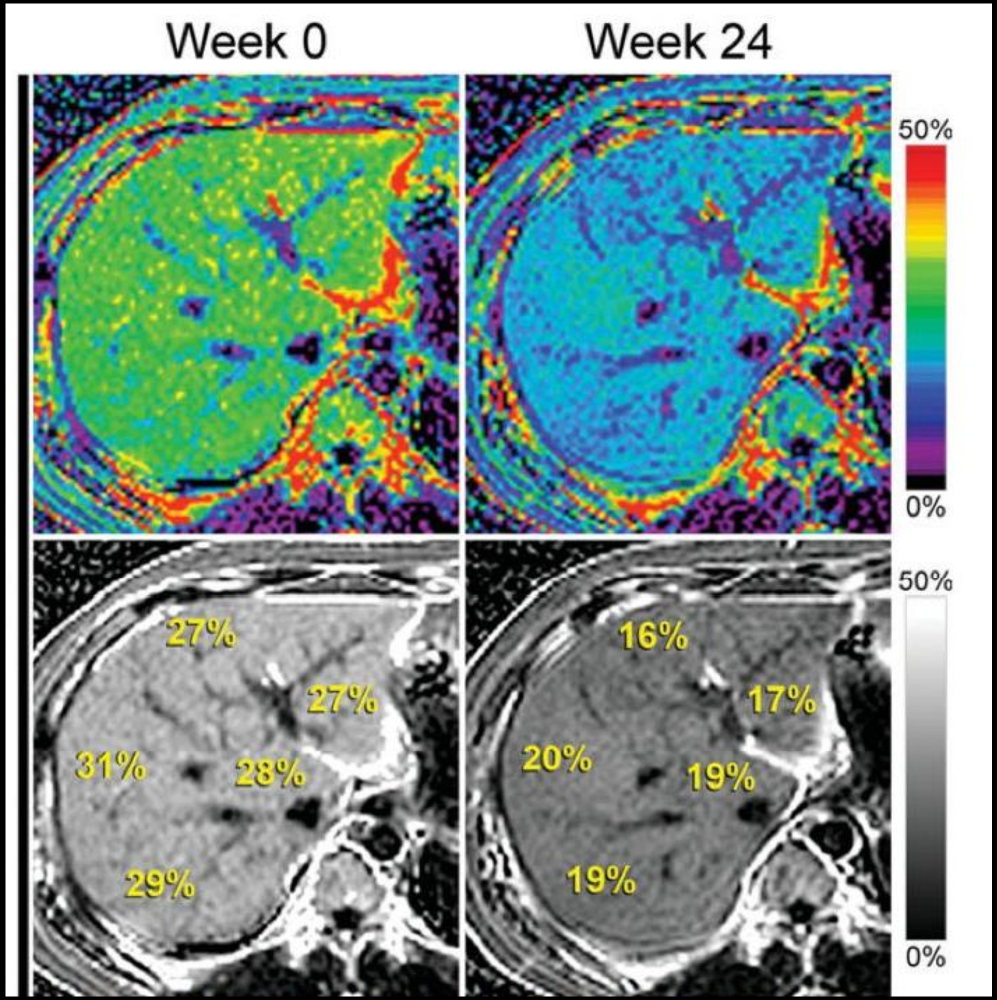
MRI-PDFF accurately quantifies steatosis in NAFLD

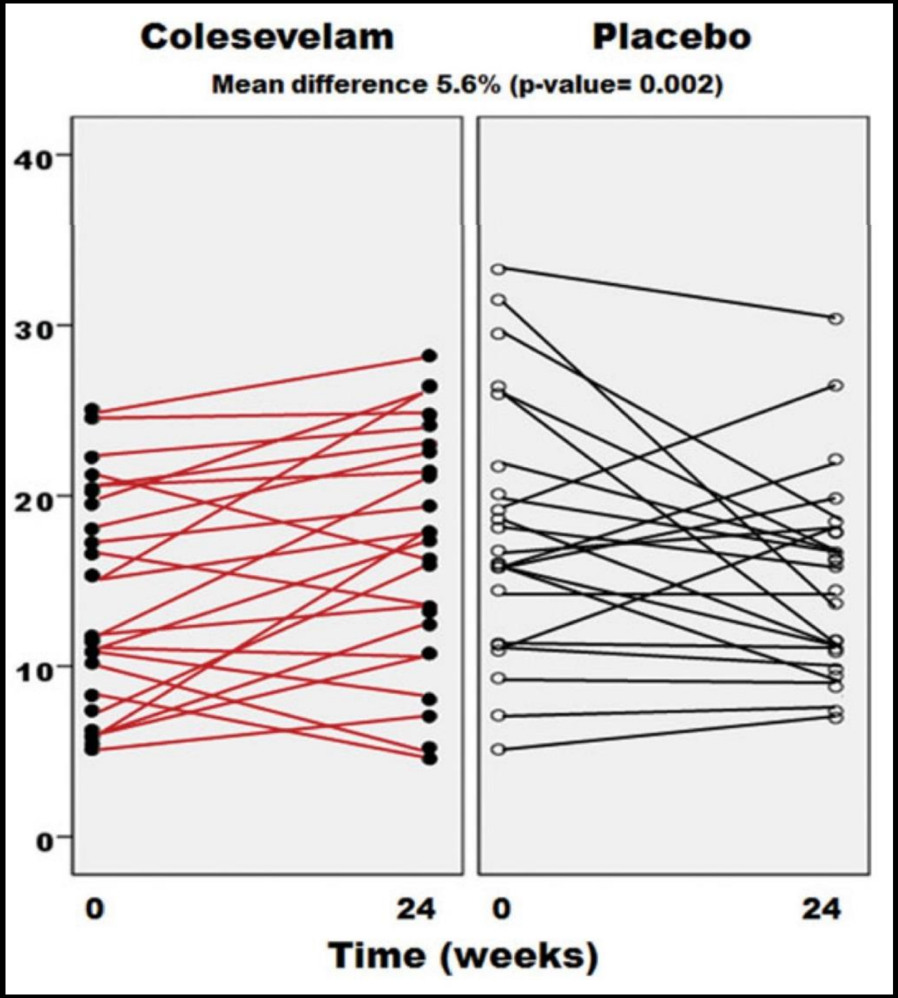
Over Entire Range



R01DK088925

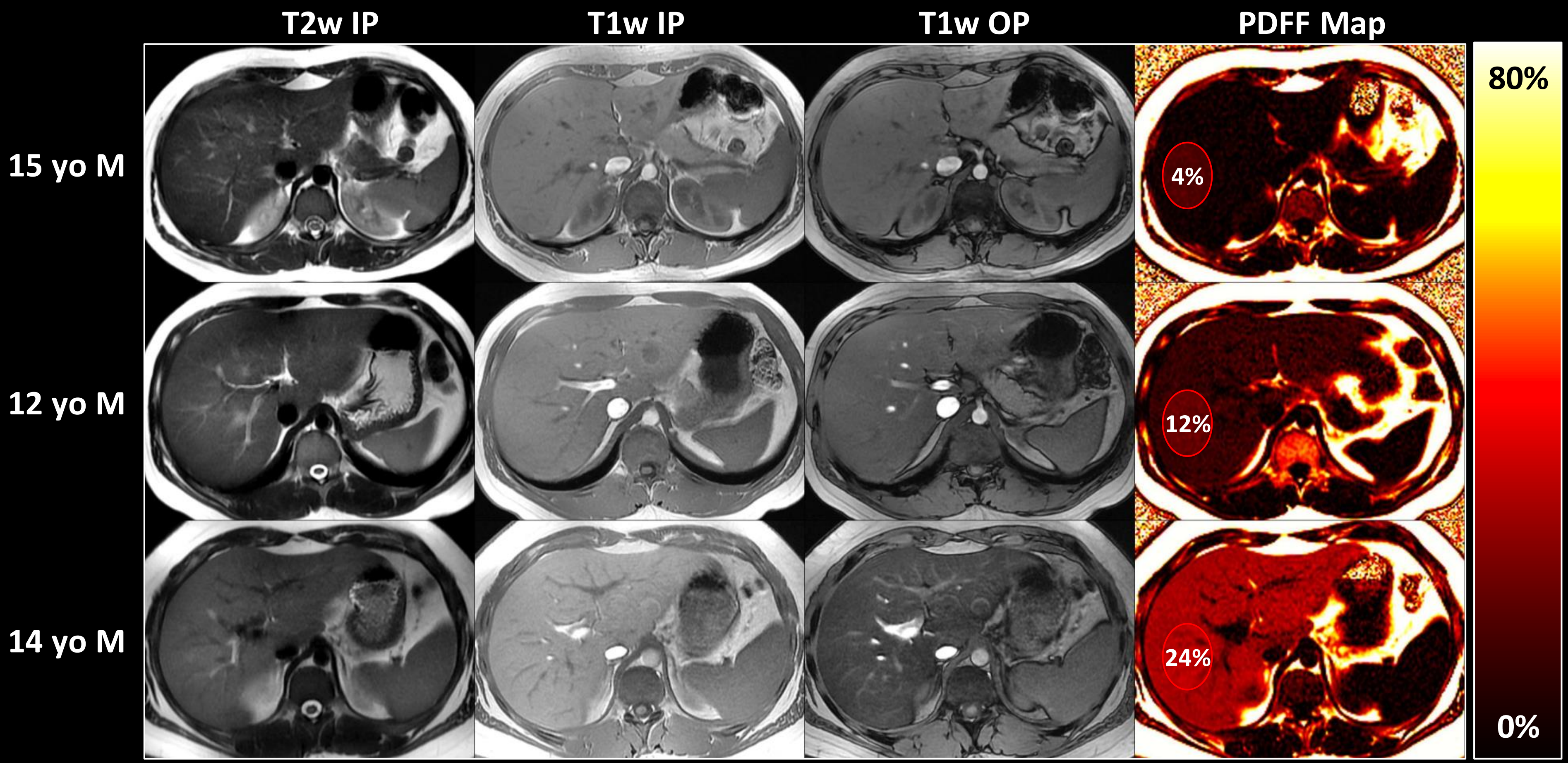
MRI-PDFF --- Endpoint in Clinical Trials in NASH





Le Hepatology 2012

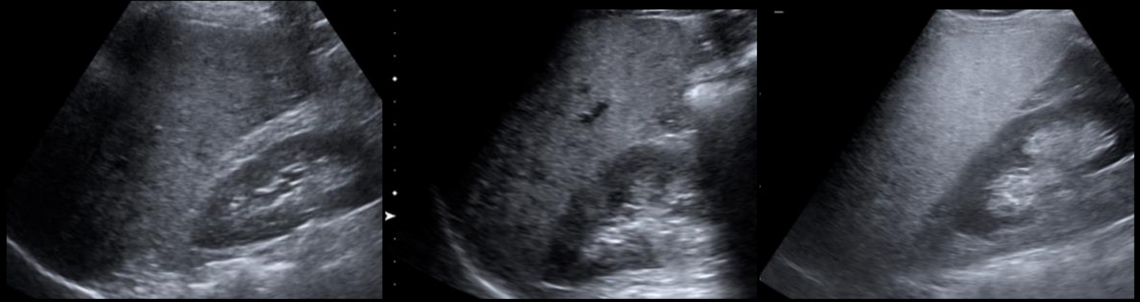
Conventional MRI *vs* MRI-PDFF



Standard Ultrasound

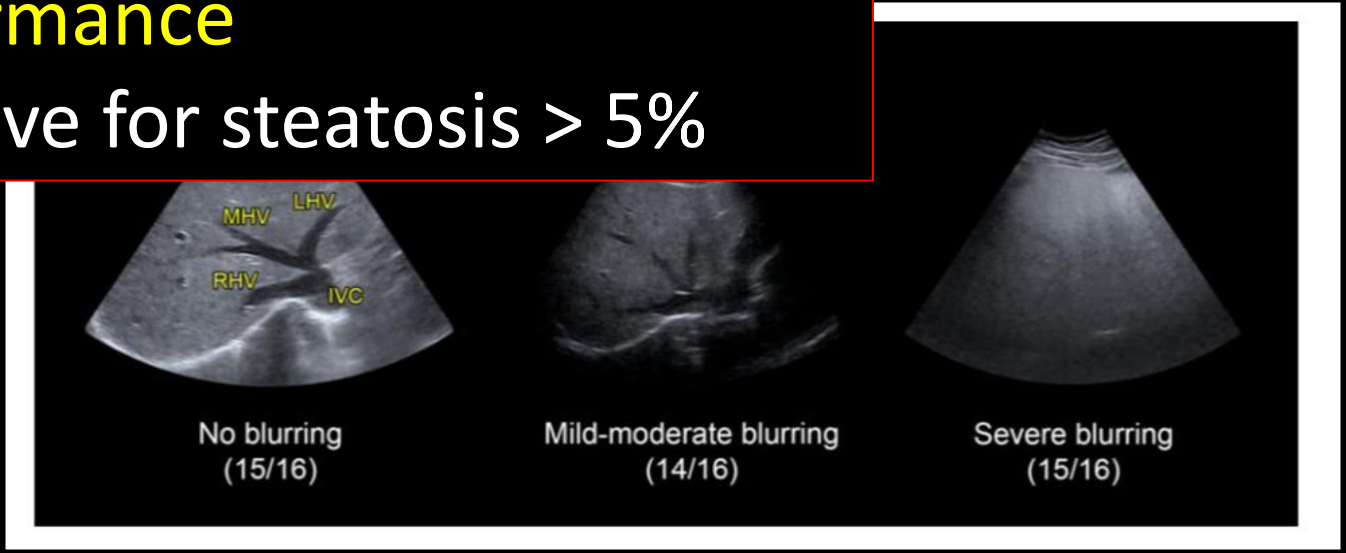
Hepatorenal Index

Steatosis Grade 1 | Steatosis Grade 2 | Steatosis Grade 3



Modest performance

50-62% sensitive for steatosis > 5%

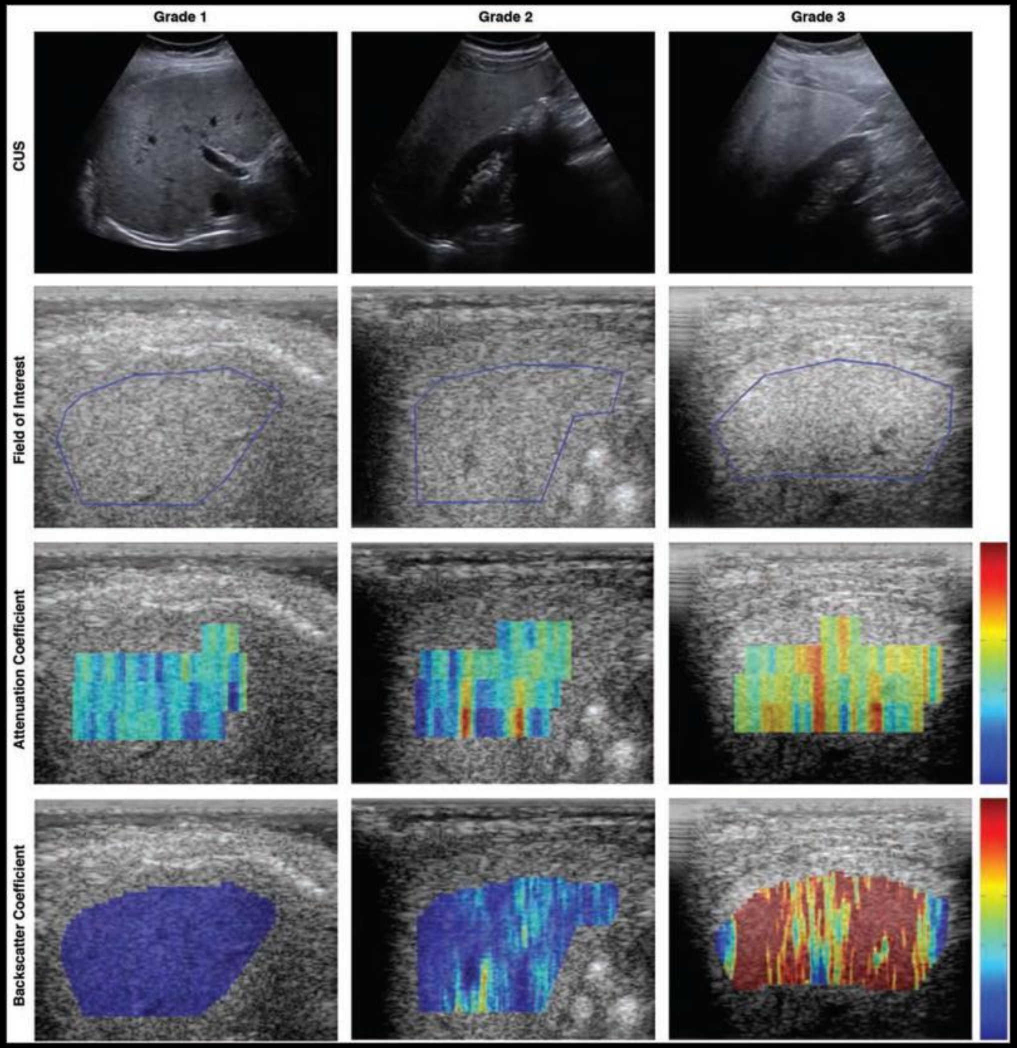


Ozturk A, Ultrasound in Medicine & Bio, 2018

Hong CW, Abdom Radiol 2019

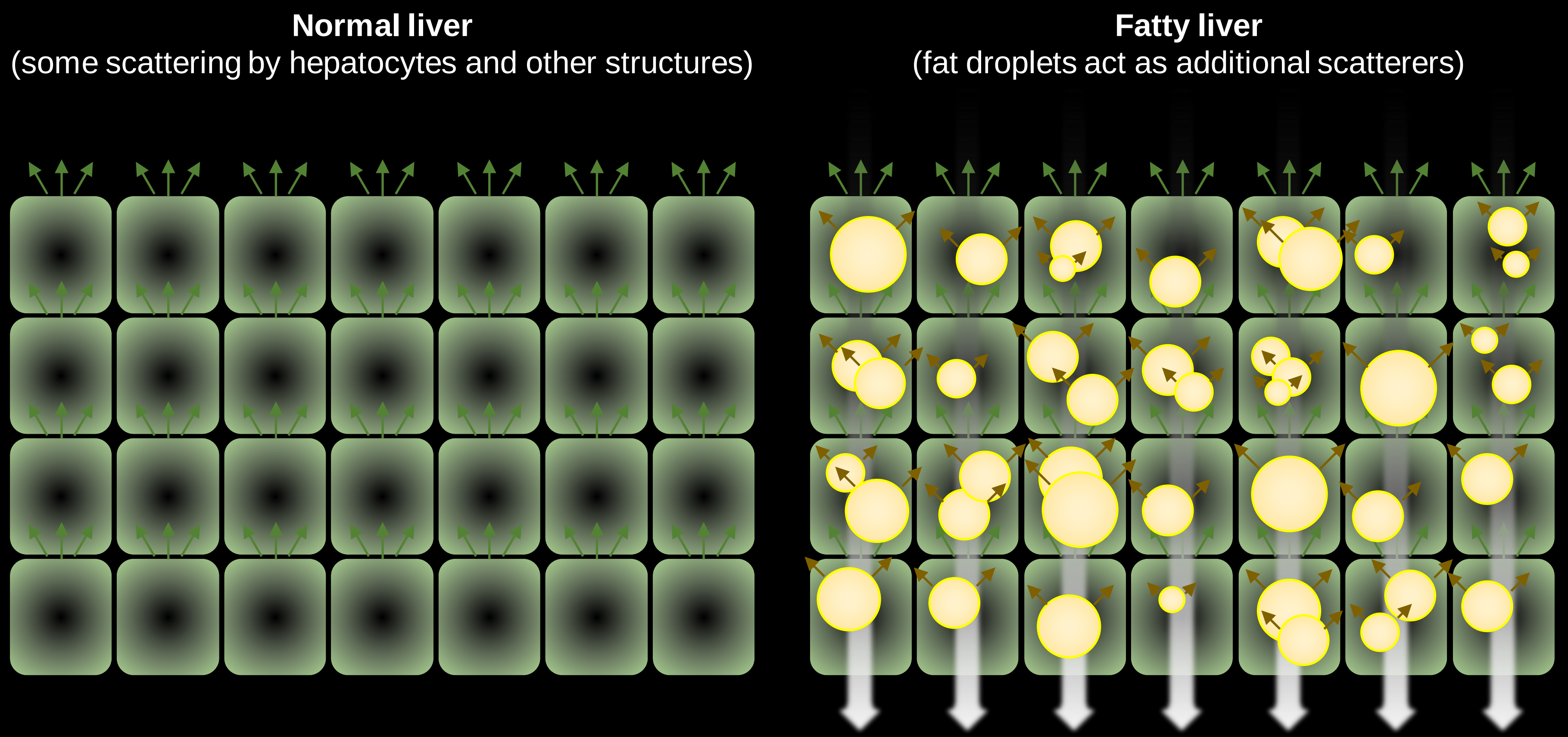
Quantitative US

- Attenuation coefficient
- -energy loss in tissue
- Backscatter coefficient
- -sound waves returning
- Speed of sound
-



