Fontan Outcomes Network
Case Review Conference

Fontan-Associated Liver Disease

Presented by Cincinnati Children's Hospital

September 20, 2022

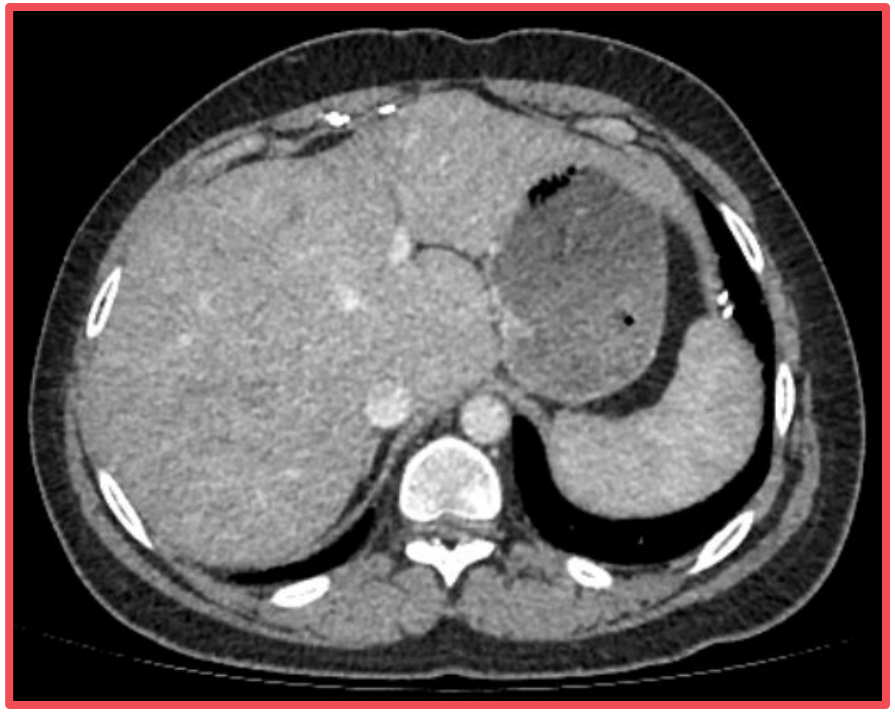
FONTAN
OUTCOMES NETWORK

We focus on the Fontan liver as a diseased organ

1. Substantial liver fibrosis is ubiquitous.
2. Decompensated cirrhosis is rare (e.g., encephalopathy).
3. There is modest correlation between the severity of hemodynamic abnormality and liver fibrosis.
4. Liver complications can be devastating (e.g., HCC) or otherwise clinically important (e.g., vasodilation, AVMs).
5. Some ‘liver issues’ (e.g., ascites) may or may not be related to liver fibrosis.