Paige J, AJR 2017

Concept: Fat droplets scatter and attenuate the ultrasound beam



Attenuation Imaging on US systems

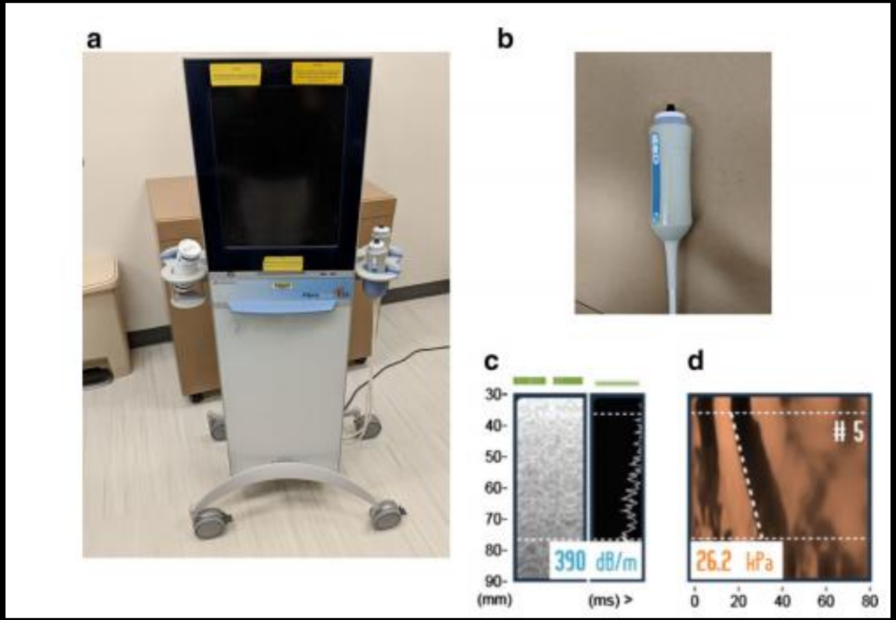
- ATI- Aplio i-series Canon
- ATT-Hitachi
- UGAP-GE systems
- UDFF-Siemens systems
- ATT Plus-Hologic
- TAI-Samsung Medison

Values above 0.5-1.1 dB/cm/MHz are abnormal

Potential confounders: fibrosis, etiology, fasting state, distribution of fat, technical parameters

Controlled Attenuation Coefficient (CAP)

- Measured on VCTE machine-since 2010
- Variable thresholds reported
- AUC 0.82 for S>0, 0.75 for S> 1
- Confounders: CLD etiology, diabetes, BMI, AST, gender

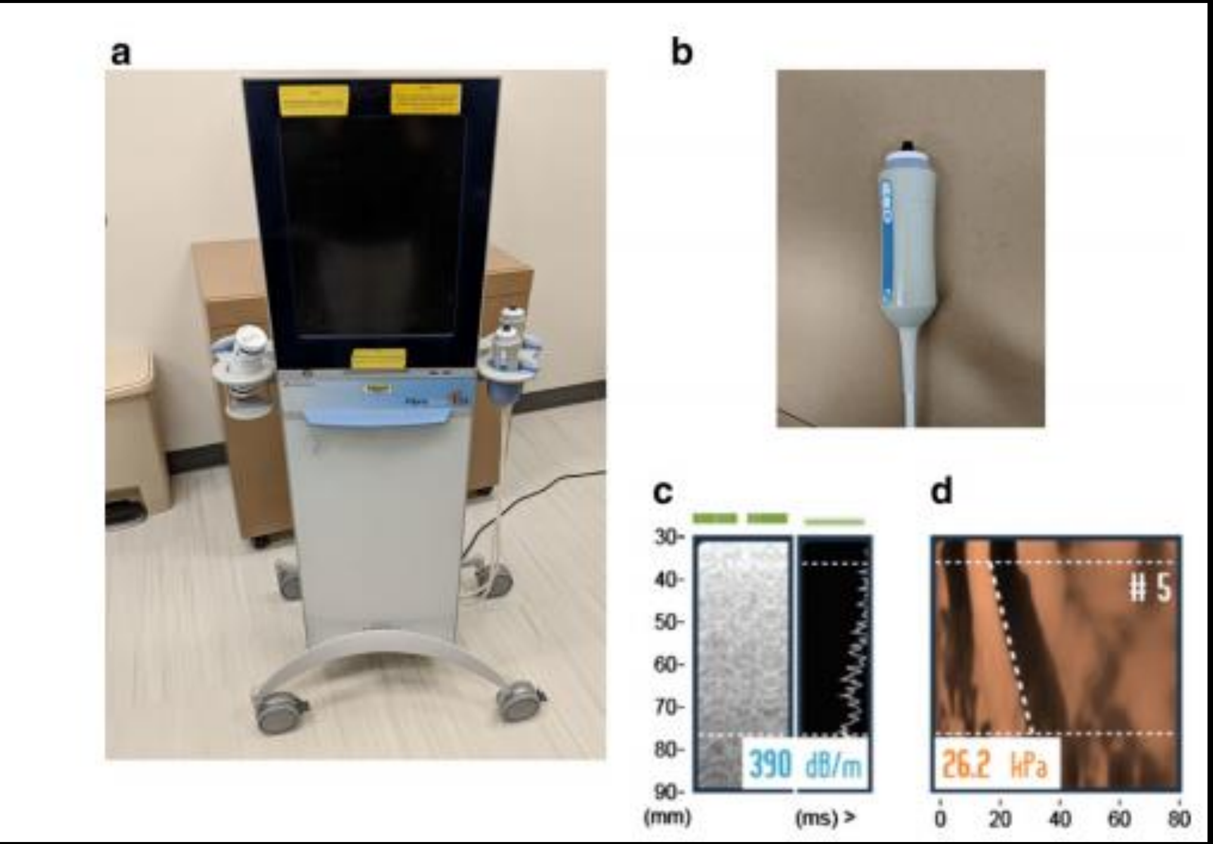


Petroff D, Lancet gastroenterol Hepatol 2021

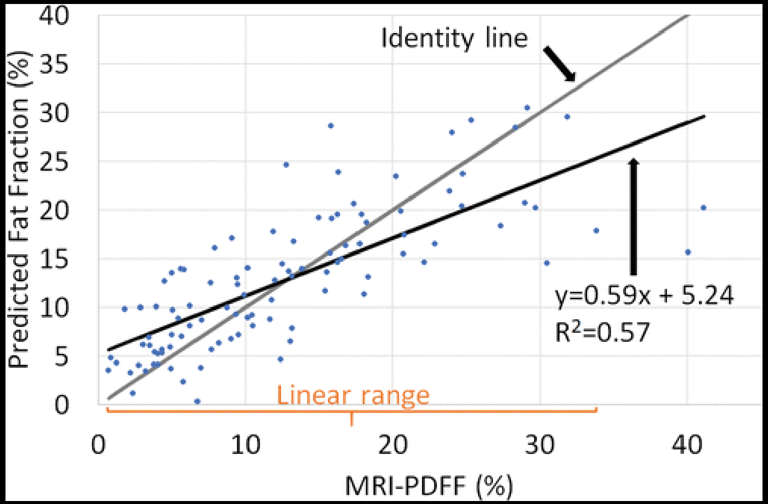
Wallpapersden.com

Improved CAP

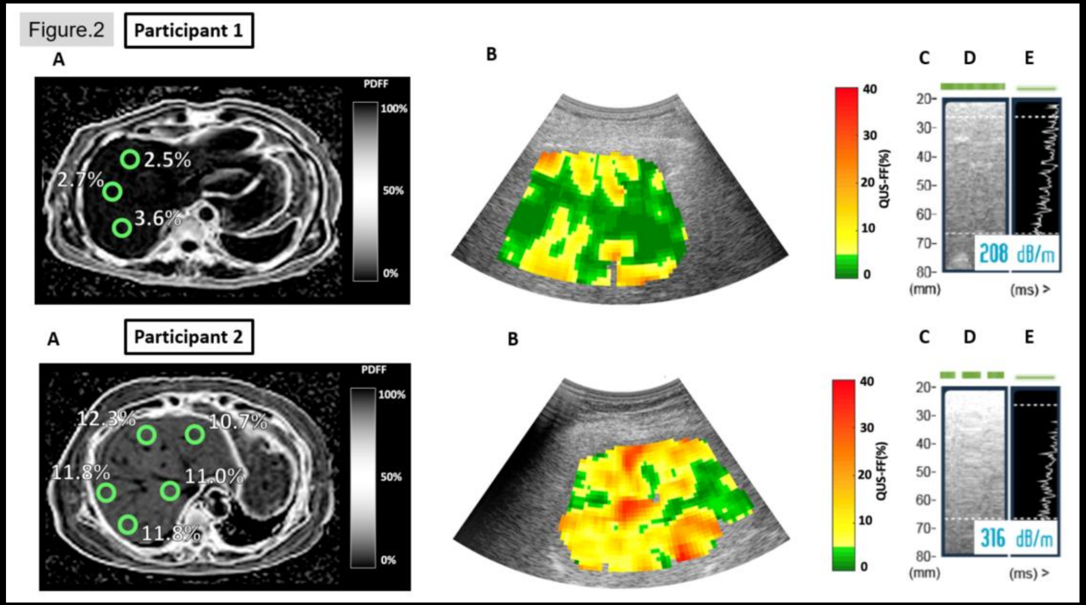
- New "Smart Exam" released in 2020

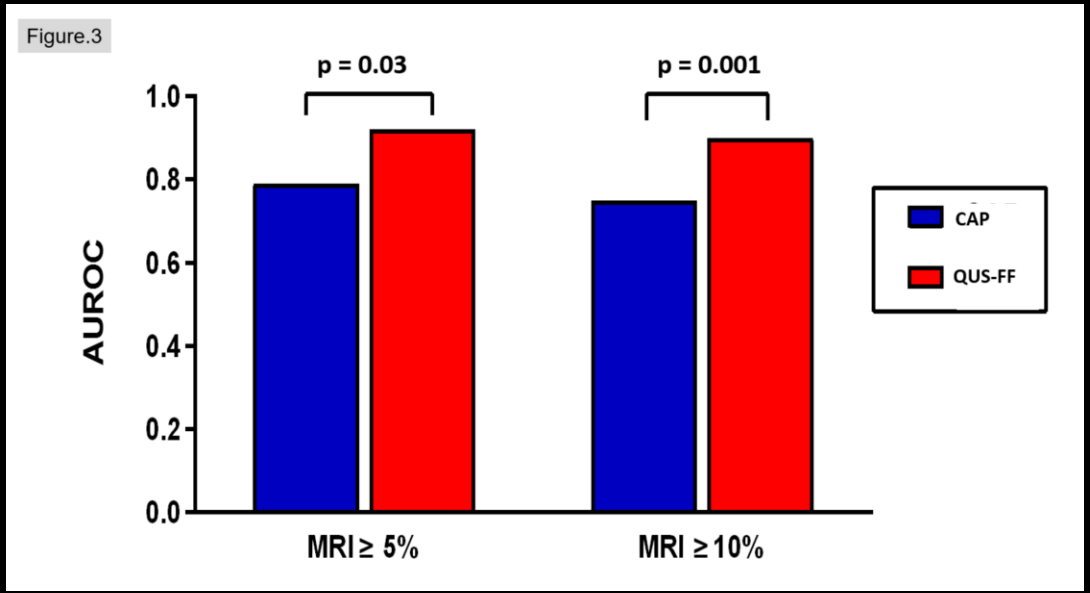


QUS FF



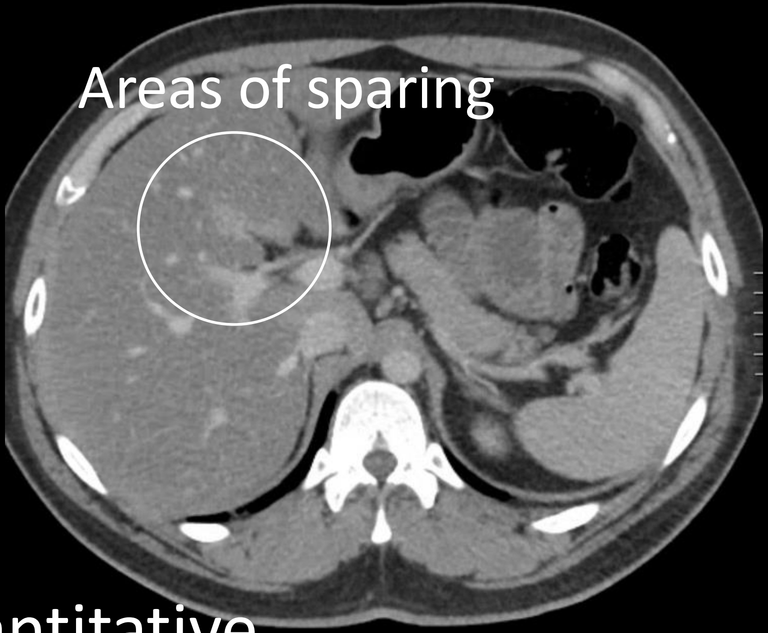
Han, Radiology 2020

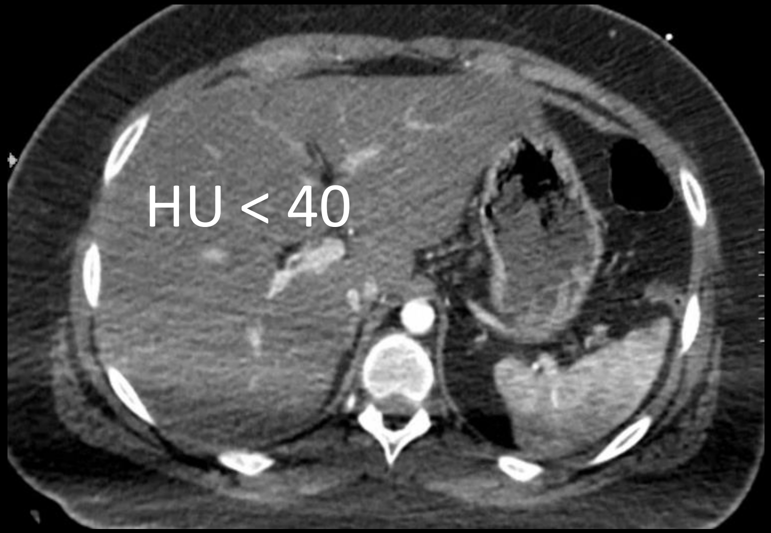




Sirlin et al, unpublished data

Identifying Fat on CT

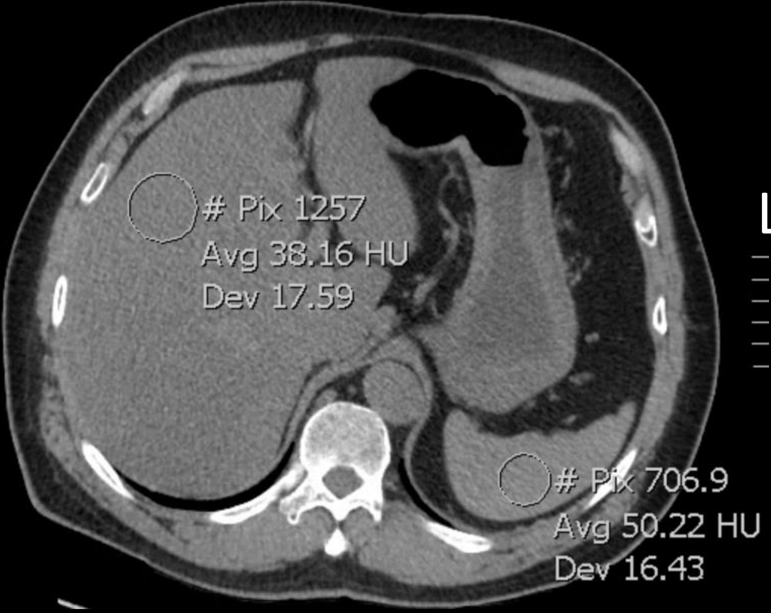




CT not quantitative

Not accurate for mild steatosis

Dependent on tube voltage



Liver HU-Splenic HU

Byun J, *Eur Radiol* 2019

Table 2 CT_{L-S} cut-off values and their ability to diagnose hepatic steatosis in the development cohort

From: CT indices for the diagnosis of hepatic steatosis using non-enhanced CT images: development and validation of diagnostic cut-off values in a large cohort with pathological reference standard

Diagnostic settings	Subjects who underwent CT at 120 kVp (*n* = 2733)				Subjects who underwent CT at 100 kVp (*n* = 579)			
	CT_{L-S} cut-off values*	Sensitivity	Specificity	Accuracy	CT_{L-S} cut-off values*	Sensitivity	Specificity	Accuracy
Diagnosis of HS ≥ 5%								
With 95% specificity	1.3 (0.8, 2.1)	33.9% (403/1188)	95.0% (1469/1545)	69.0% (1872/2733)	3.7 (2.7, 4.2)	38.7% (97/251)	95.1% (312/328)	70.6% (409/579)
With 95% sensitivity	13.6 (12.9, 14.0)	95.0% (1129/1188)	15.7% (242/1545)	50.2% (1371/2733)	15.2 (14.1, 16.6)	95.2% (239/251)	19.2% (63/328)	52.2% (307/579)
Diagnosis of HS > 33%								
With 95% specificity	− 2.1 (− 2.9, − 1.2)	64.0% (165/258)	95.0% (2358/2475)	92.0% (2523/2733)	− 3.9 (− 4.4, 0.8)	90.0% (27/30)	97.6% (536/549)	97.2% (563/579)
With 95% sensitivity	7.6 (6.0, 9.0)	95.3% (246/258)	54.3% (1344/2475)	58.2% (1590/2733)	1.6 (− 4.4, 1.8)	96.7% (29/30)	91.1% (500/549)	91.3% (529/579)

Unless otherwise specified, data are percentages, with the number of subjects used to calculate the percentage in parentheses. Percentages were rounded

HS hepatic steatosis

*Data are CT_{L-S} cut-off values, and data in parentheses are 95% confidence intervals. Dual CT_{L-S} cut-off values were determined for either a highly specific diagnosis of HS (with 95% specificity) or a reliable elimination of HS (with 95% sensitivity)

CT thresholds

- Threshold 48HU on non-con CT
- 100% specific (PDFF $\geq$ 30%)
- ~ 55% sensitivity

- L-S difference -19 on non-con CT
- optimal for $\geq$ 30% steatosis

https://en.wikipedia.org/wiki/Rotary_dial

Kodama Y, AJR 2007; Kim DY, Eur Radiol 2010

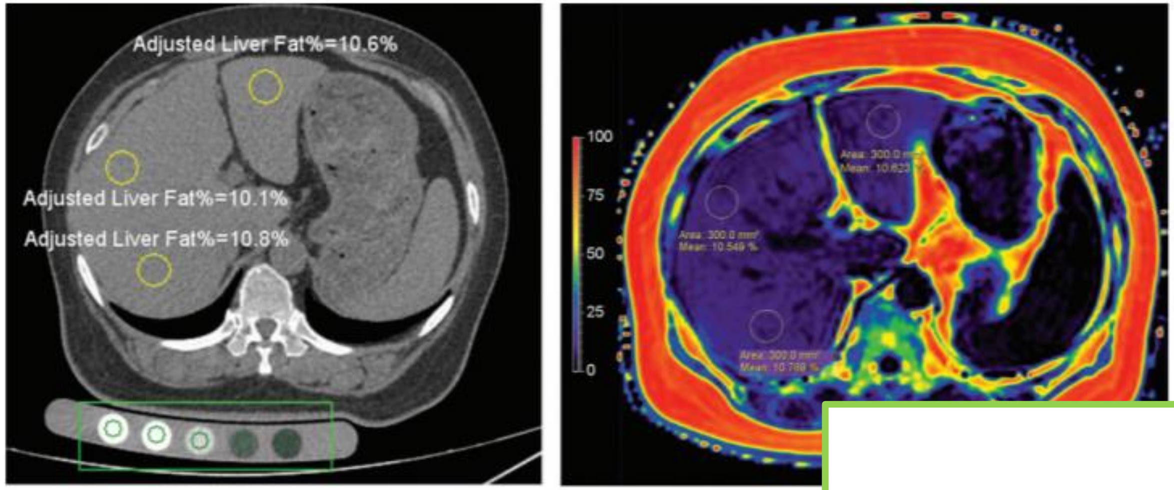
What is on the horizon?