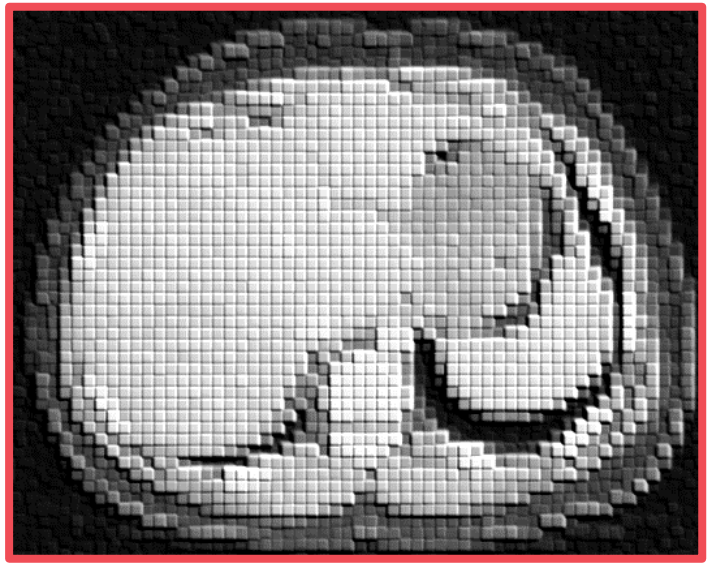
Pre-Case: Unintended consequences

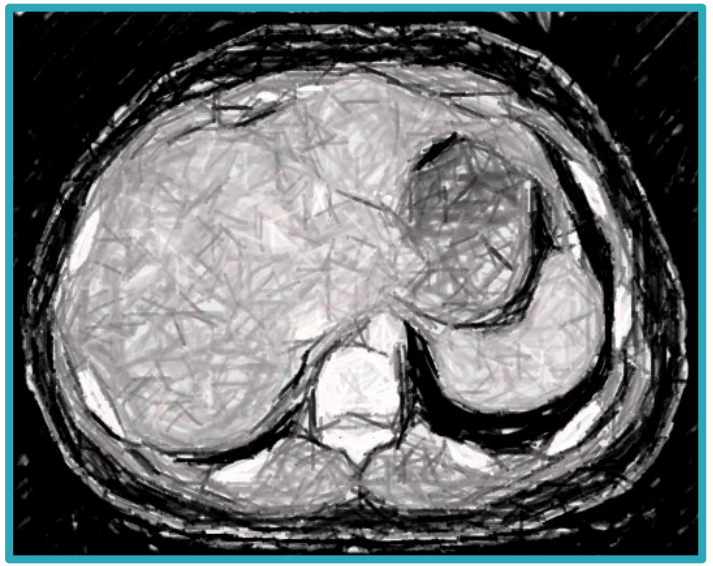
- 20-year-old man with a Fontan circulation presented to an ER c/o abdominal pain
- Based on abdominal CT, ER diagnosed end stage cirrhosis → referred to liver tx surgeon
- The pain, of course, was unrelated to the liver



Pre-Case: Unintended consequences

- 20-year-old man with a Fontan circulation presented to an ER c/o abdominal pain
- Based on abdominal CT, ER diagnosed end stage cirrhosis → referred to liver tx surgeon