Wallpapersden.com

Radiology
ORIGINAL RESEARCH • GASTROINTESTINAL IMAGING

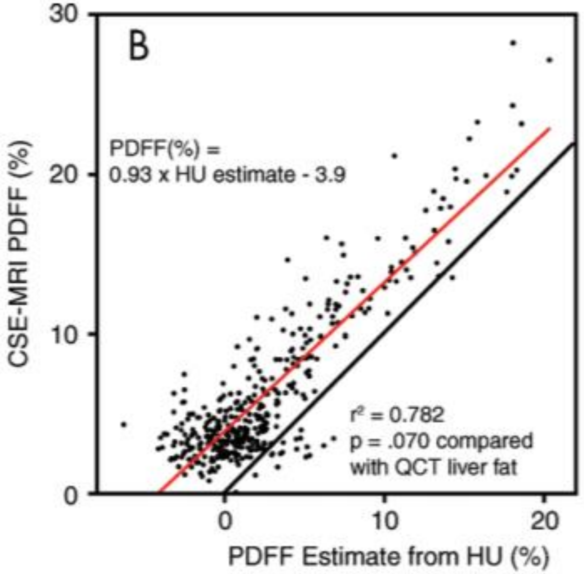
Liver Fat Content Measurement with Quantitative CT Validated against MRI Proton Density Fat Fraction: A Prospective Study of 400 Healthy Volunteers

Zhe Guo, MD • Glen M. Blake, PhD • Kai Li, MD • Wei Liang, BS • Wei Zhang, BS • Yong Zhang, MD • Li Xu, MD • Ling Wang, MD • J. Keenan Brown, PhD • Xiaoguang Cheng, MD • Perry J. Pickhardt, MD



a. b.

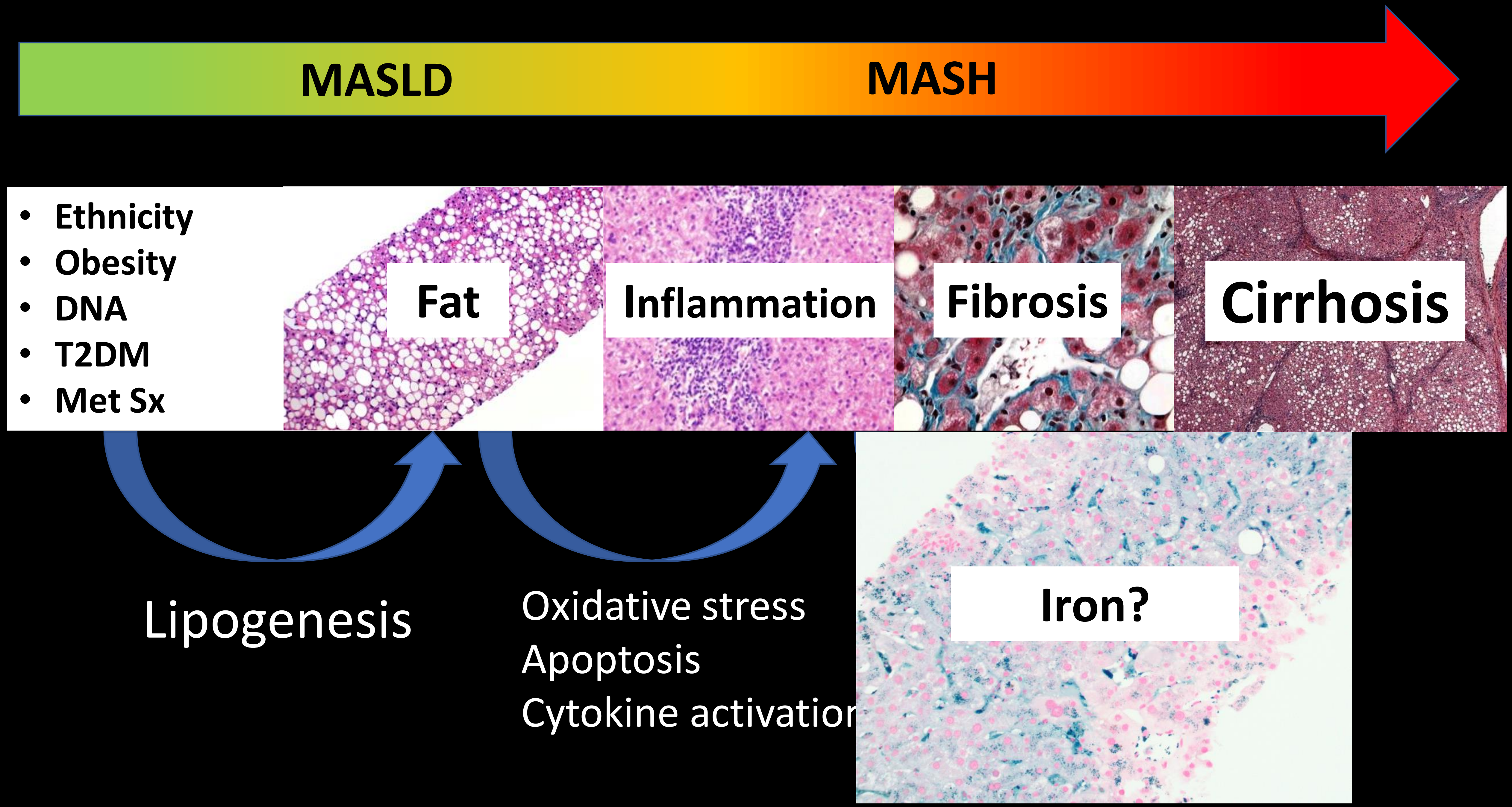
Figure 1: Liver fat content measurement with **(a)** quantitative CT and **(b)** chemical s… woman. Three regions of interest (ROIs) were placed in the peripheral areas of the left l… posterior lobe of the liver, and the average of the three ROIs was chosen for the liver fat…



$$\text{Adjusted quantitative CT liver fat} = \left(\frac{CTFF'}{CTFF' + \alpha(1 - CTFF')} \right)$$

What about DECT?

- may add value with virtual non-con
- -otherwise, no clear advantage over simple HU measures


MASLD
MASH
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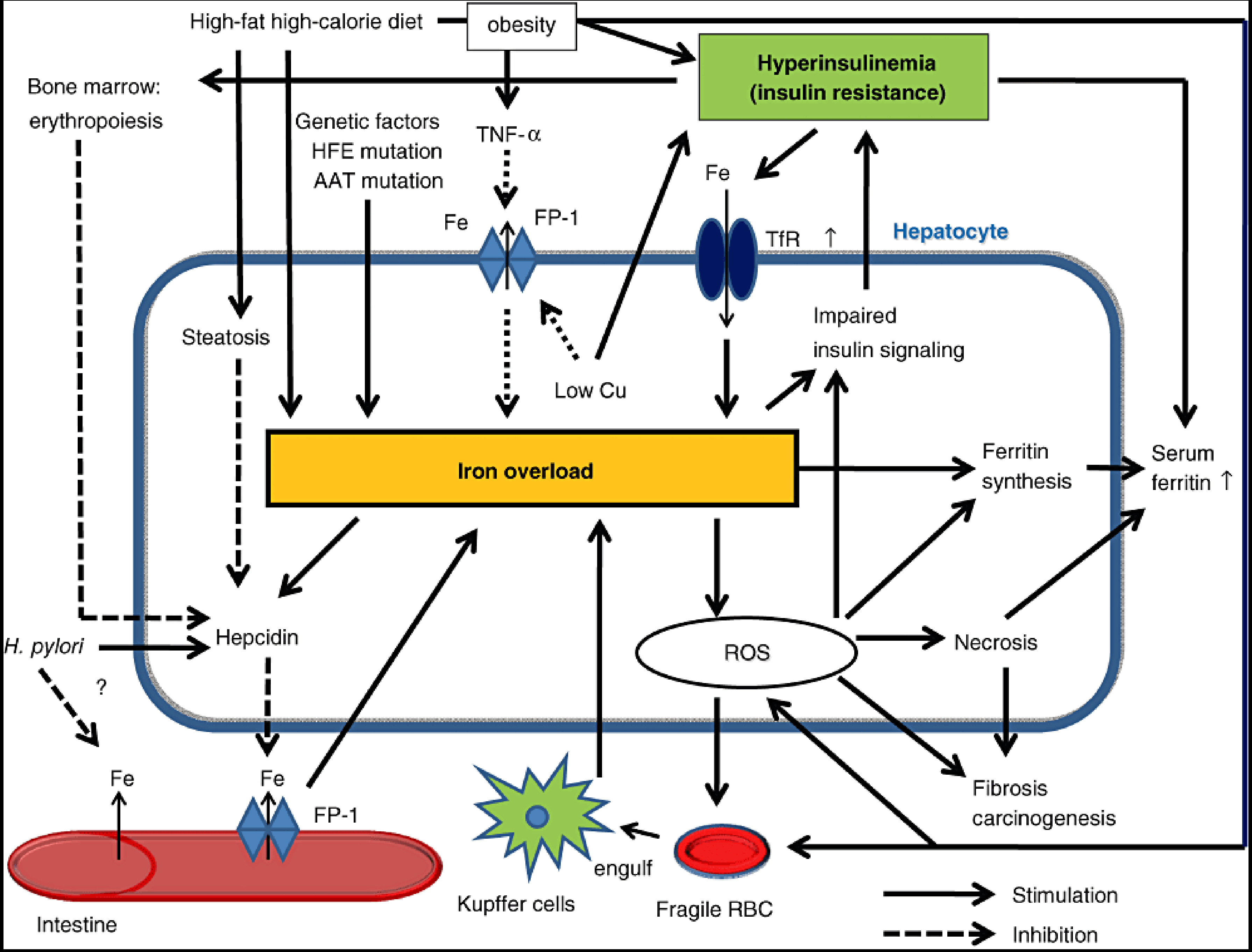
Fibrosis
Cirrhosis
Lipogenesis
Oxidative stress
Apoptosis
Cytokine activatior
Iron?

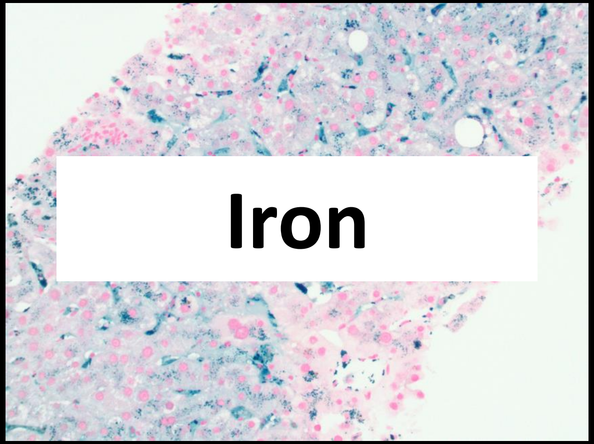
Iron in MASH

- Uptake in liver increases in MASLD

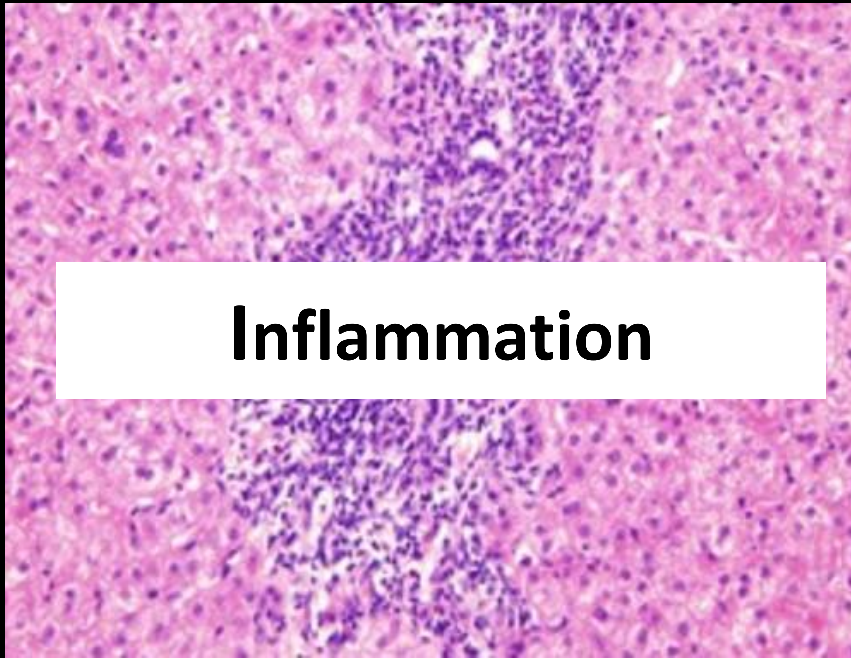


Sumida Y, Liv Int 2009

- **Obesity**
- **DNA**
- **T2DM**
- **Met Sx**



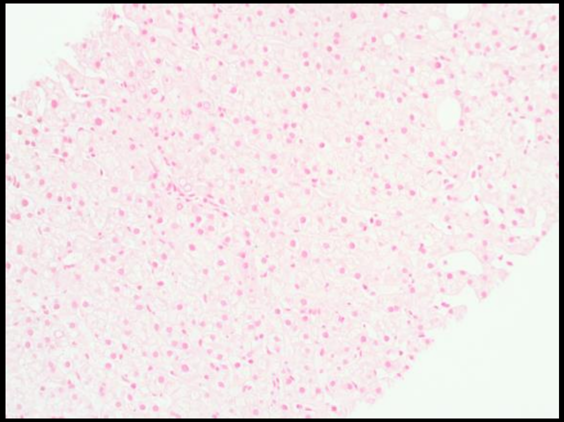
Oxidative stress
Apoptosis
Cytokine activation



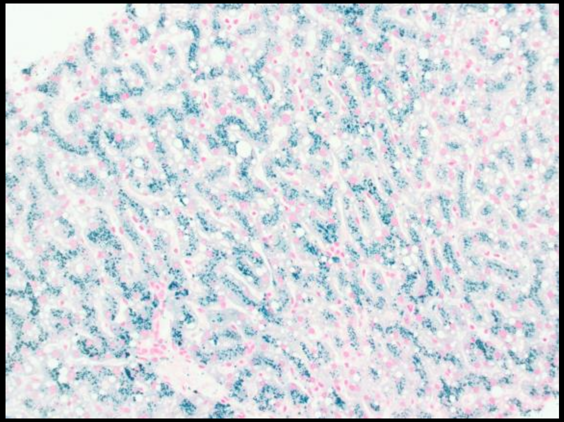
Iron may be a co-factor exacerbating oxidative stress!

Liver Iron

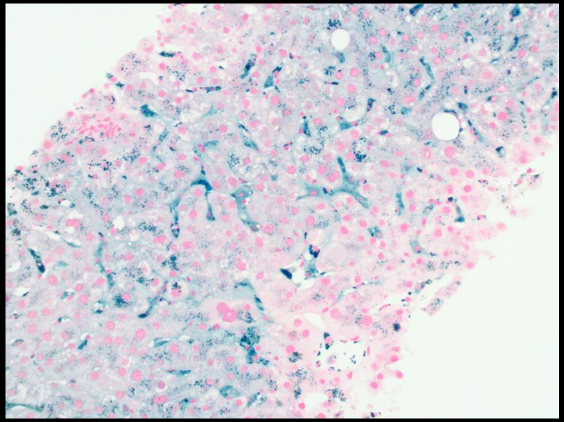
- Iron overload is excess iron in:
- *hepatocytes*
- *kupffer cells*
- *or both*