- The pain, of course, was unrelated to the liver
- We met him in clinic 2 weeks later:
  - Asymptomatic
  - Assessment c/w expected Fontan; no liver mass or other complications
  - In the interim, he had cancelled a trip to Disney World and dropped out of college





"Our group expert consensus found it reasonable to consider surveillance testing every 3 to 4 years in the child (<12 years of age) with Fontan circulation."

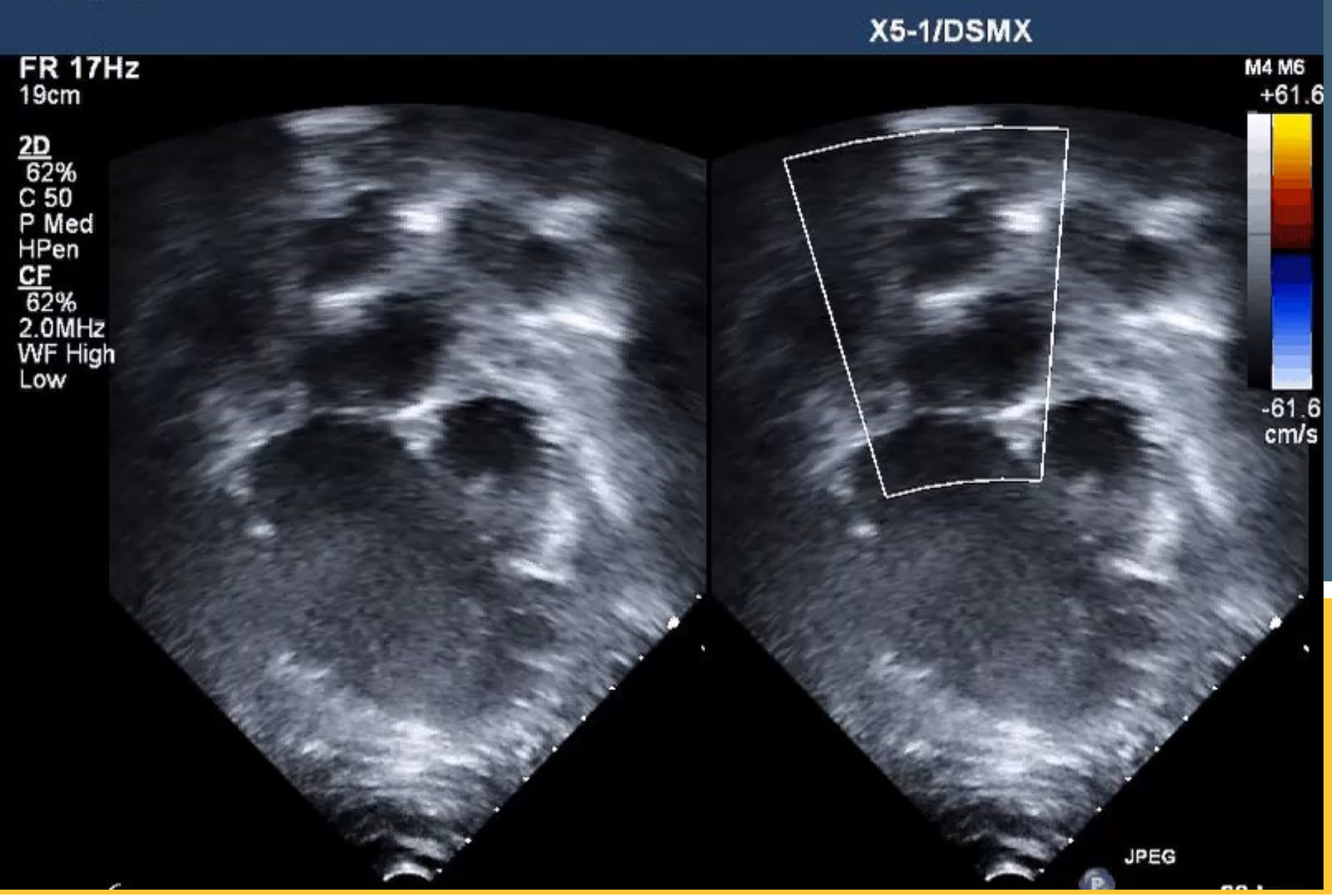
Reasons for imaging include:

- Hepatocellular carcinoma (HCC)
- "Cirrhosis"?
  - Architecture
  - Stiffness
- Other prognostic factors (e.g., size, splenomegaly, ascites, portosystemic collateral vessels)

Rychik J, Atz AM, Celermajer DS, Deal BJ, Gatzoulis MA, Gewillig MH, Hsia T-Y, Hsu DT, Kovacs AH, McCrindle BW, Newburger JW, Pike NA, Rodefeld M, Rosenthal DN, Schumacher KR, Marino BS, Stout K, Veldtman G, Younoszai AK, d'Udekem Y; Evaluation and management of the child and adult with Fontan circulation: a scientific statement from the American Heart Association. *Circulation.* 2019;140:e234–e284.

Case 1

- 18-year-old young man with hypoplastic left heart syndrome.
  - 2 days: Norwood procedure
  - 6 months: Bidirectional Glenn
  - 3 years: Extracardiac fenestrated Fontan (20 mm Gore-Tex conduit)
- His only medication is a baby aspirin.
- He is asymptomatic (albeit sedentary).
- His mother refers to him as “The poster child of success for HLHS.”
- There has been no prior liver evaluation.

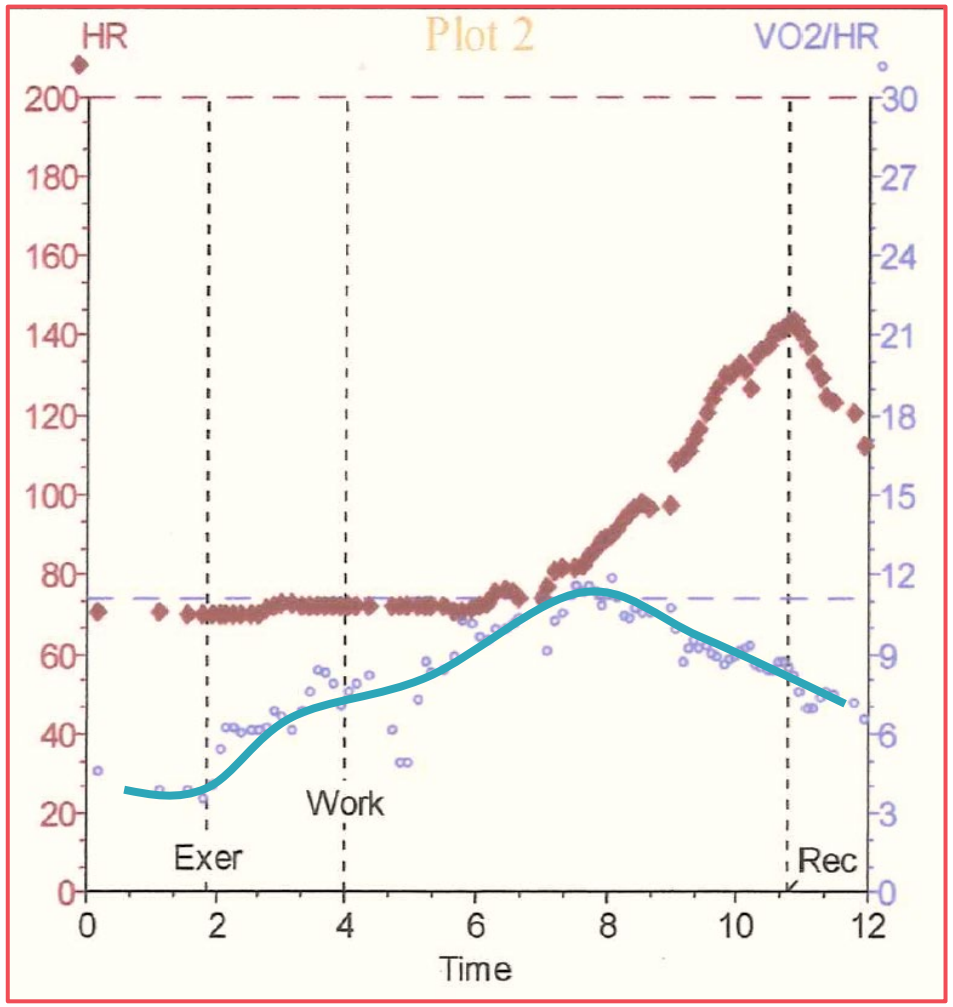


Echo-cardiogram

FONTAN OUTCOMES NETWORK

Cardio-pulmonary exercise testing

Cycle ergometer, ramp protocol.	
Peak work rate	179 watts
Peak VO_2	26 mL/kg/min *65% predicted*
Peak heart rate	175 beats / minute
Peak O2 pulse	14 mL/beat *74% predicted*



$$VO_2 = Cardiac\ output\ x\ (cAO_2 - cVO_2)$$

- heart rate
- stroke volume
  - EDV
  - EF
  - Valve reg

FONTAN OUTCOMES NETWORK

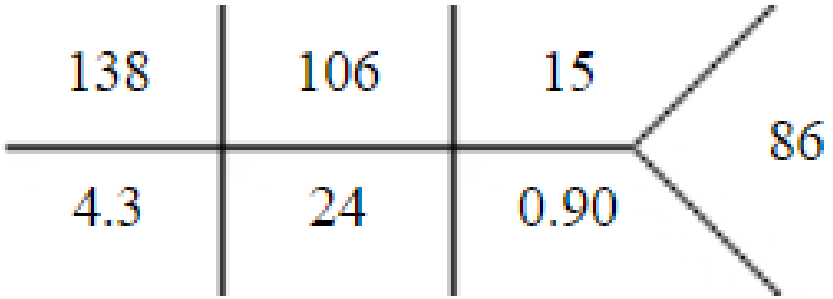
Cardiac MRI

Generally reassuring:

RV end-diastolic volume	116 mL/m^2
RV end-systolic volume	62 mL/m^2
RV ejection fraction	47%