No Iron

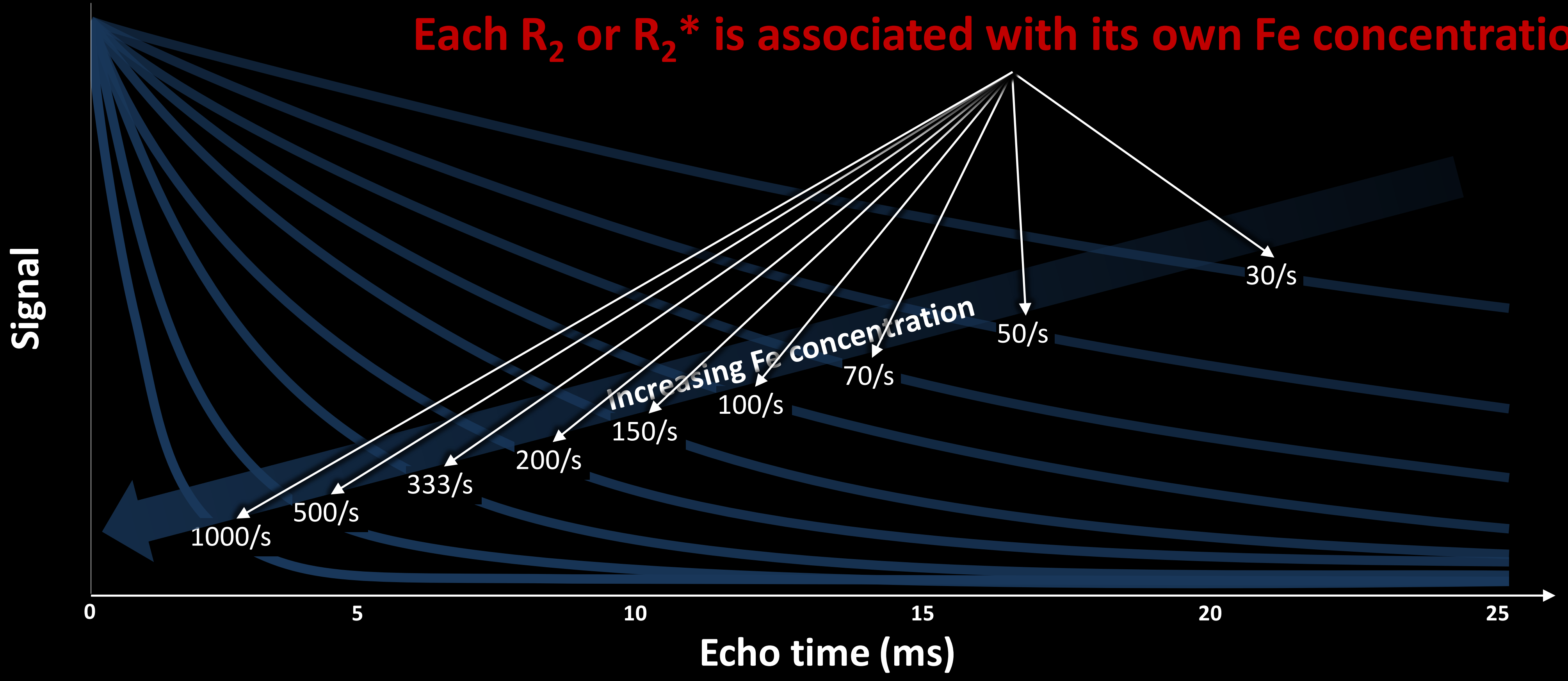


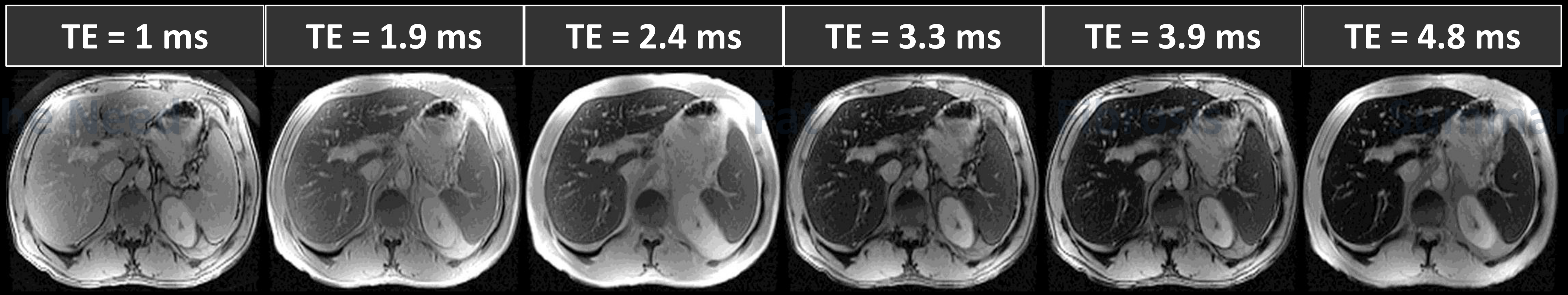
Iron in hepatocytes

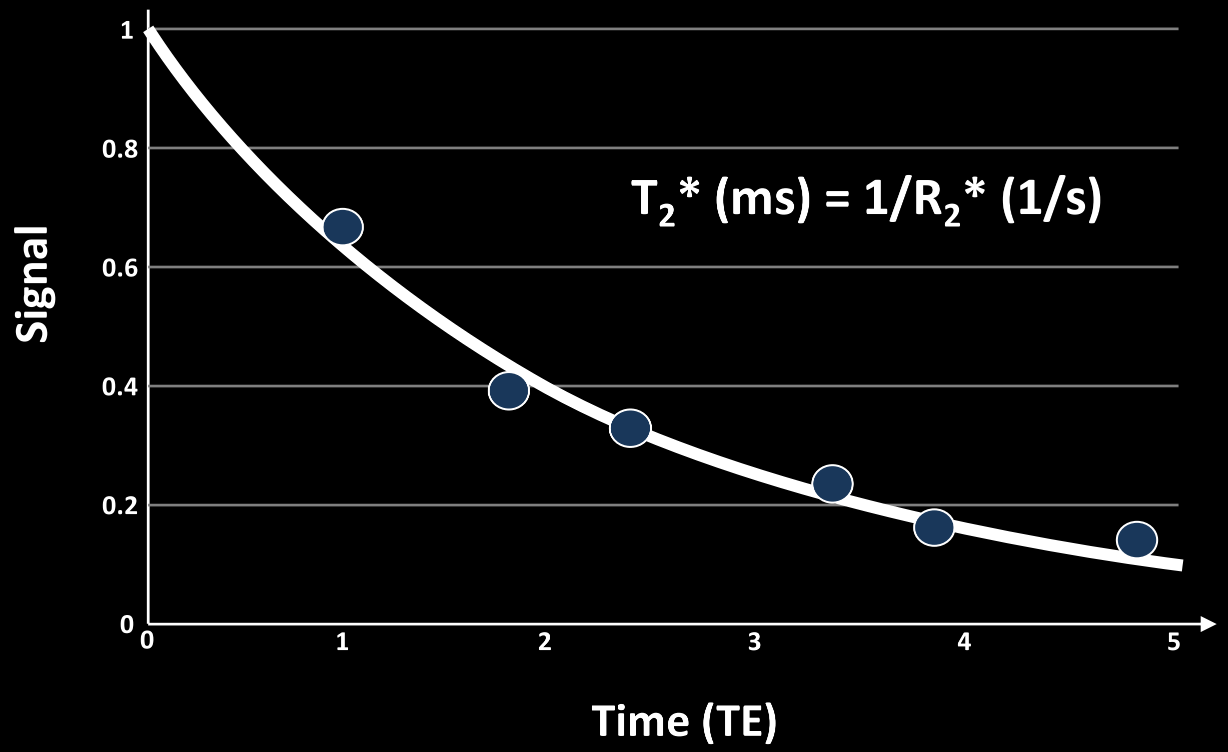


Iron in Kupffer cells

As **Fe** increases, **R_2*** increase





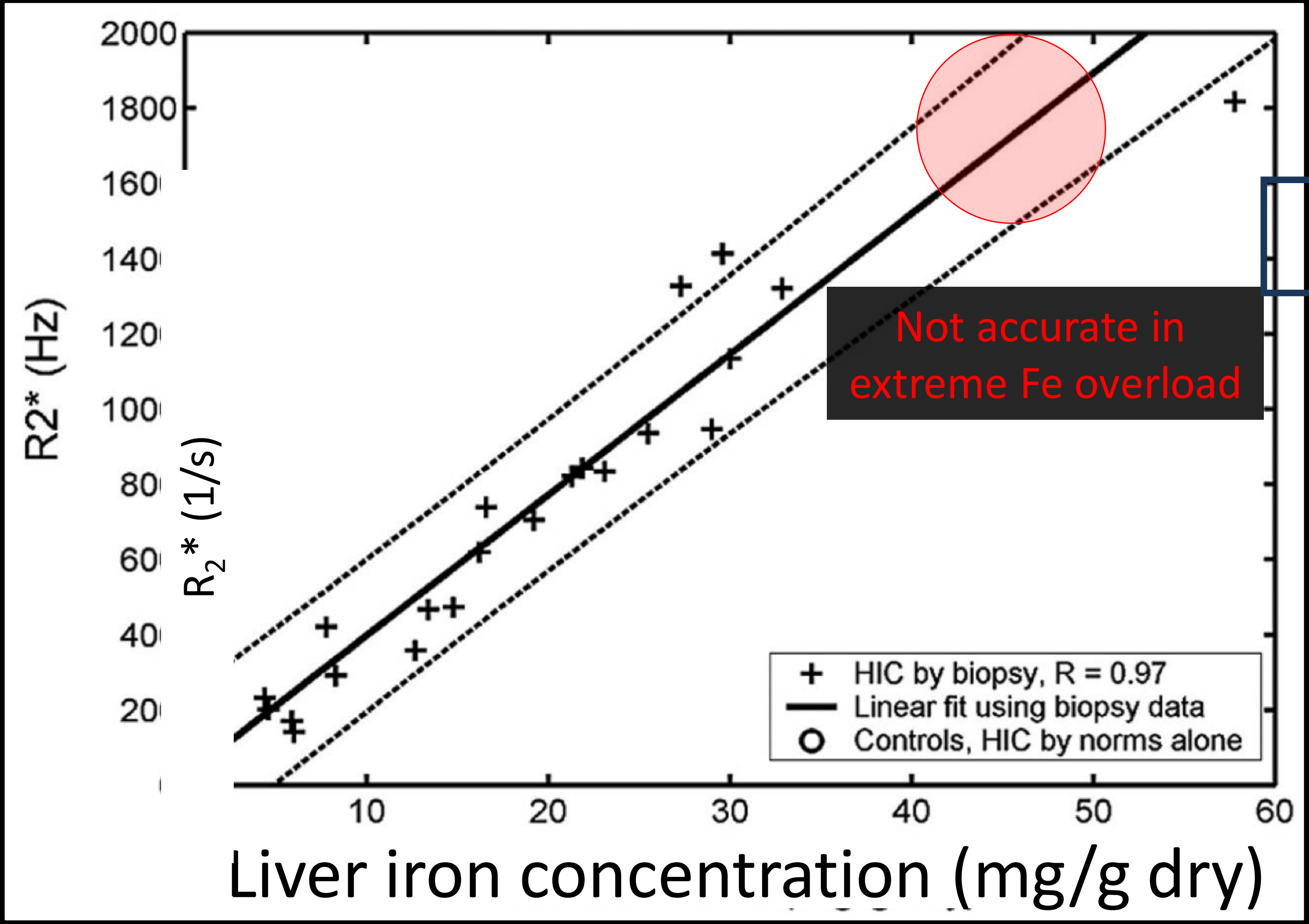


Modeling:

R_2* computed from observed signal decay

Many modeling approaches (beyond scope)

R_2* is Biomarker of Fe Overload

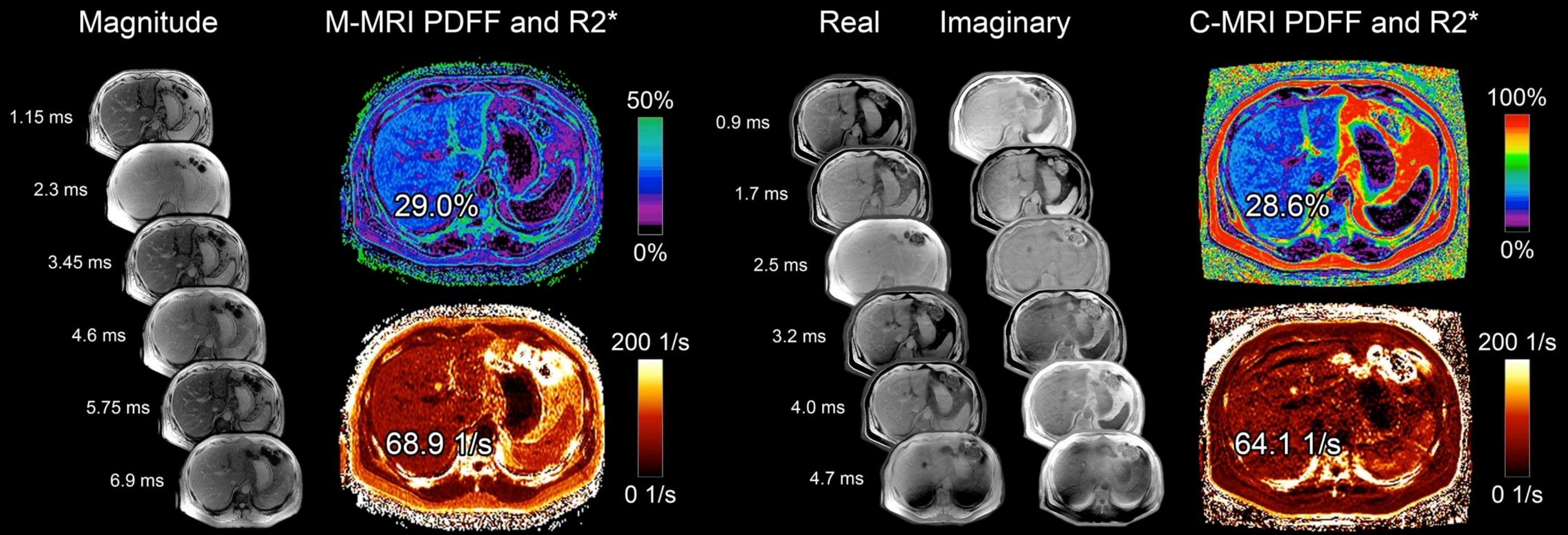


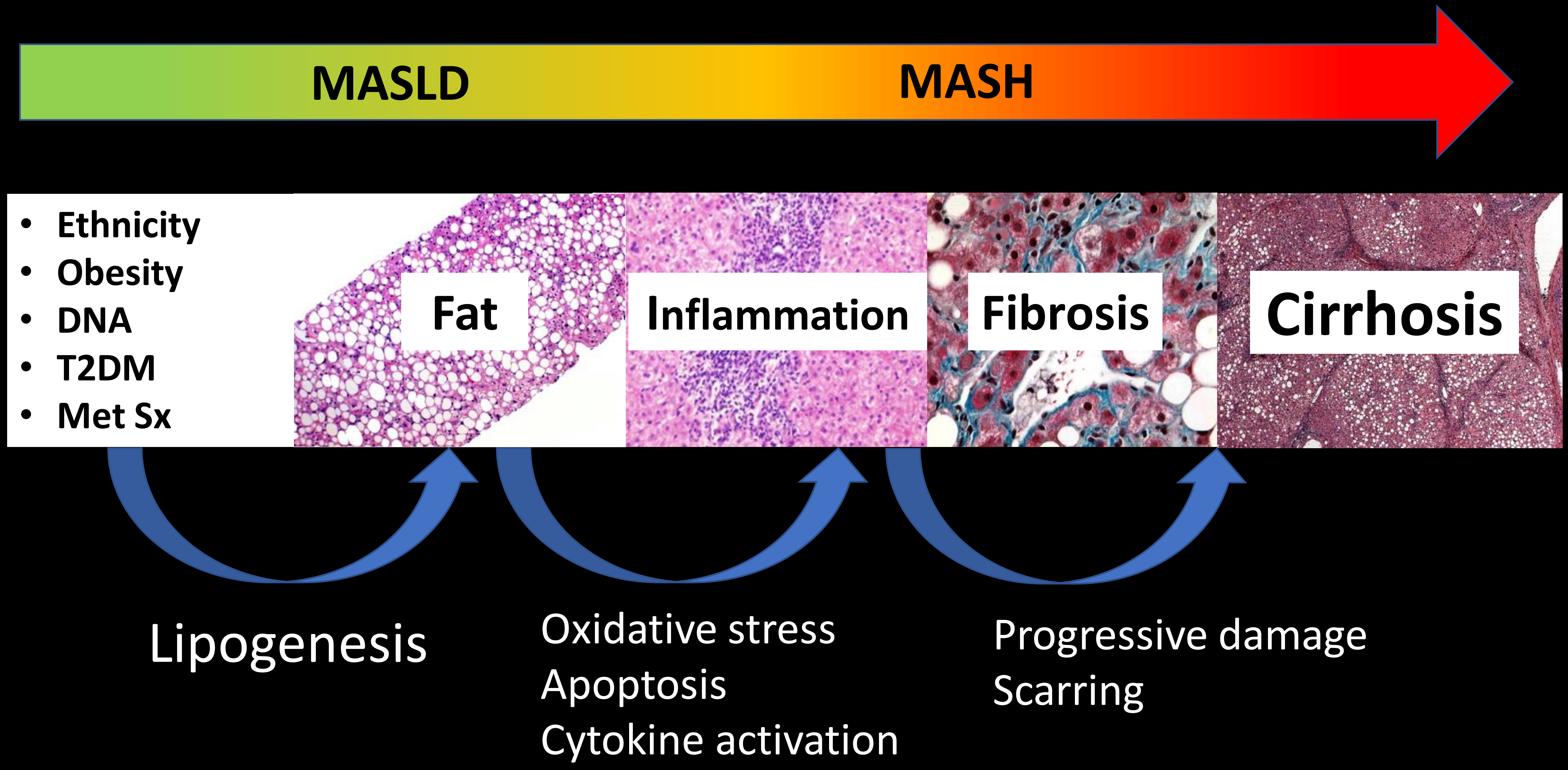
$[Fe] = -0.63 + 0.0267R_2^*$

Calibration Line

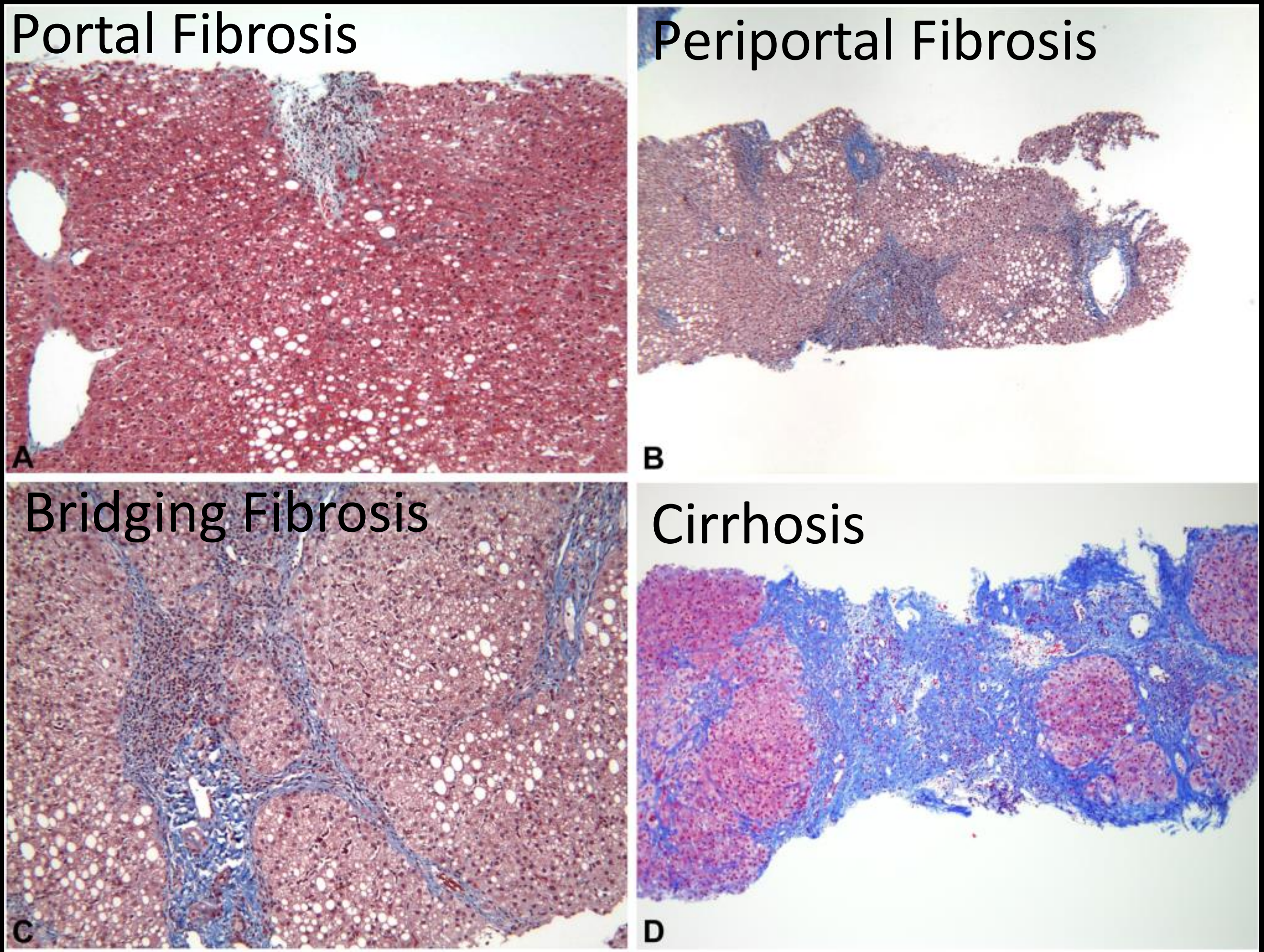
Wood et al (2005) Blood 106: 1460-1465

PDFF: R_2* Map For Free




MASLD
MASH
• Ethnicity
• Obesity
• DNA
• T2DM
• Met Sx
Fat
Inflammation
Fibrosis
Cirrhosis
Lipogenesis
Oxidative stress
Apoptosis
Cytokine activation
Progressive damage
Scarring

Quantifying Fibrosis

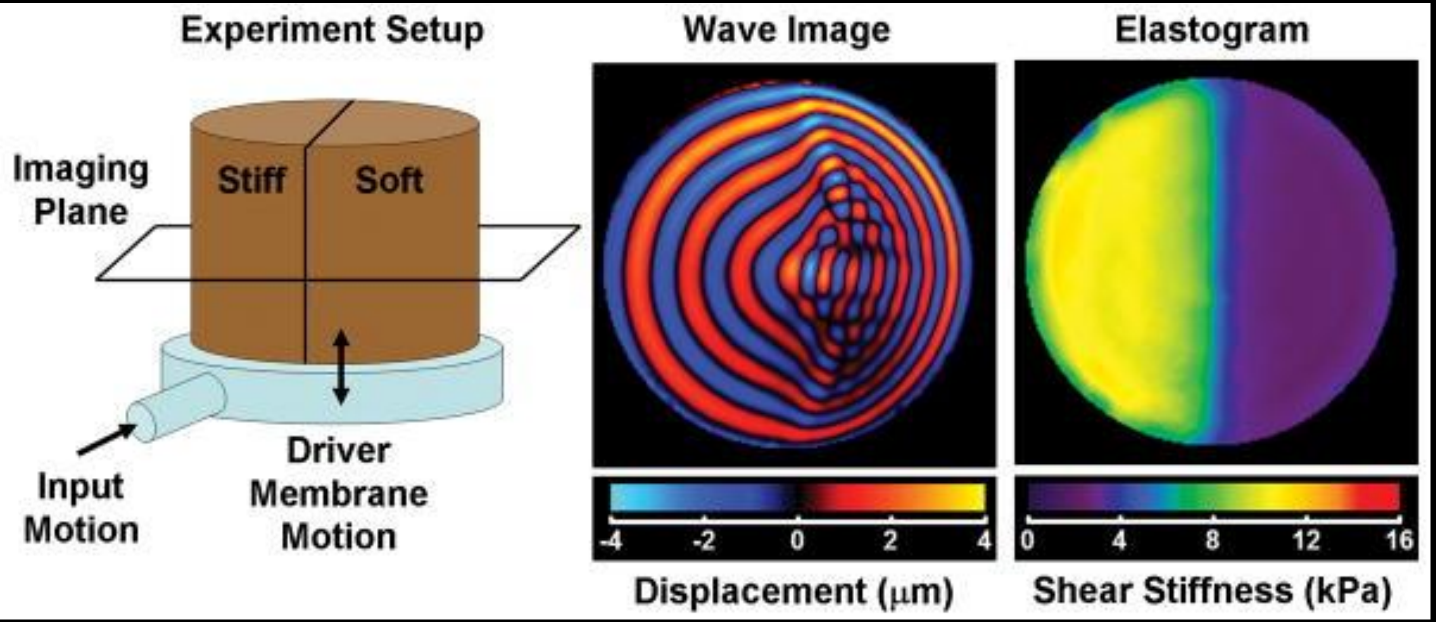


Courtesy of Elizabeth Brunt, M.D.