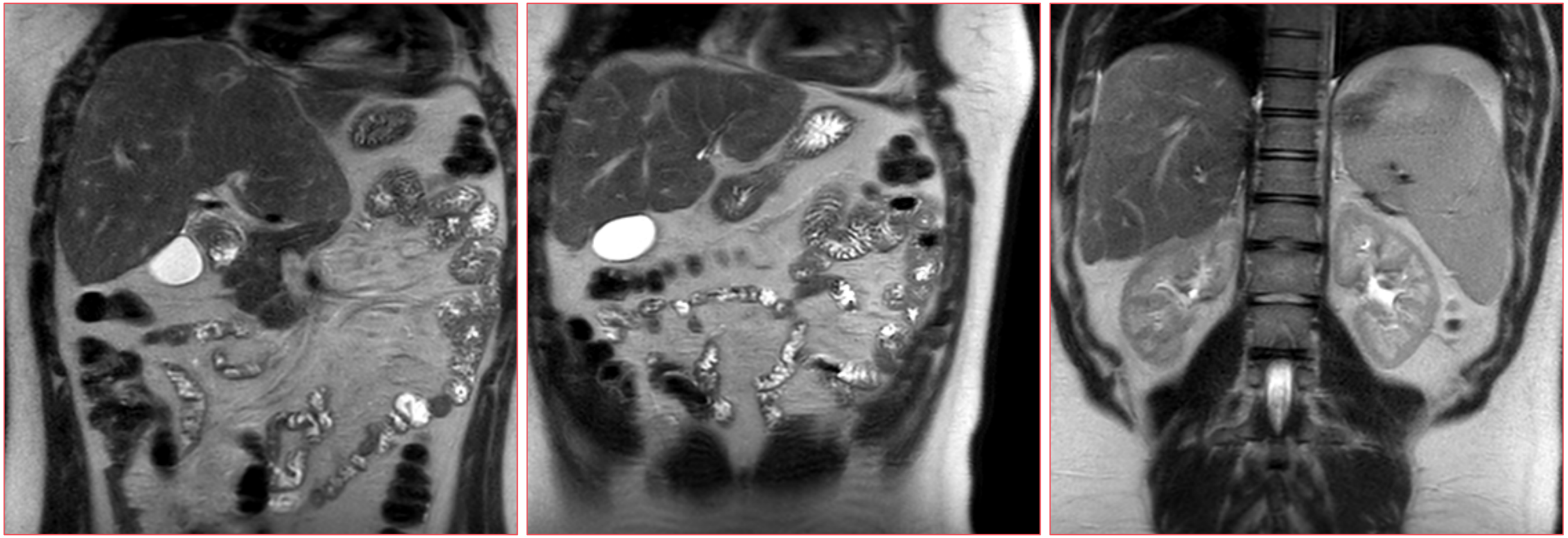
Susceptibility artifact limited evaluation of the Fontan pathway and pulmonary arteries.

Laboratory testing



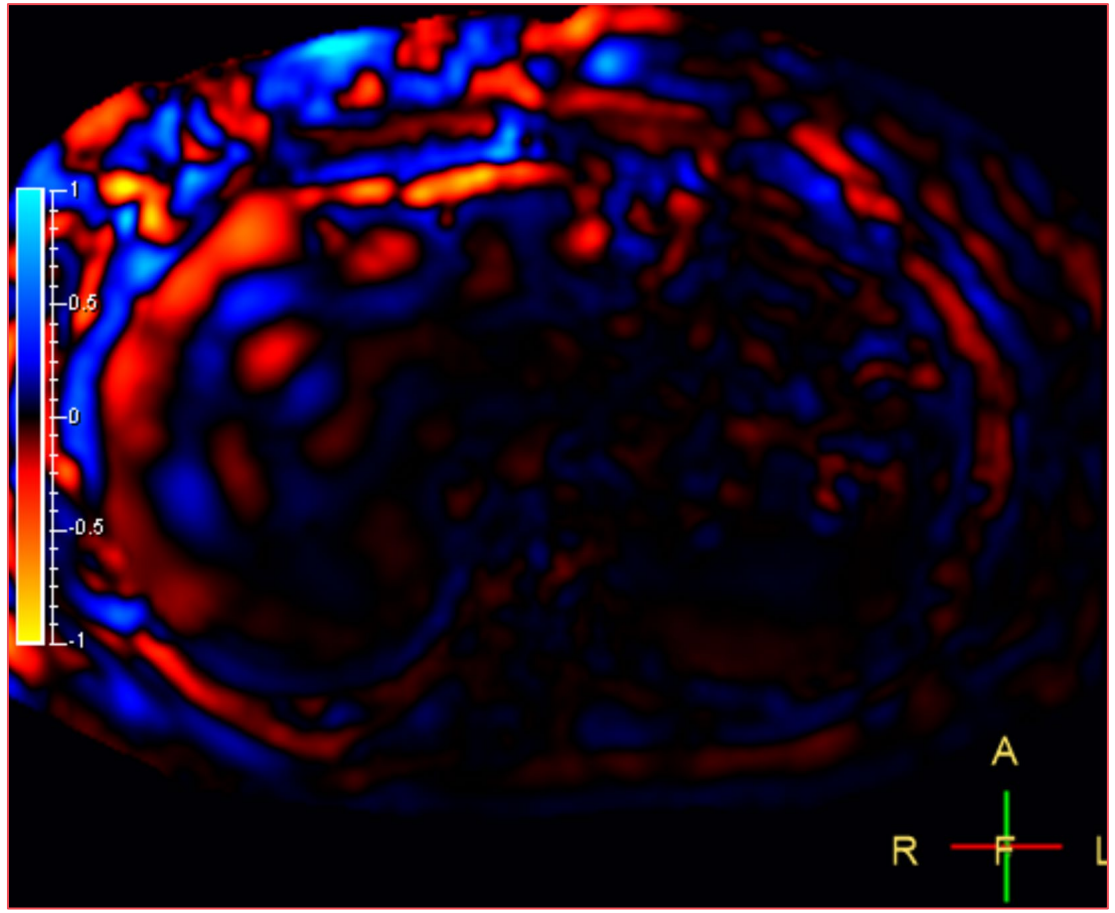
AST	34
ALT	32
Alk Phos	124
Total Bili	1.0
Direct Bili	0.4
Albumin	4.9