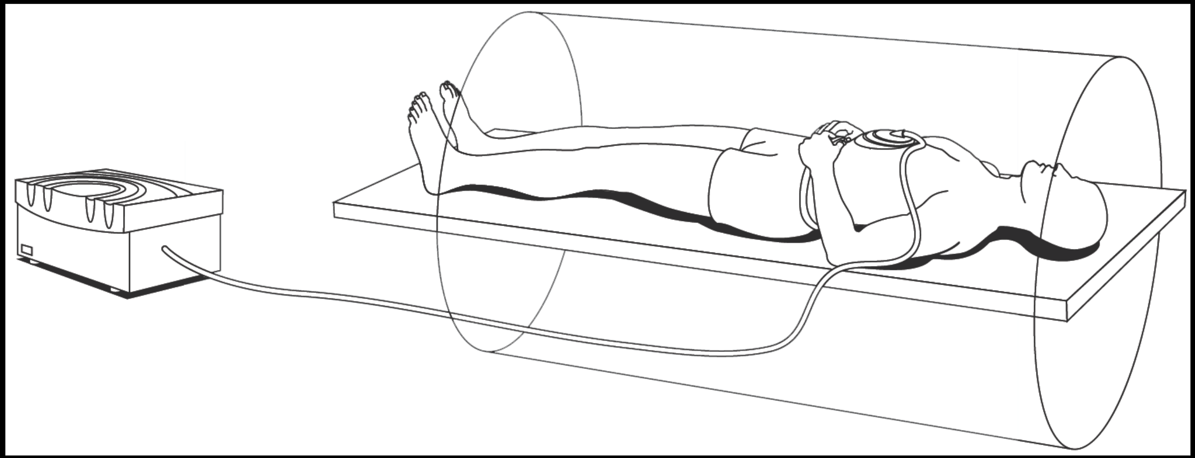
Histology

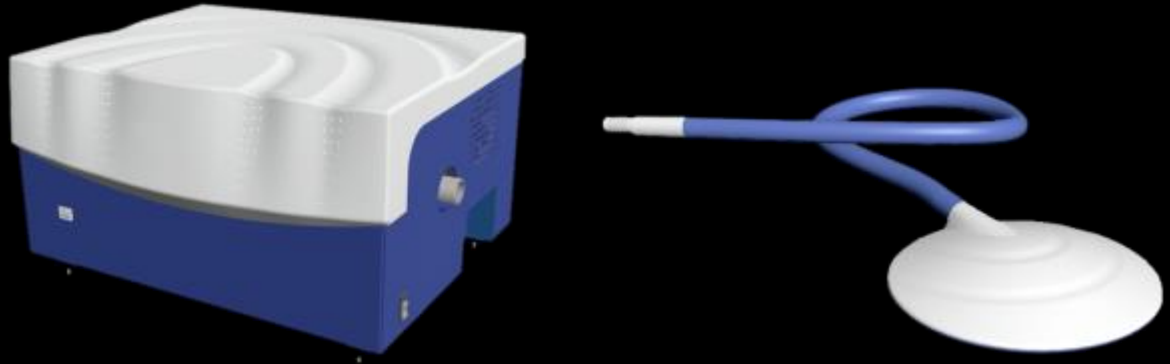
How do we quantify fibrosis?

Elastography



MRE --- Standardized across vendors



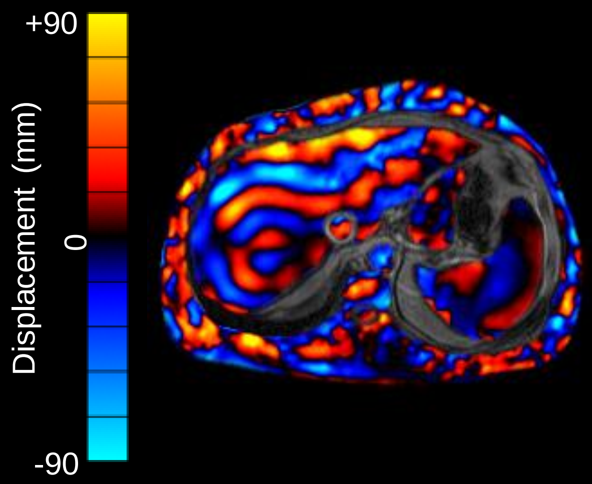


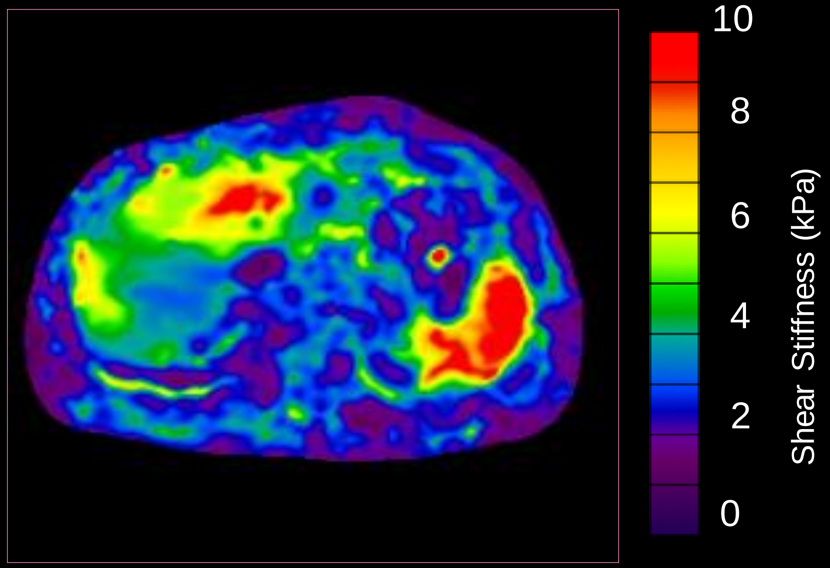
Resoundant

Images courtesy of Dick Ehman, M.D.

What are we measuring?

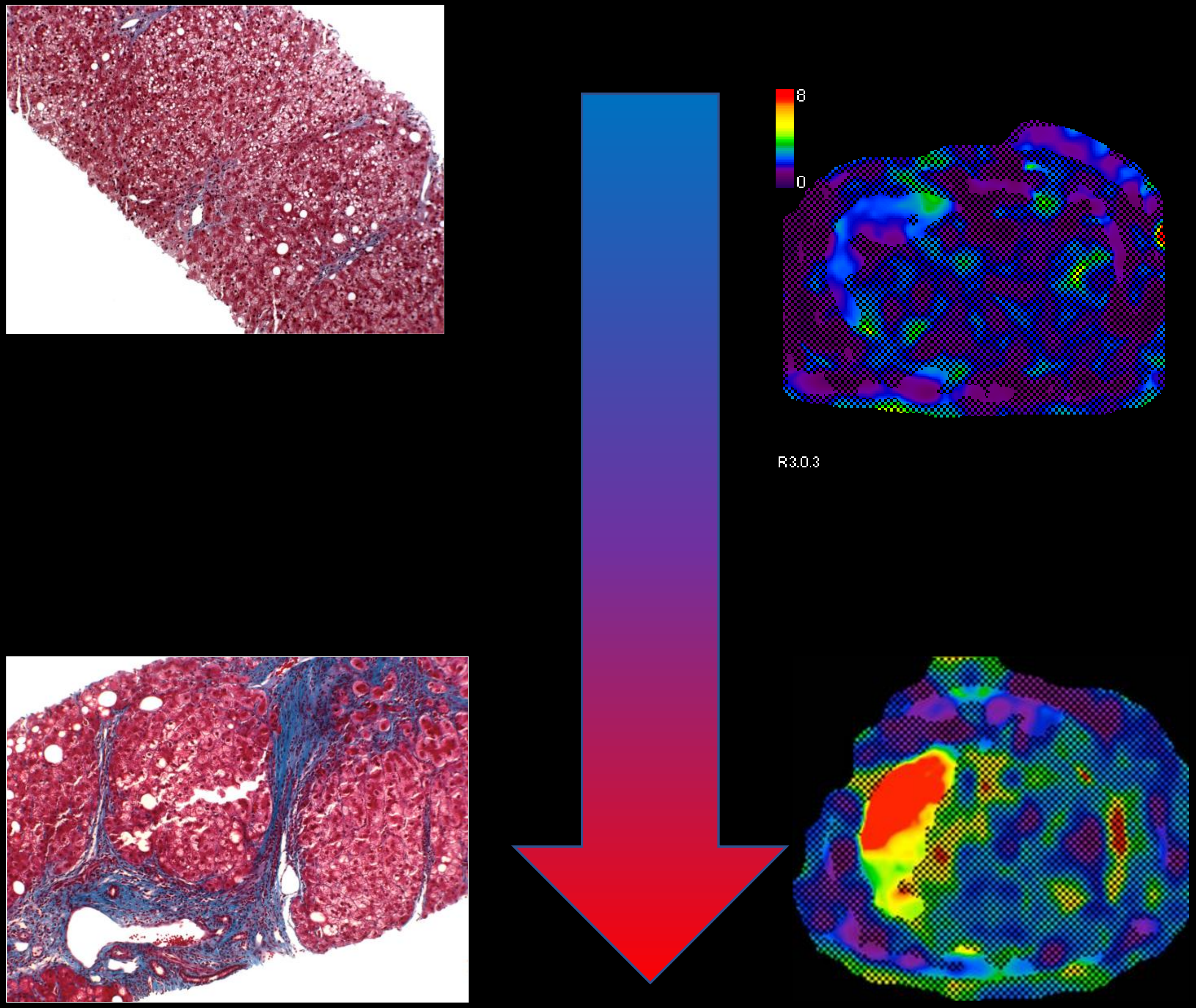
- MRE introduces mechanical waves
- Wave propagation depicted on “Elastogram” via inversion algorithm
  - Shear stiffness (kPa) derived from magnitude of complex shear modulus





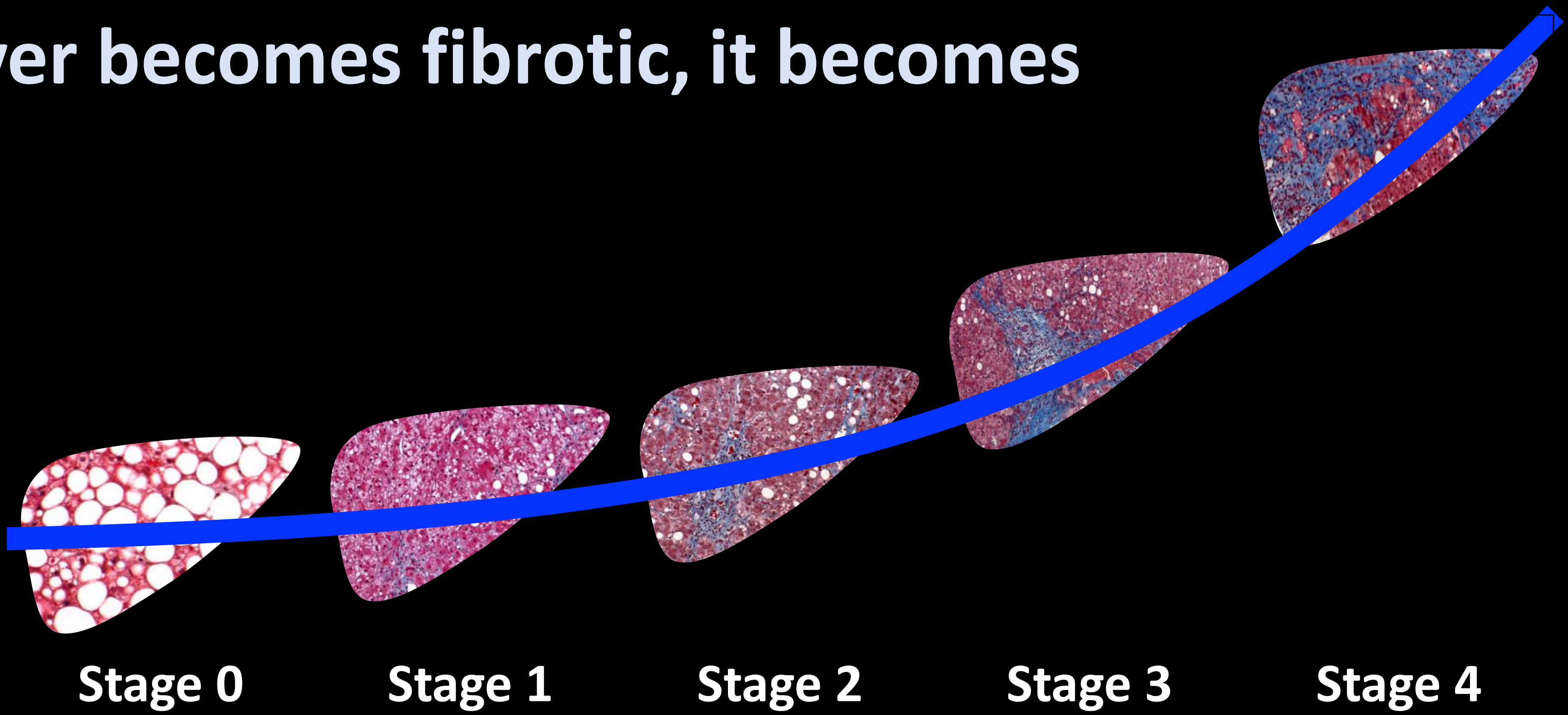
Images courtesy of Dick Ehman, M.D.

Stiffness increases with stage of fibrosis

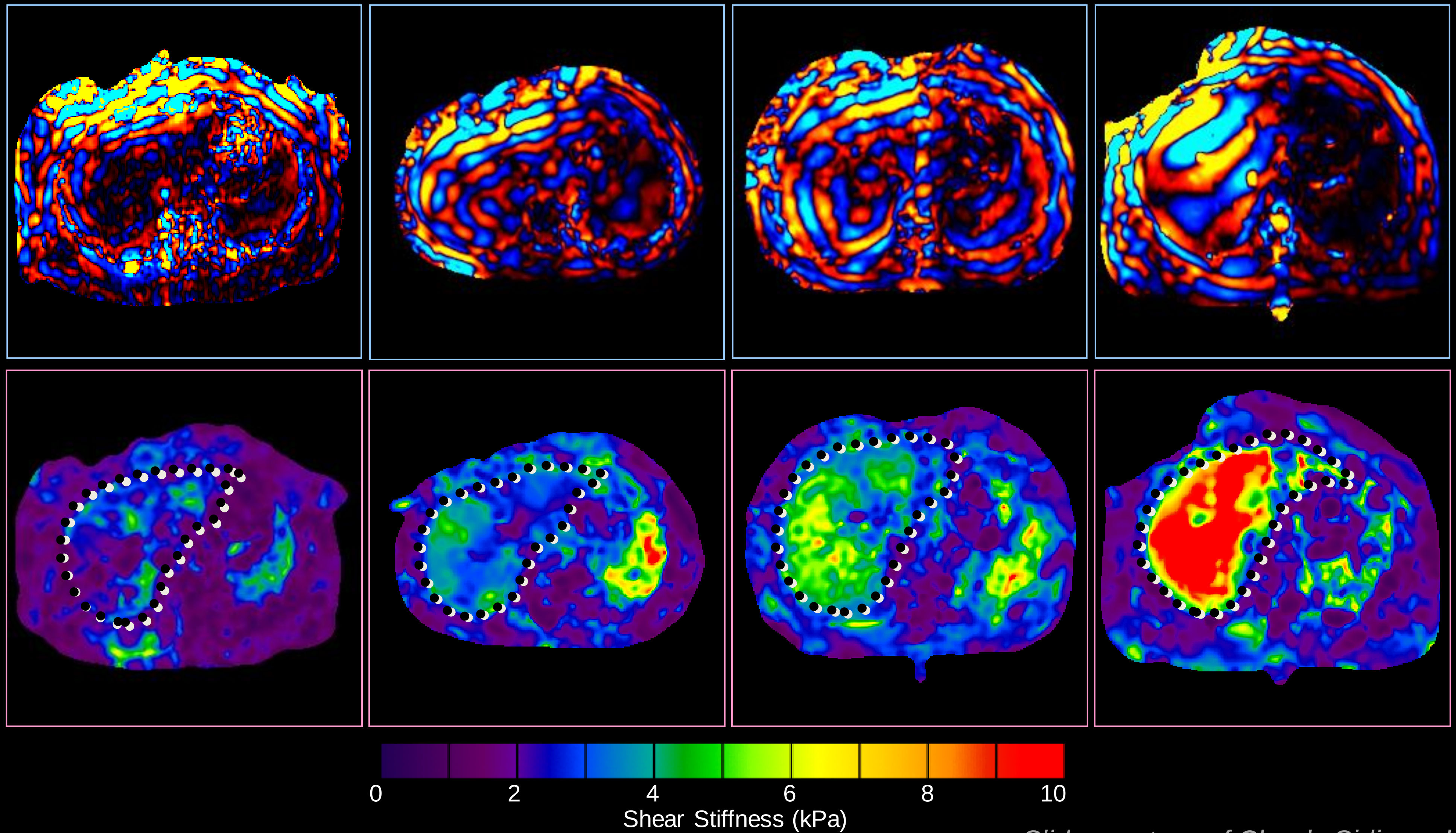


What is Relationship of stiffness to Fibrosis?

As liver becomes fibrotic, it becomes stiff



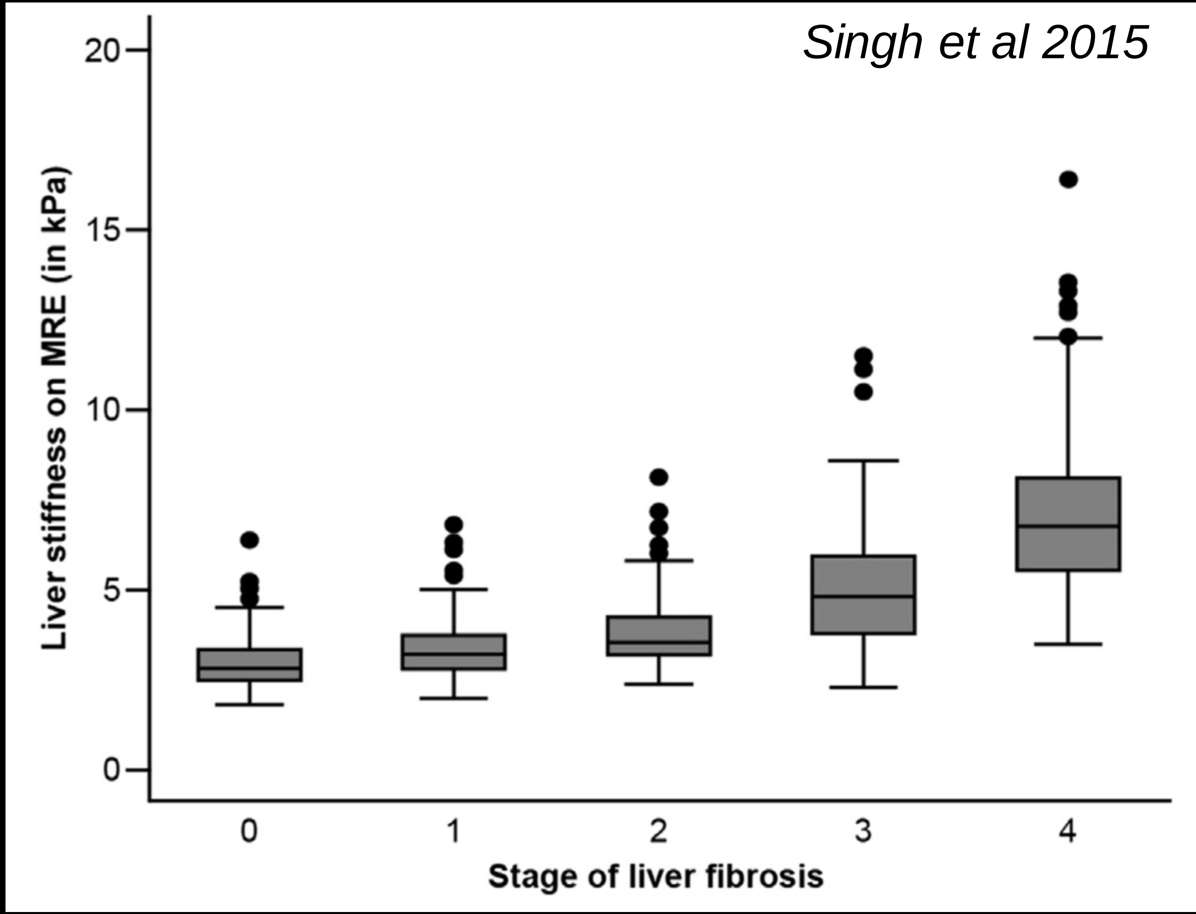
Liver Fibrosis



Slide courtesy of Claude Sirlin and Dick Ehman, MD

MRE --- Accurate in cross sectional studies

MRE more accurate than simple noninvasive tests (e.g. FIB-4) for diagnosing advanced fibrosis in NAFLD-Xiao, Hepatology 2017



Meta-Analysis of 12 Studies

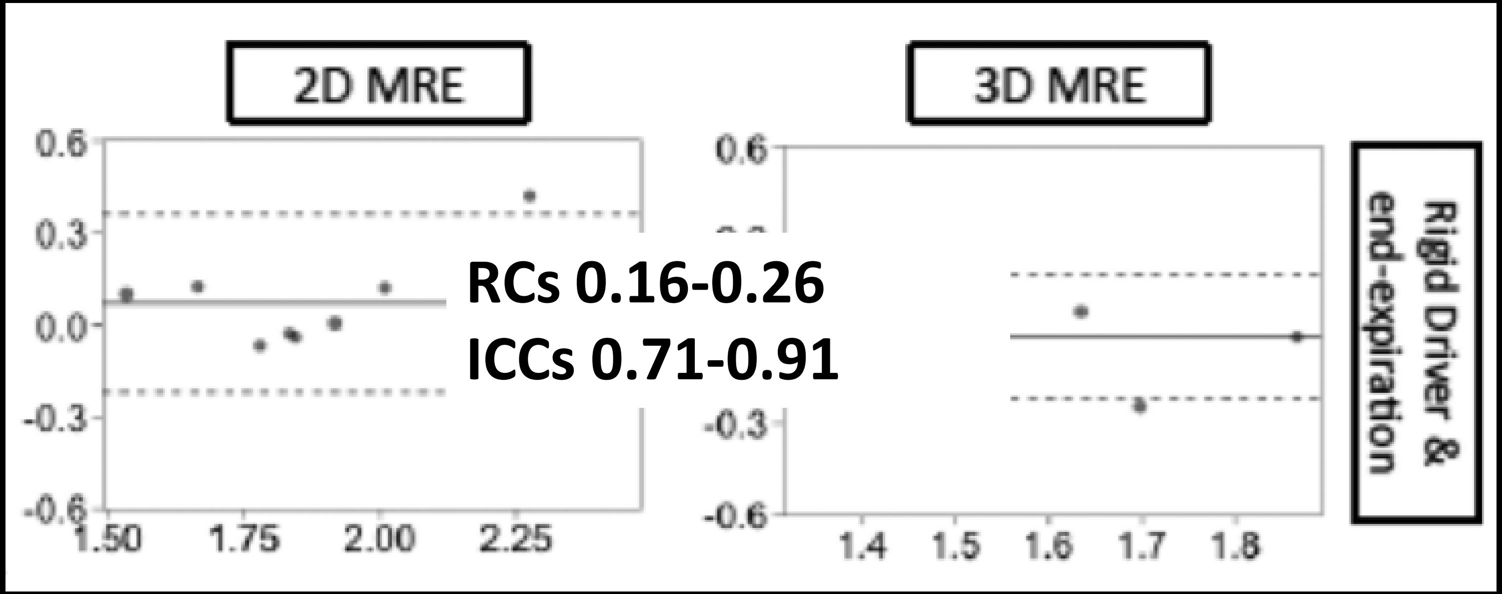
(Individual Participant Data, n=697)

MRE --- Repeatability/Reproducibility?

Stay Tuned for Definitive work on this: Nimble 1.2: Work in progress!

Within subject coefficient of variation ~7%

Normal volunteer repeatability



Wang et al, 2017

Quantitative Imaging Biomarkers Alliance

RSNA

Change in stiffness of $\geq$ 19% represents a true change with 95% certainty

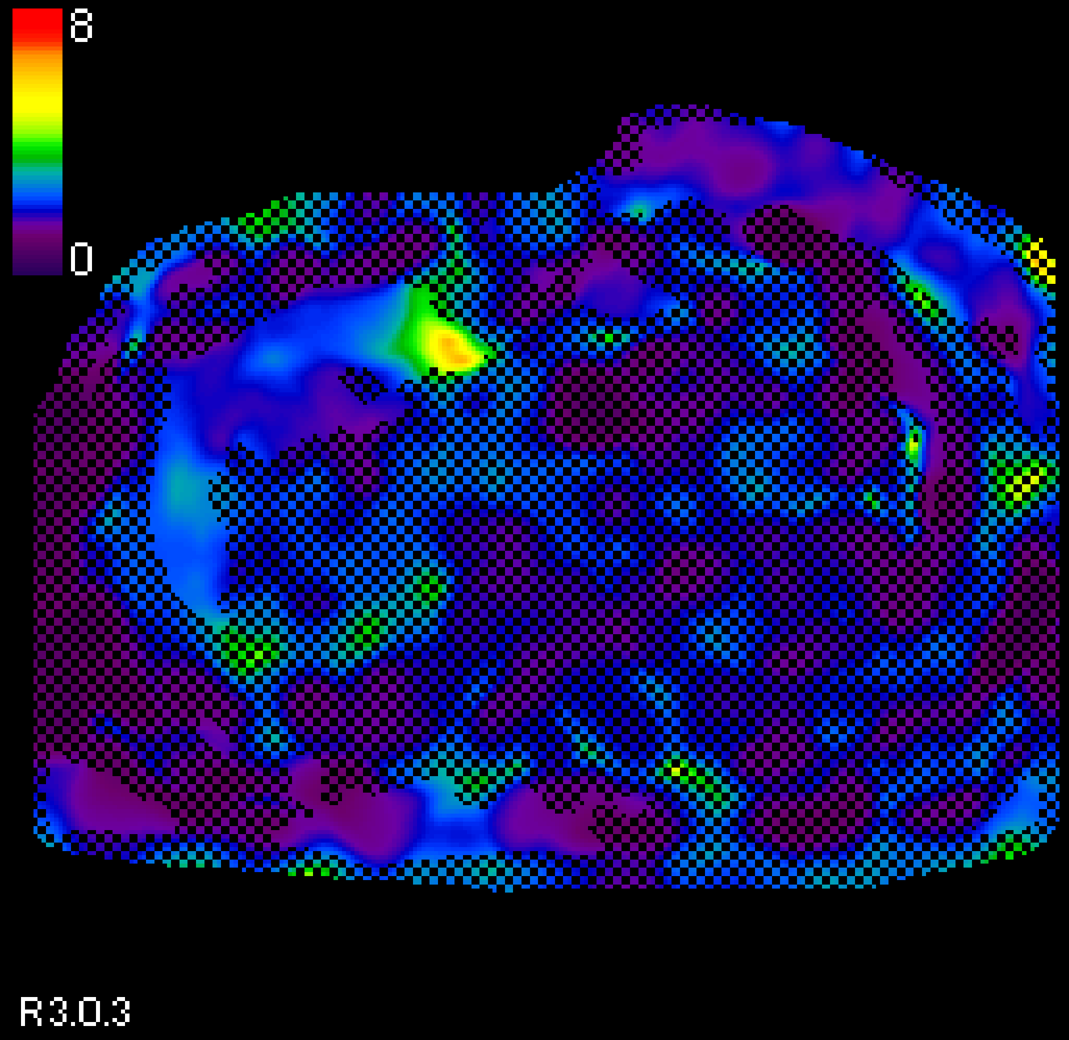
RC 2.77 x wCV=19%

MRE profile

Elastography

- **MRI-**
- 2D (*and 3D elastography*)

- **Ultrasound-**
- Transient elastography
- Point shear wave
- 2D shear wave

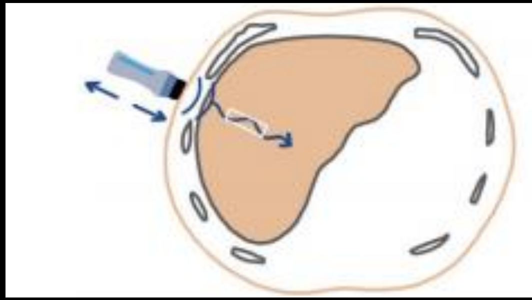


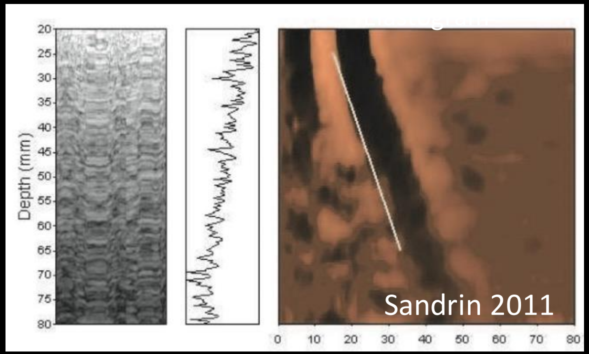
Elastography broken down

Ultrasound			Steps	MRI
			1. Generate shear waves	
			2. Track shear waves	
Measure shear wave speed			**3. Analyze shear waves**	Visualize shear wave motion
Young modulus (Simple arithmetic)			**4. Convert to "stiffness"**	Shear modulus (Advanced inversion algorithm)
Number + graph	Number + location	"Elastogram" in small ROI	**5. Display values**	"Elastogram" of entire field of view
(Automated)			**6. Analyze values**	Manually draw region of interest in areas with valid data

US Elastography varieties

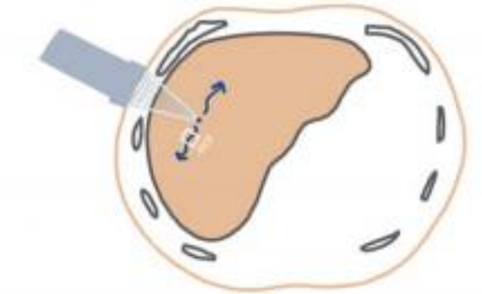
Vibration controlled Transient (VCTE; Fibroscan)

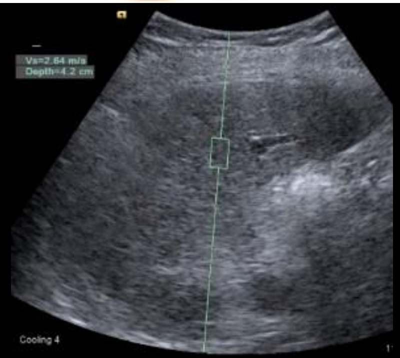




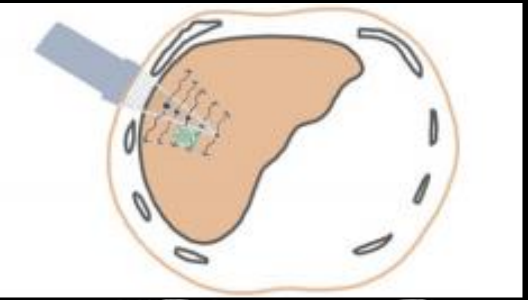
Sandrin 2011

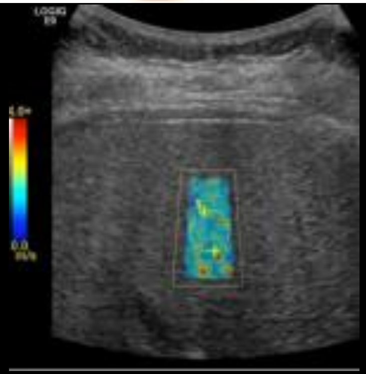
Point Shear Wave (PSW)





2D Shear Wave (2D SWE)





Summary of US accuracy

- All are potentially impacted by obesity
- Poor for early fibrosis (Stage 1 vs. 2)
- OK for Stage $\geq$2 (AUCs 0.62-0.91)
- Excellent for detecting Stage 4 (AUCs 0.80-0.97)

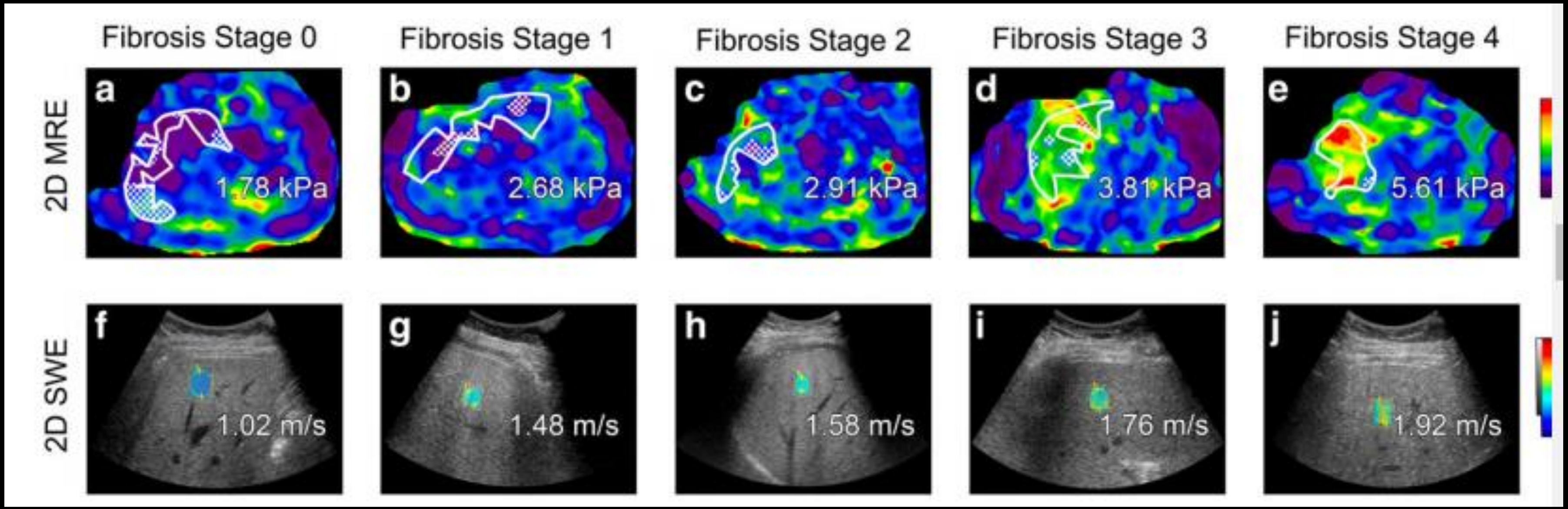
- No consensus on which is most accurate

  pSWE/2D SWE > VCTE
- Results between vendors/methods may differ

Yoneda, 2015; Paul 2017; Gao 2018; Rizzo 2011; Cassinotto 2013

US vs. MR Elastography

- MRE slightly more accurate, especially at lower stages
- Stage > 2 MRE AUCs 0.89-0.93 v. US 0.81-0.91
  Stage > 3 MRE AUCs 0.87-0.96 v. US 0.80-0.90
- Stage > 4 MRE AUCs 0.87-0.95 v. US 0.69-0.92



Chen 2017; Park 2017; Imajo 2016; Chou 2017; Cui 2016

Liver Fibrosis Imaging: A Clinical Review of Ultrasound and Magnetic Resonance Elastography

Yingzhen N. Zhang, MD,[1] Kathryn J. Fowler, MD,[1] Arinc Ozturk, MD,[2] Chetan K. Potu, BS,[1] Ashley L. Louie, BA,[1] Vivian Montes, BA,[1] Walter C. Henderson, BA,[1] Kang Wang, MD,[1] Michael P. Andre, PhD,[3] Anthony E. Samir, MD,[2] and Claude B. Sirlin, MD[1*]

Liver fibrosis is a histological hallmark of most chronic liver diseases, which can progress to cirrhosis and liver failure, and predisposes to hepatocellular carcinoma. Accurate diagnosis of liver fibrosis is necessary for prognosis, risk stratification, and treatment decision-making. Liver biopsy, the reference standard for assessing liver fibrosis, is invasive, costly, and impractical for surveillance and treatment response monitoring. Elastography offers a noninvasive, objective, and quantitative alternative to liver biopsy. This article discusses the need for noninvasive assessment of liver fibrosis and reviews the comparative advantages and limitations of ultrasound and magnetic resonance elastography techniques with respect to their basic concepts, acquisition, processing, and diagnostic performance. Variations in clinical contexts of use and common pitfalls associated with each technique are considered. In addition, current challenges and future directions to improve the diagnostic accuracy and clinical utility of elastography techniques are discussed.

Level of Evidence: 5
Technical Efficacy Stage: 2

J. MAGN. RESON. IMAGING 2019.

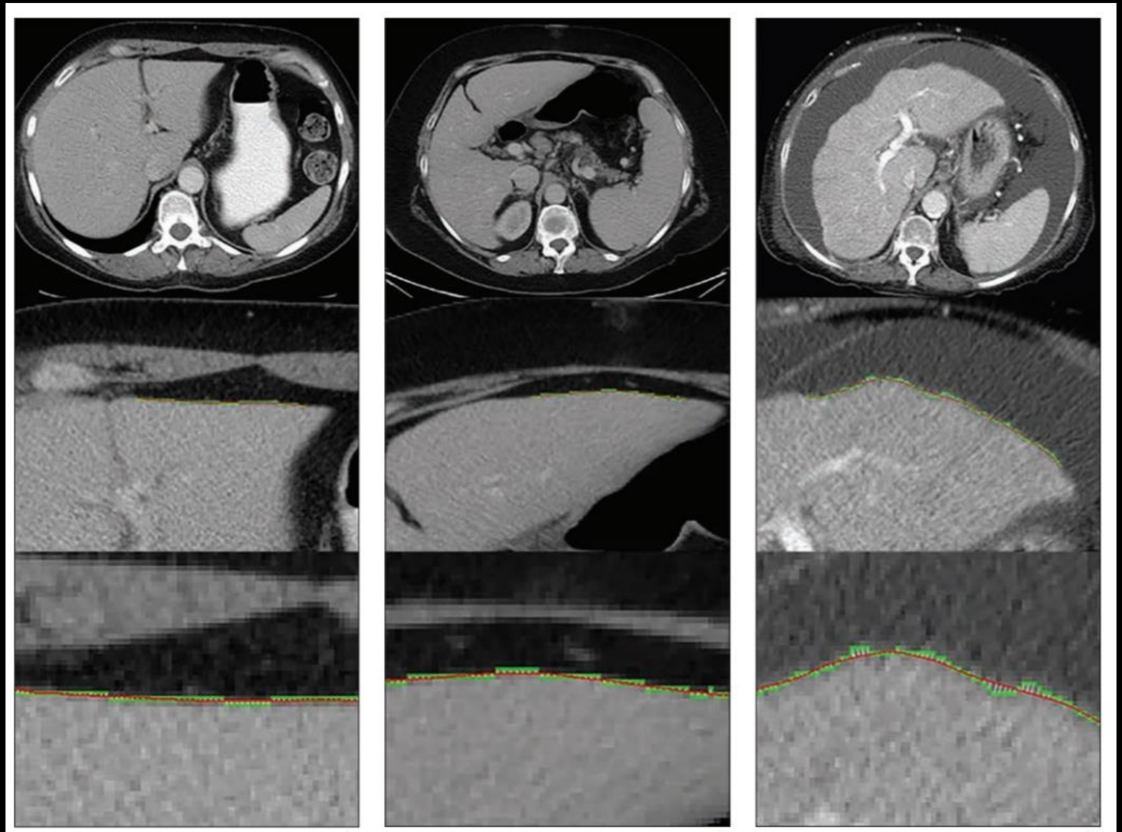
Wallpapersden.com

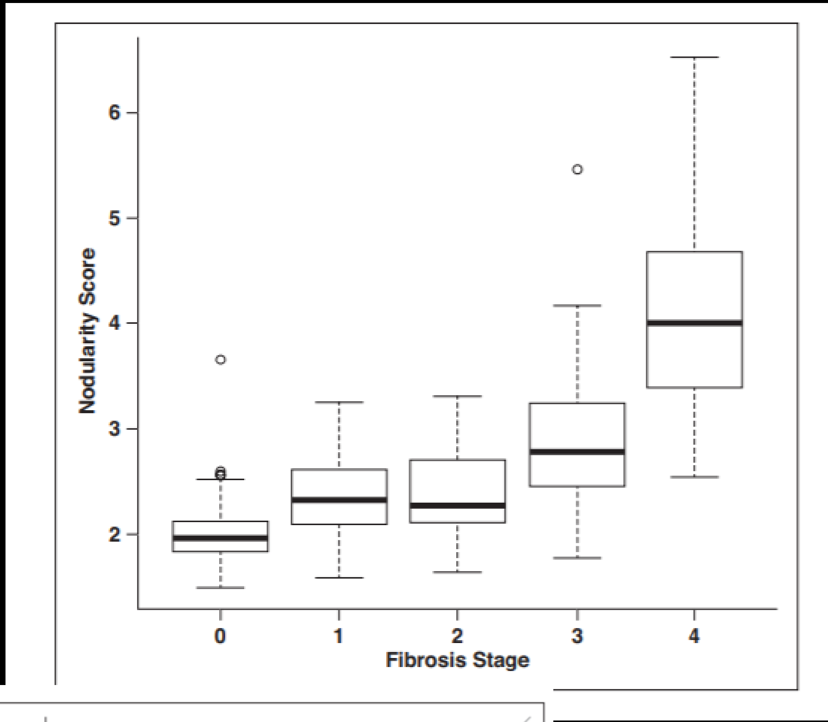
Accuracy of Liver Surface Nodularity Quantification on MDCT as a Noninvasive Biomarker for Staging Hepatic Fibrosis

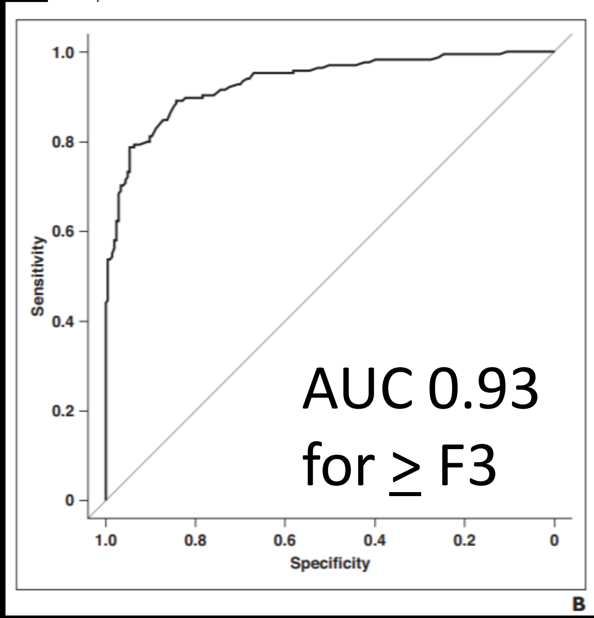
Perry J. Pickhardt[1]
Kyle Malecki
John Kloke
Meghan G. Lubner

OBJECTIVE. The purpose of this study was to investigate objective semiautomated measurement of liver surface nodularity on MDCT for prediction of underlying hepatic fibrosis (stages F0–F4).