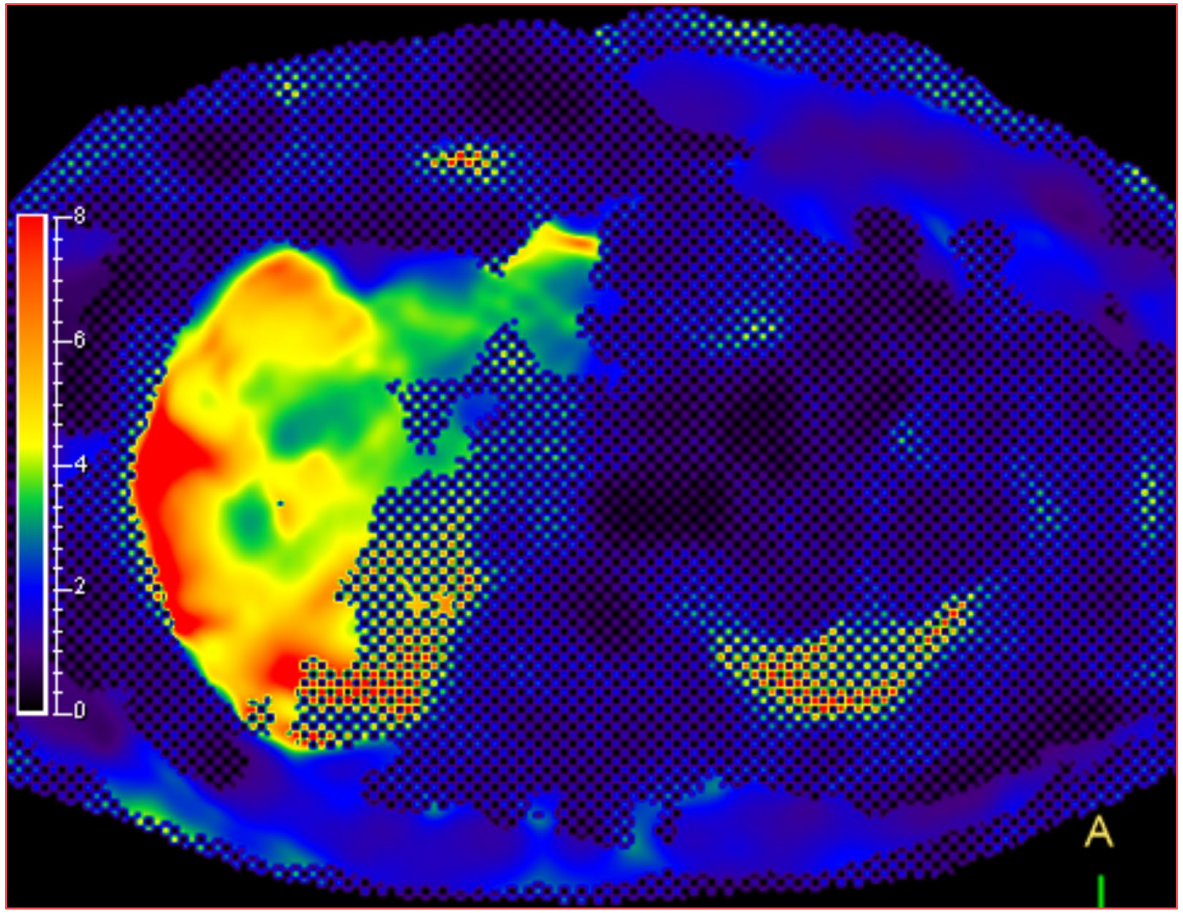
INR	1.3
PT	13.5
PTT	31.8



Liver MRI (2018)

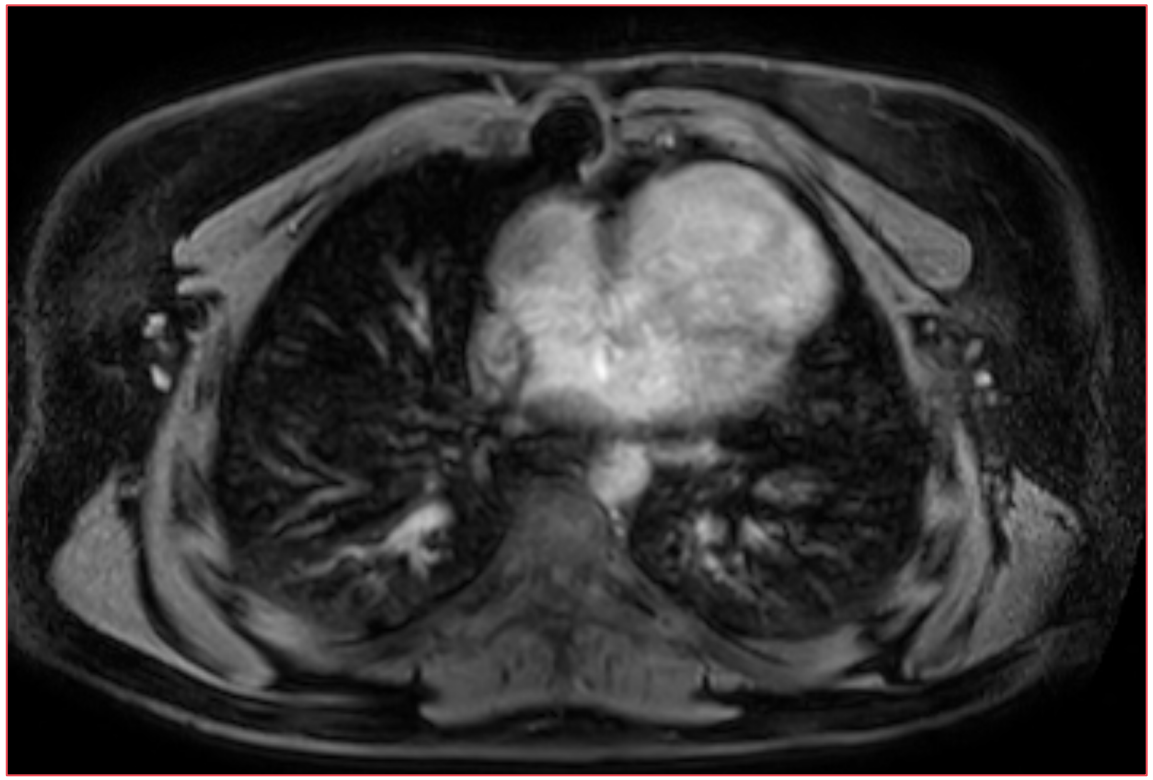
FONTAN OUTCOMES NETWORK

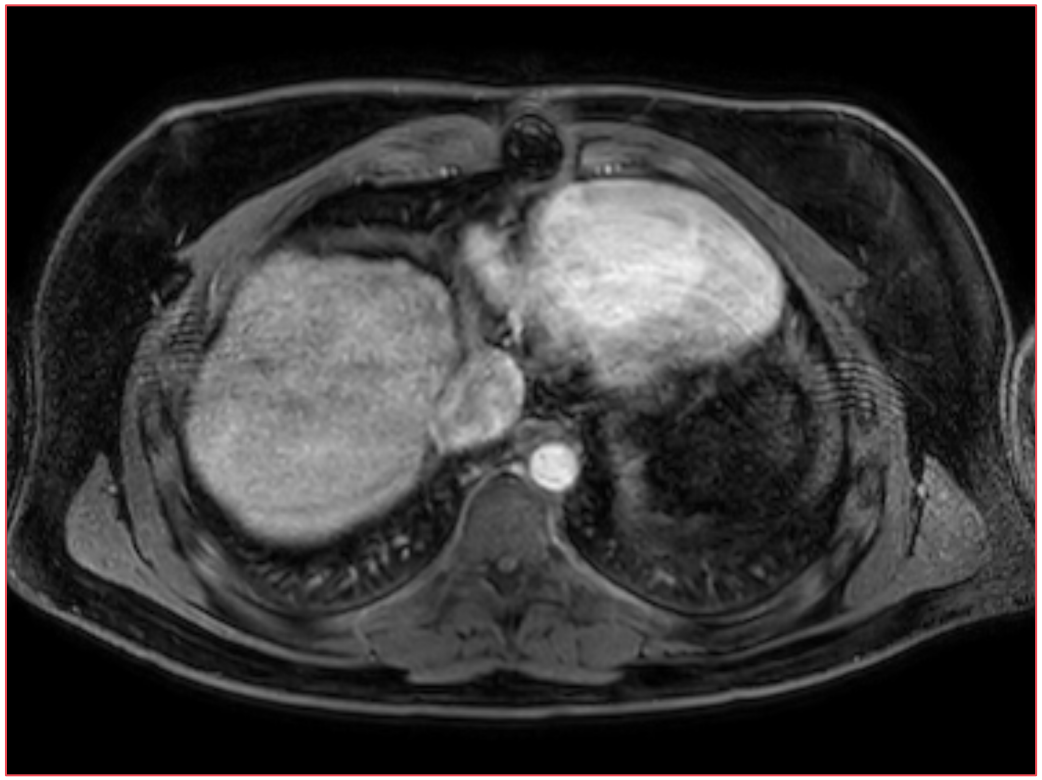