MATERIALS AND METHODS. Contrast-enhanced abdominal MDCT scans were assessed with an independently validated semiautomated surface nodularity tool. A series of 10 or more consecutive ROI measurements along the anterior aspect of the liver totaling a length







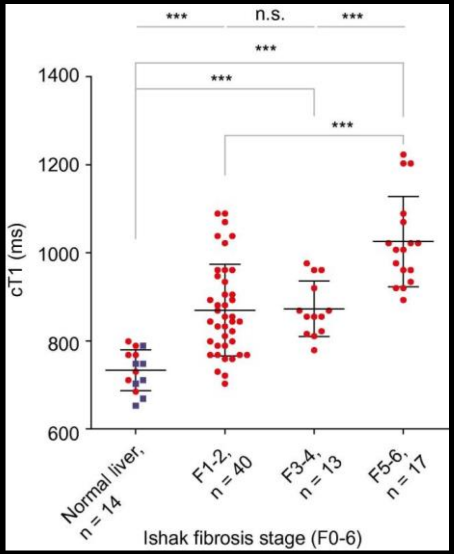
T1 relaxometry and mapping

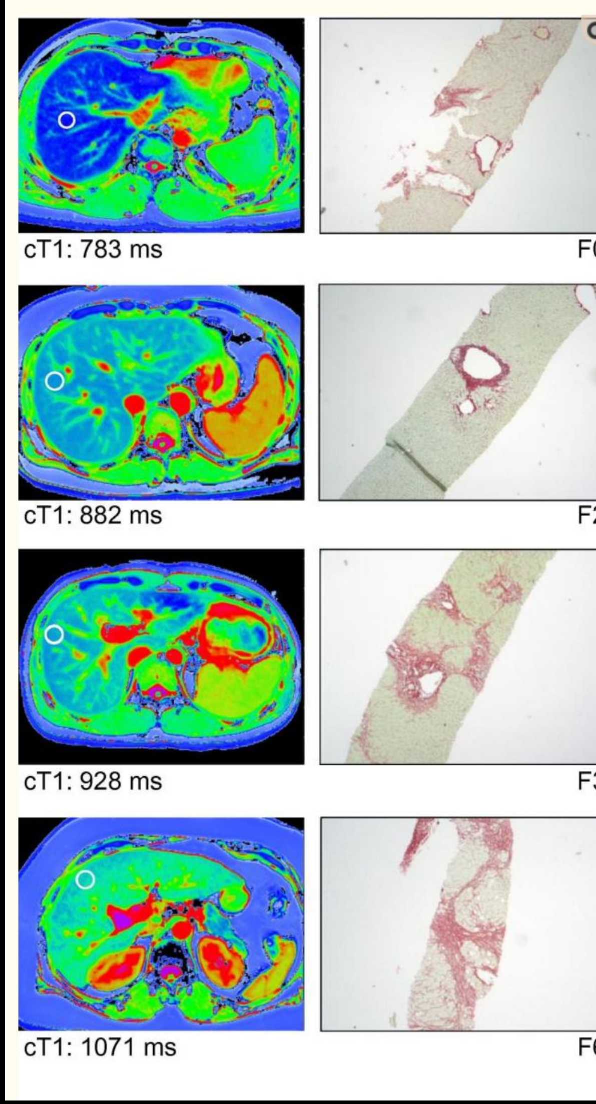
- T1 rho may detect macromolecules in tissue

  collagen and proteoglycans alter T1 relaxation

- Similar to PDFF, must be corrected for confounders (cT1)

- Prelim data promising!





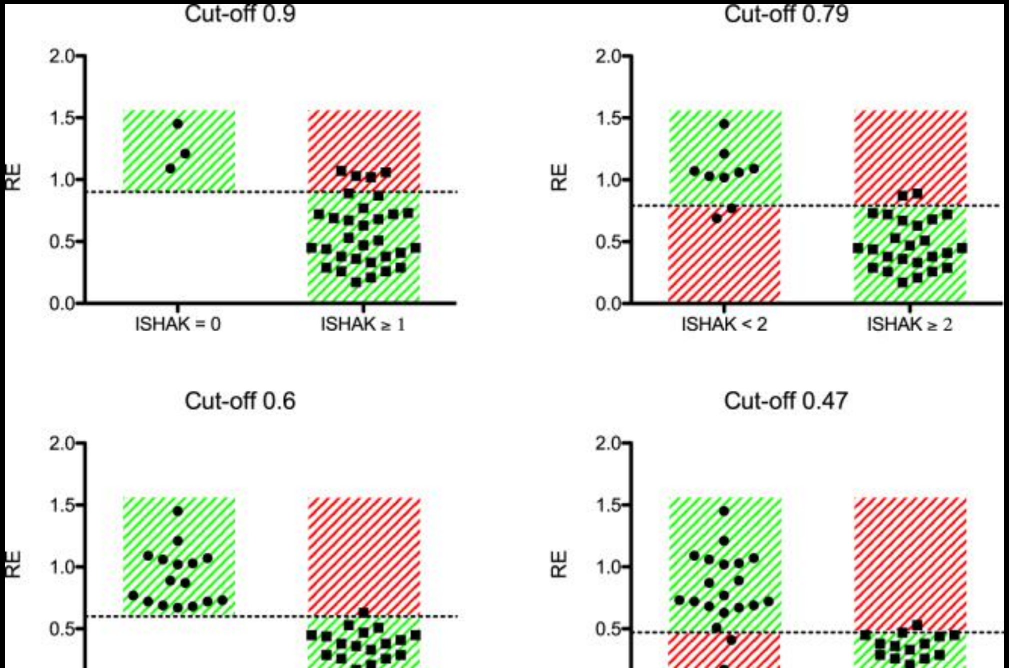
Banerjee R, J Hepatol 2014

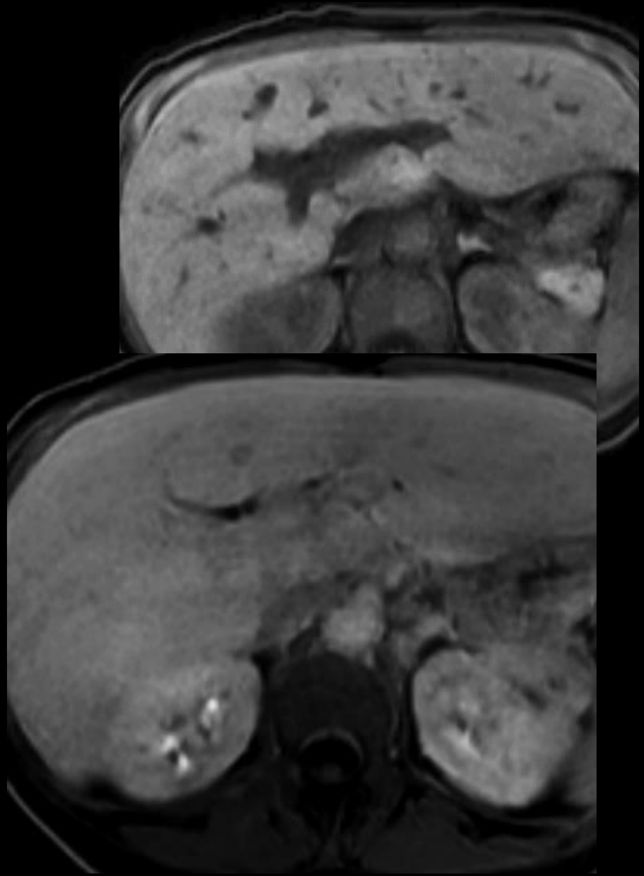
Sci Rep. 2018; 8: 6207. PMCID: PMC5906481
Published online 2018 Apr 18. doi: 10.1038/s41598-018-24316-z PMID: 29670136

Detecting liver fibrosis with Gd-EOB-DTPA-enhanced MRI: A confirmatory study

Niklas Verloh,[1] Kirsten Utpatel,[2] Michael Haimerl,[1] Florian Zeman,[3] Lukas Beyer,[1] Claudia Fellner,[1] Frank Brennfleck,[4] Marc H Dahlke,[4] Christian Stroszczynski,[1] Matthias Evert,[2] and Philipp Wiggermann[1]

$$\text{Relative enhancement (RE) } \textit{of signal intensity (SI)} = \frac{SI_{post} - SI_{pre}}{SI_{pre}}$$





Relative enhancement EOB

Sensitivity ≥ 86%

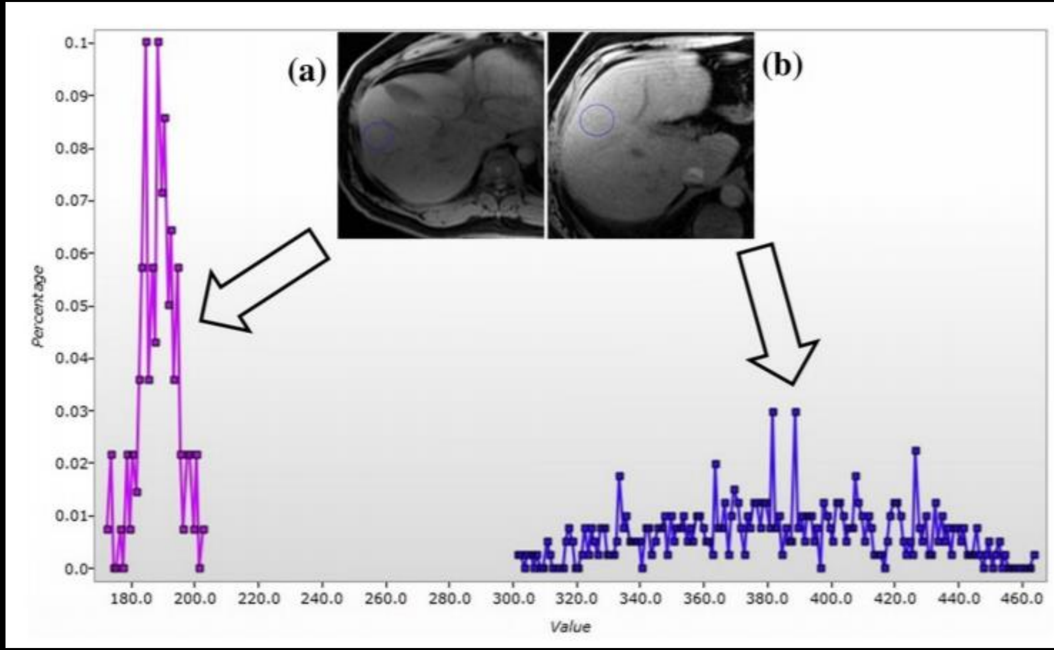
PPV ≥ 86%

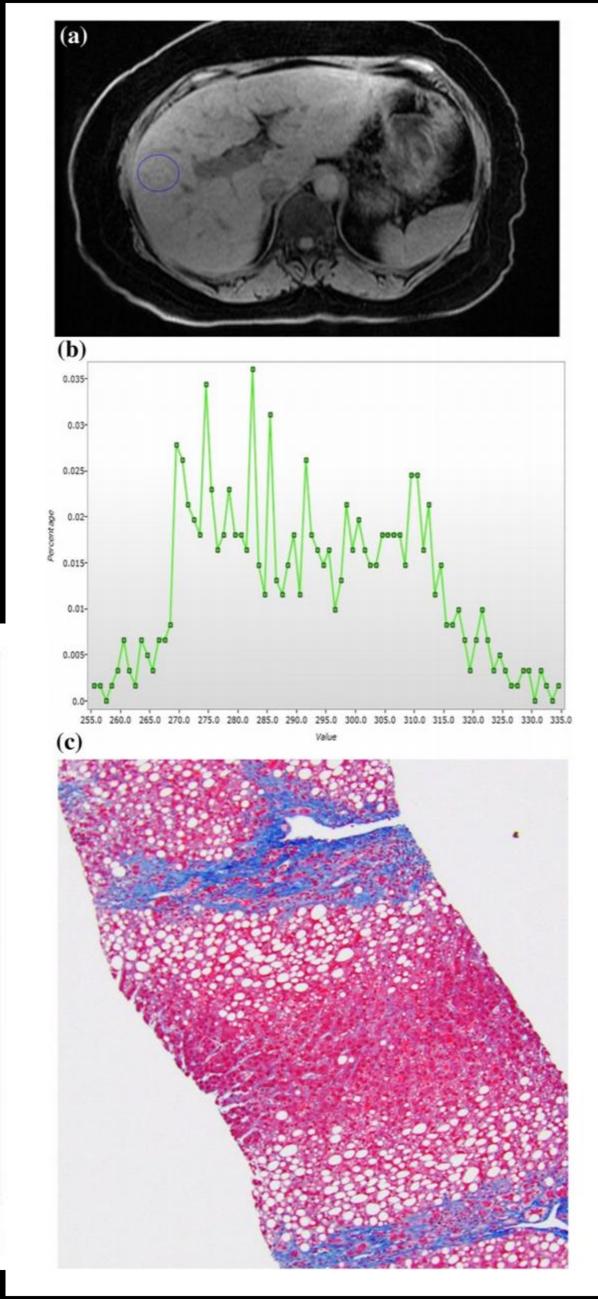
Correctly classified most patients

Texture analysis

- Characterizes spatial variation of gray levels

- Single center studies show some discriminatory ability
- Further testing needed

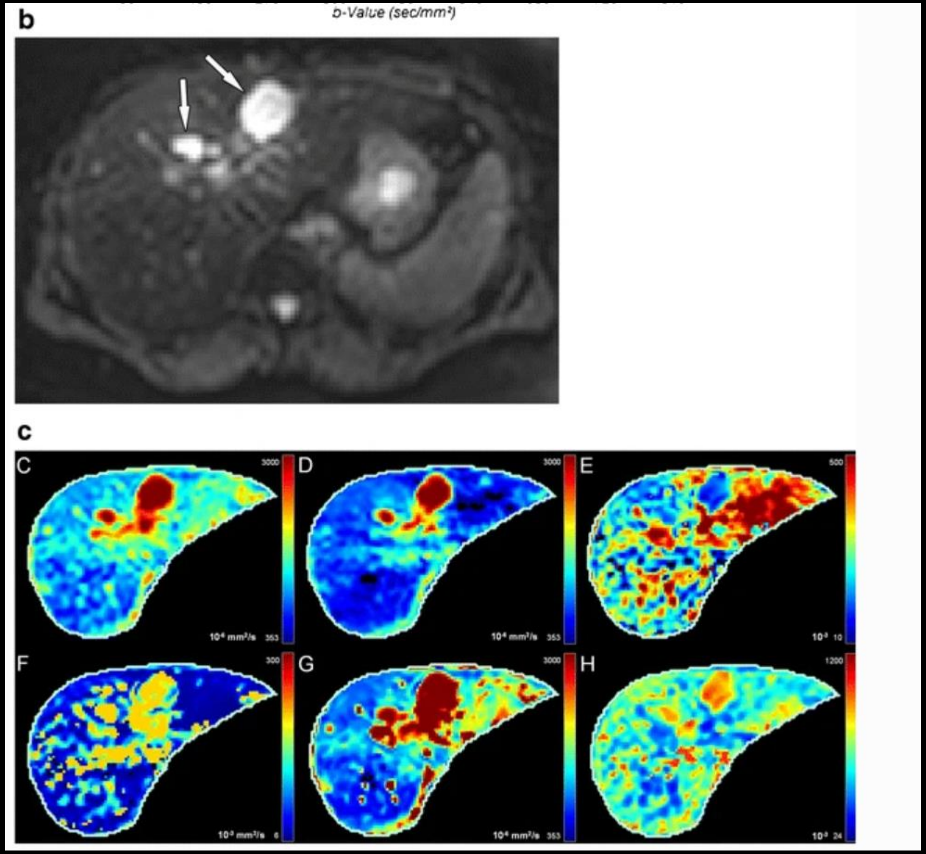




Canella R, Abdominal Radiology 2019

Advanced DWI

- Collagen deposition expands extracellular space and alters proton diffusion
- IVIM-intravoxel incoherent motion
- Prelim studies show some potential

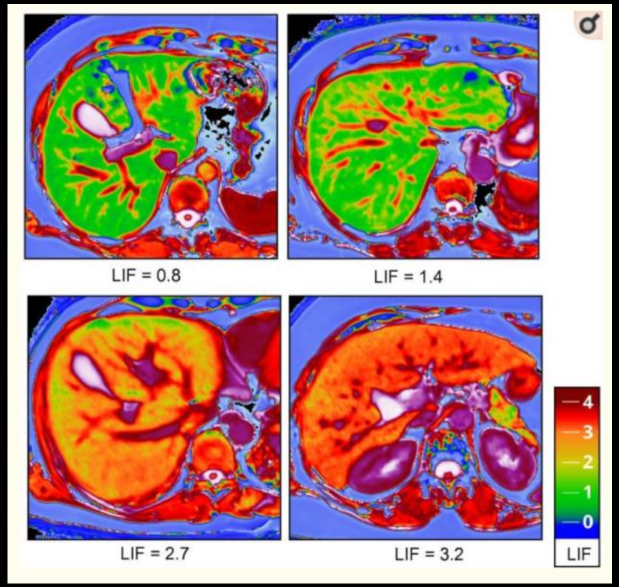


Seo N, Magnetic Resonance 2018

Multi-parametric approach

- Liver *MultiScan* (LMS, Perspectum Diagnostics)

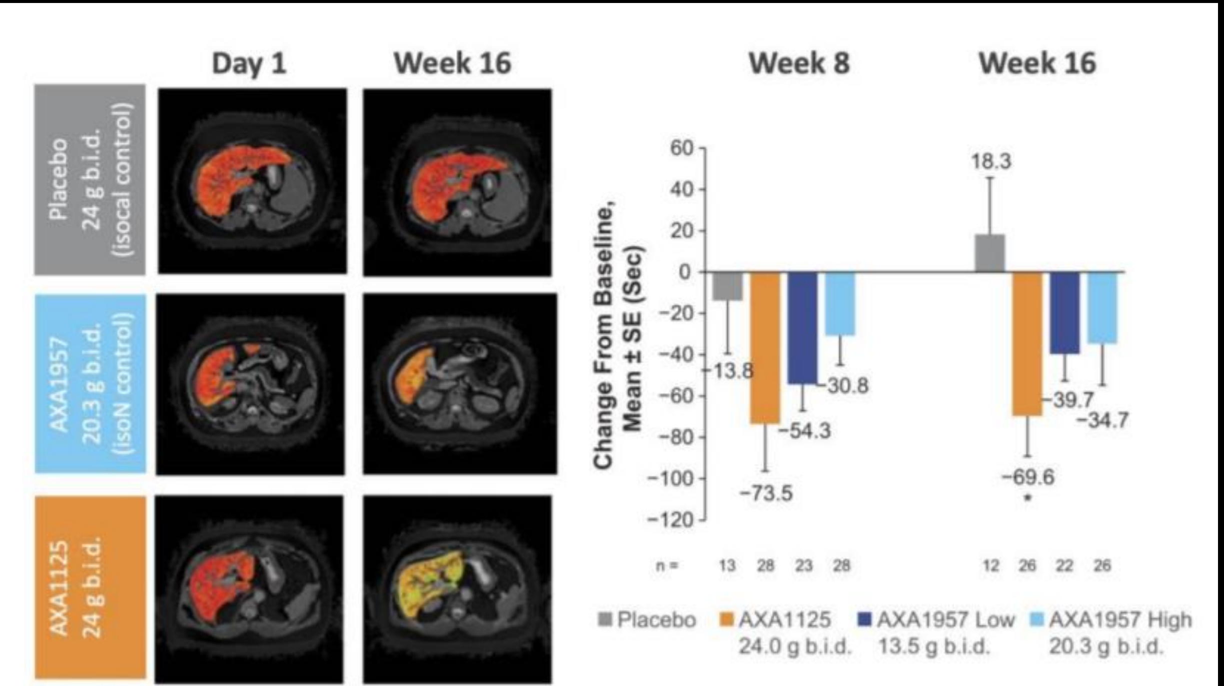
  T1 map, T2*, MRS or PDFF



Pavlides M, J Hepatol 2016

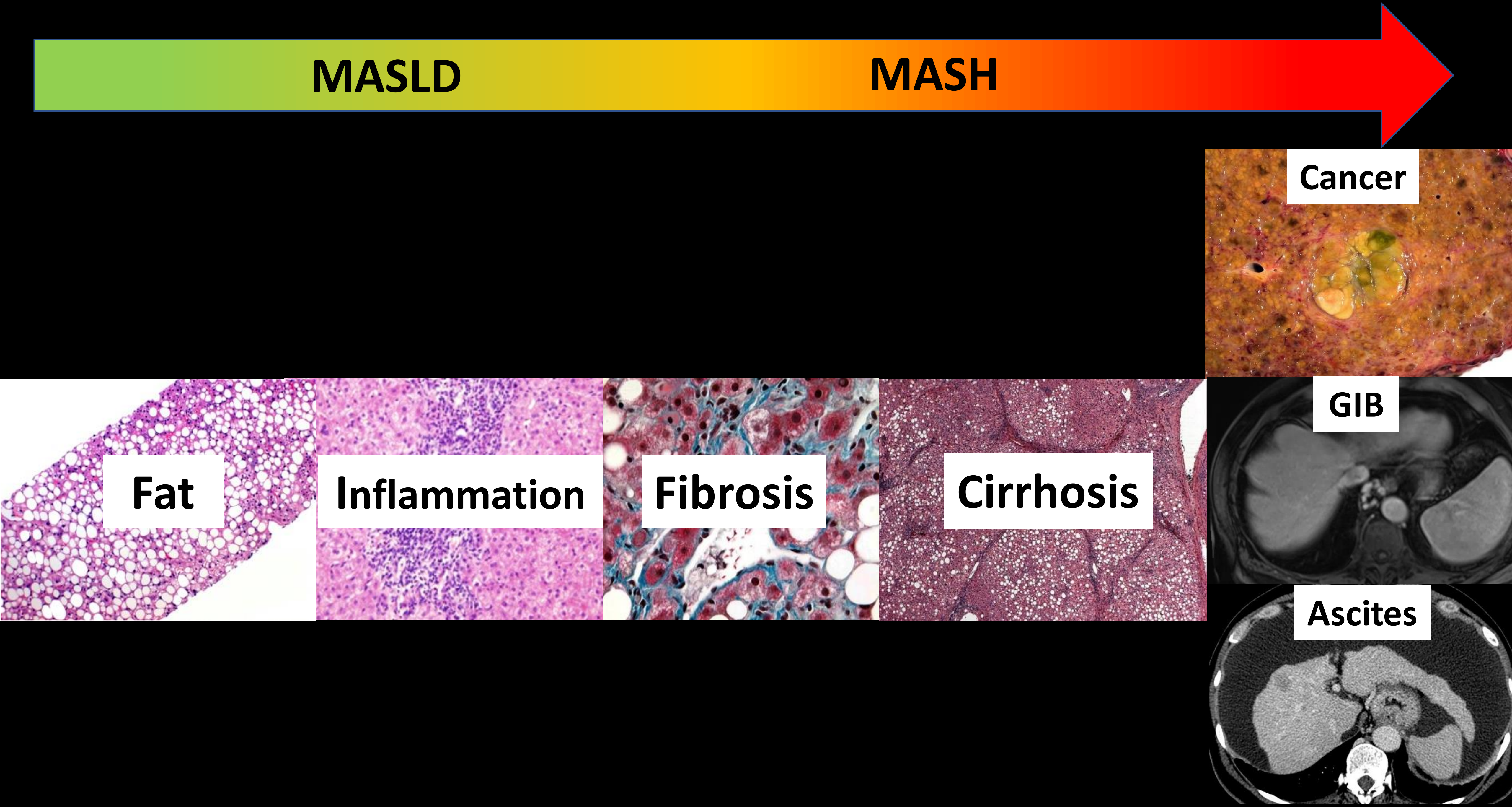
Emerging evidence (sample):

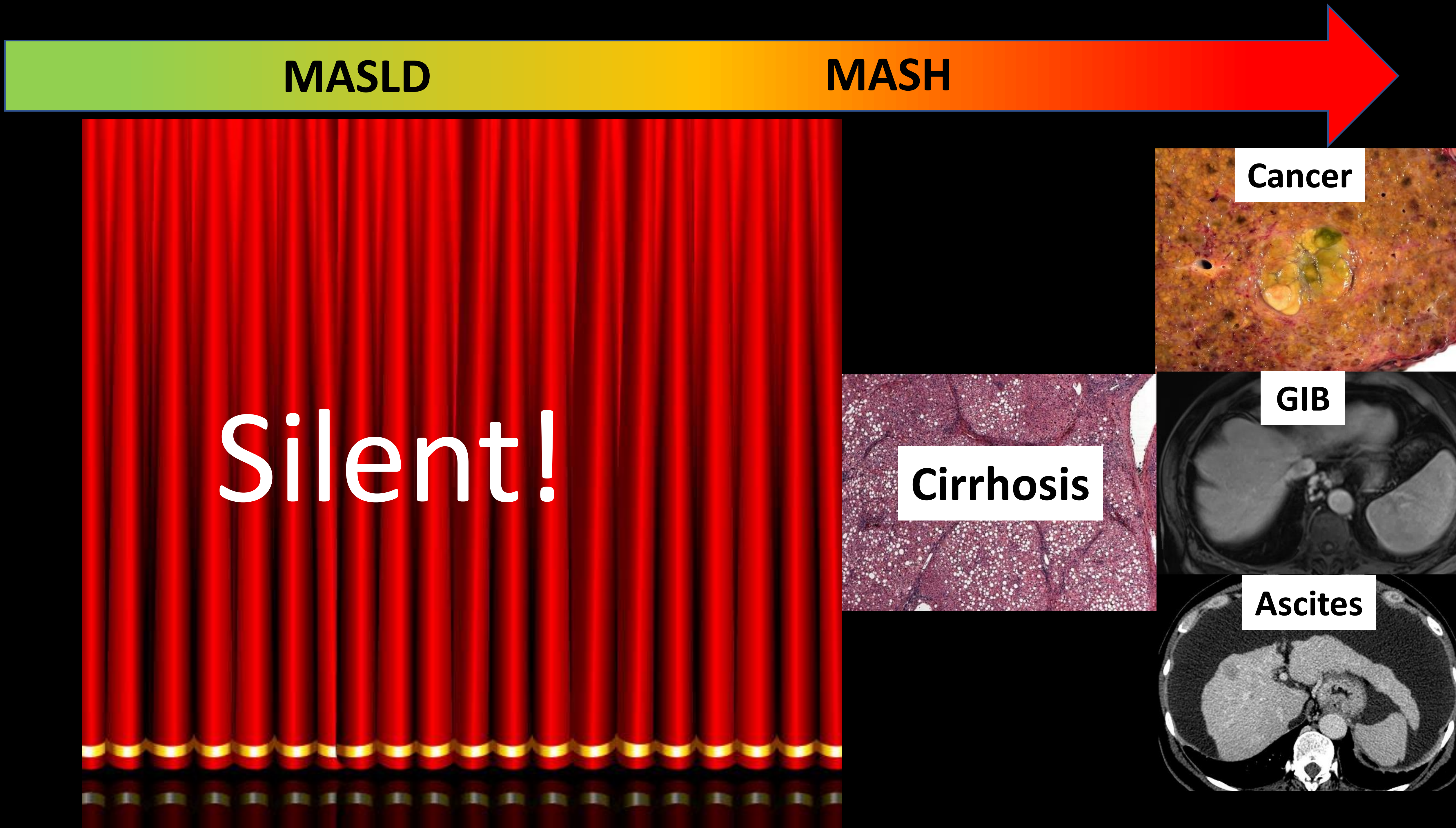
Andersson A, Clin Gastro and Hepatol. 2021
Beyer C, Plos One 2021
Imajo K, World J Gastro. 2021
Dennis A, Frontiers in Endo. 2021
Pavlides M, Liver Inter. 2017



Harrison SA, AJG 2021

Summary


MASLD
MASH
Cancer
GIB
Ascites
Fat
Inflammation
Fibrosis
Cirrhosis

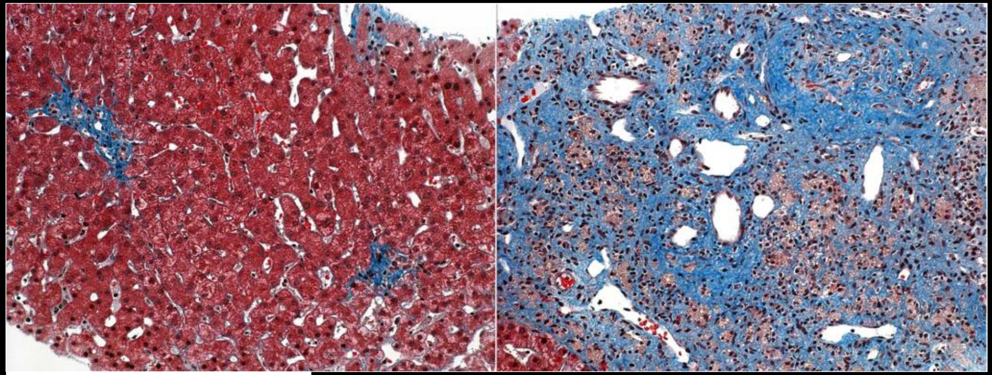

MASLD
MASH
Silent!
Cirrhosis
Cancer
GIB
Ascites

MRI-PDFF is a QIB for liver fat

- Uses complex modeling- ‘pure measure’
- Accurate and Precise
- Easy to perform, Single breath hold
- Validated across vendors and field strength

Noninvasive

Minimal risk

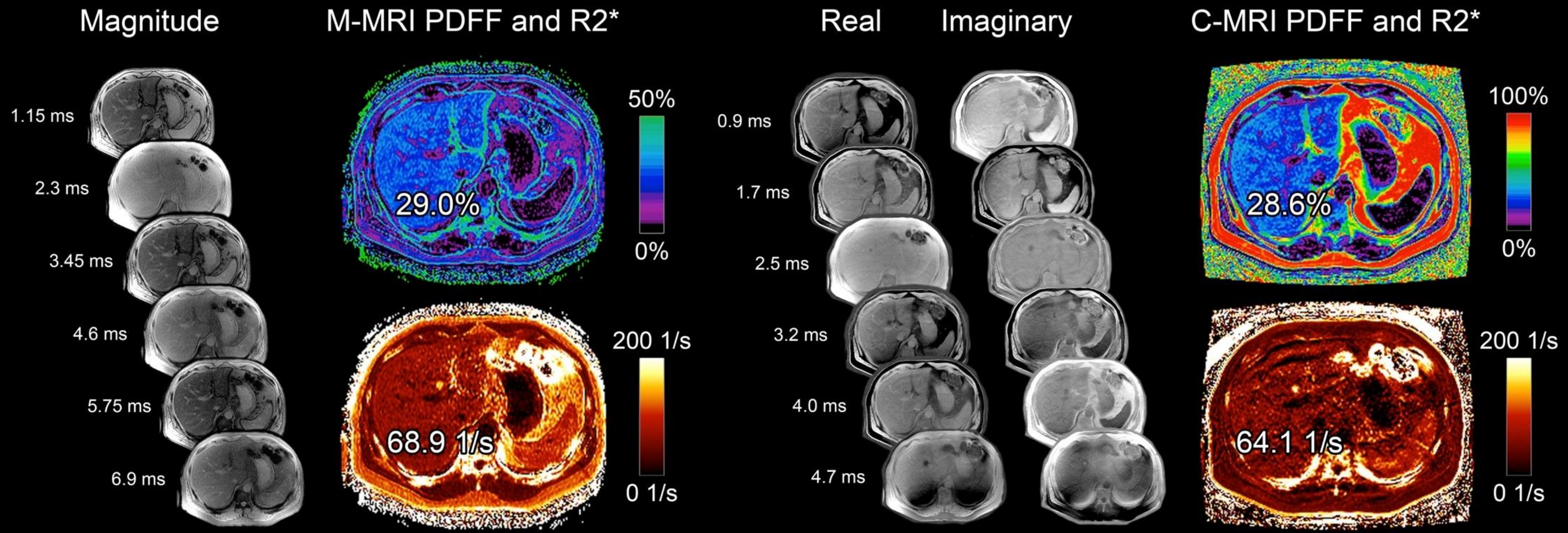


Global

Same Patient-two biopsy cores

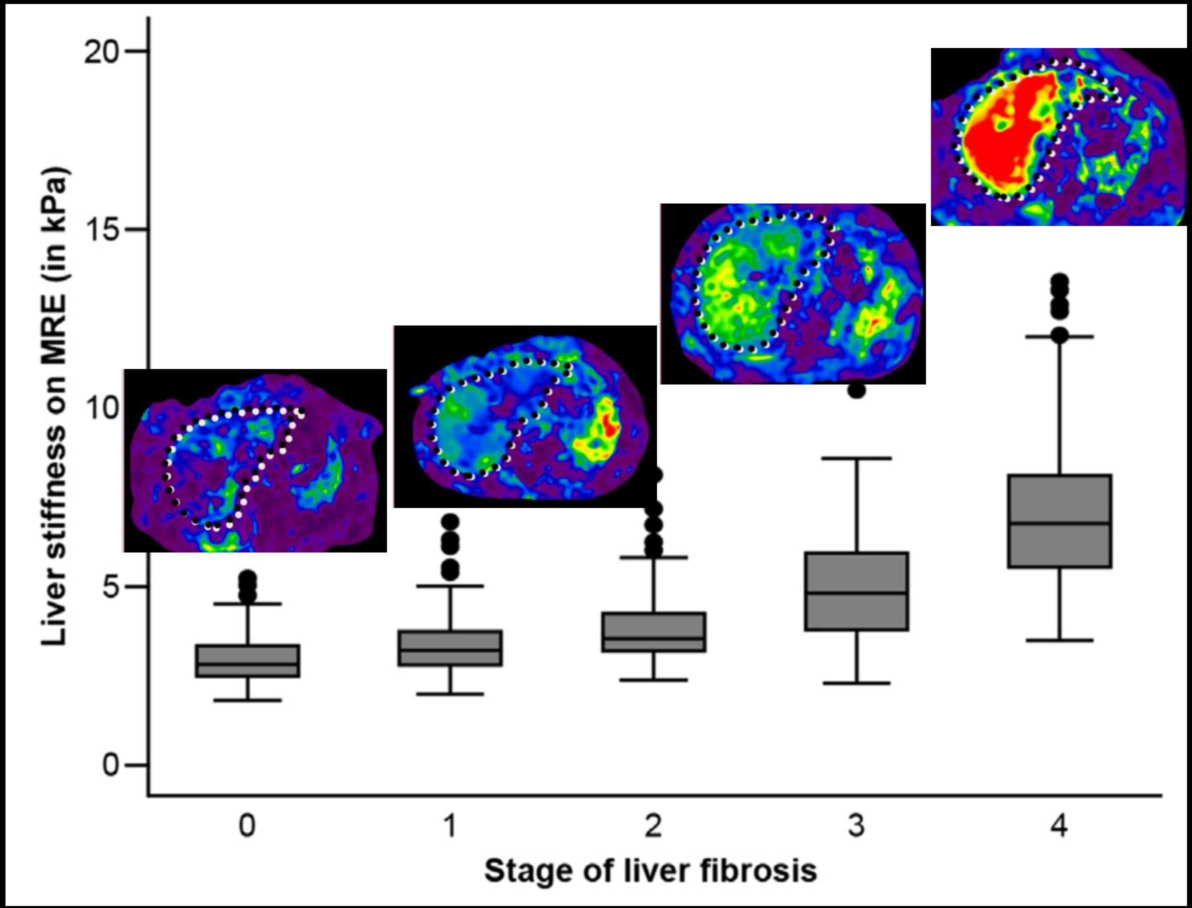
Kang B, Invest Radiol 2012; Kang, JMRI 2011

R_2* Is a QIBM for Iron



MRE is a QIB for liver fibrosis

- Non-invasive, minimal risk
- Standardized across systems
- Easy to perform
- Automated analysis now available
- Correlates with fibrosis/stages



Conclusion

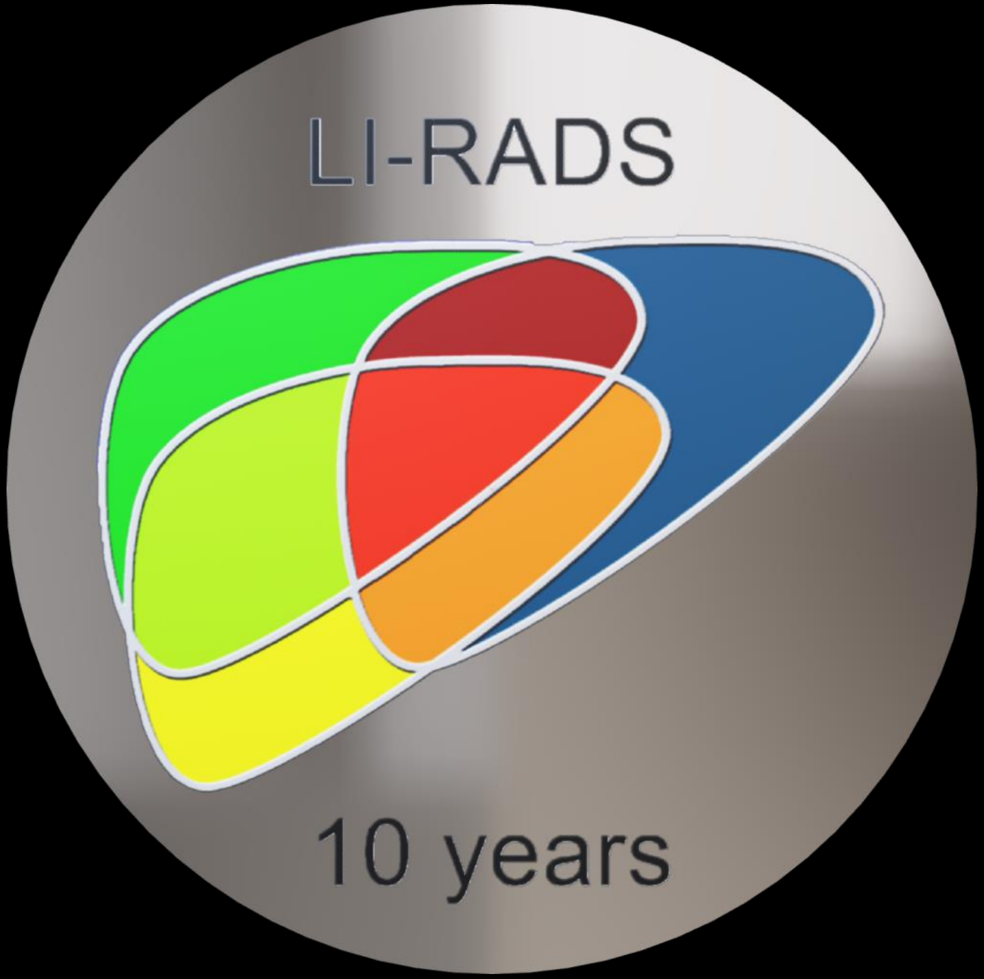
- MRI methods for fat, fibrosis, and iron are validated and in clinical use

- Inflammatory imaging biomarkers are still needed

Backontrackproducts.com

Thanks!

- k1fowler@ucsd.edu
- @chemshift1



- Stay tuned for quantitative imaging lexicon and guidance from LI-RADS