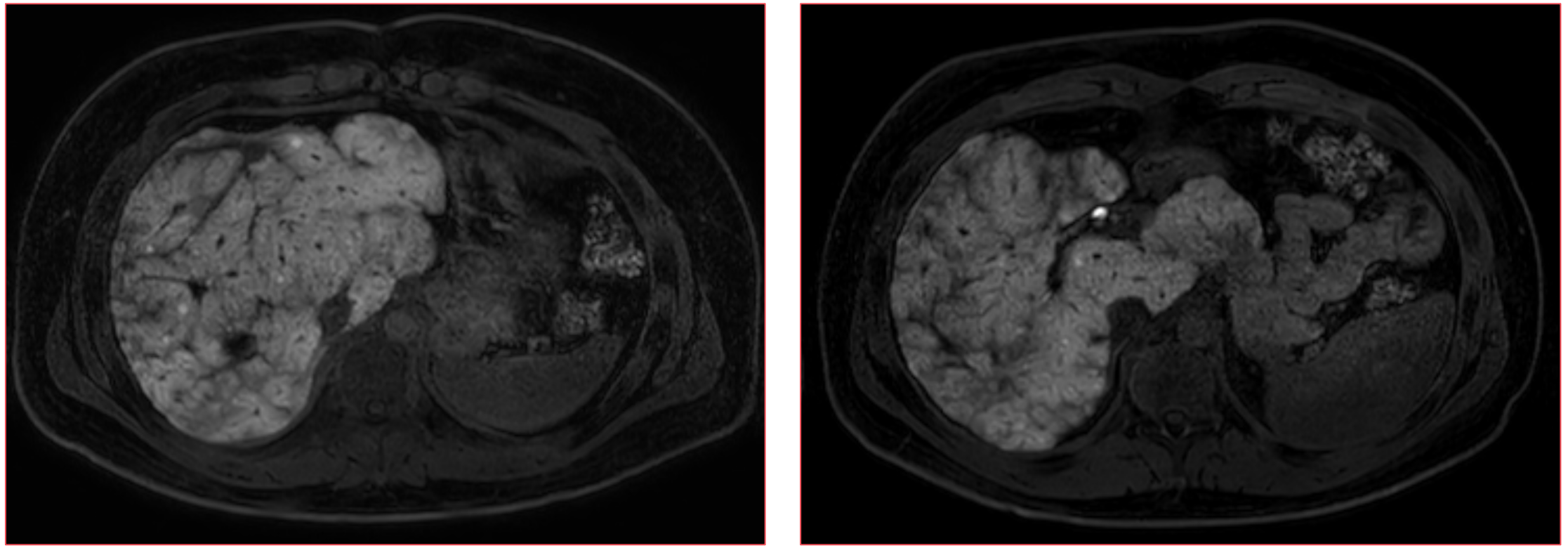
Liver MRI (2018)
4.9 kPa

FONTAN OUTCOMES NETWORK





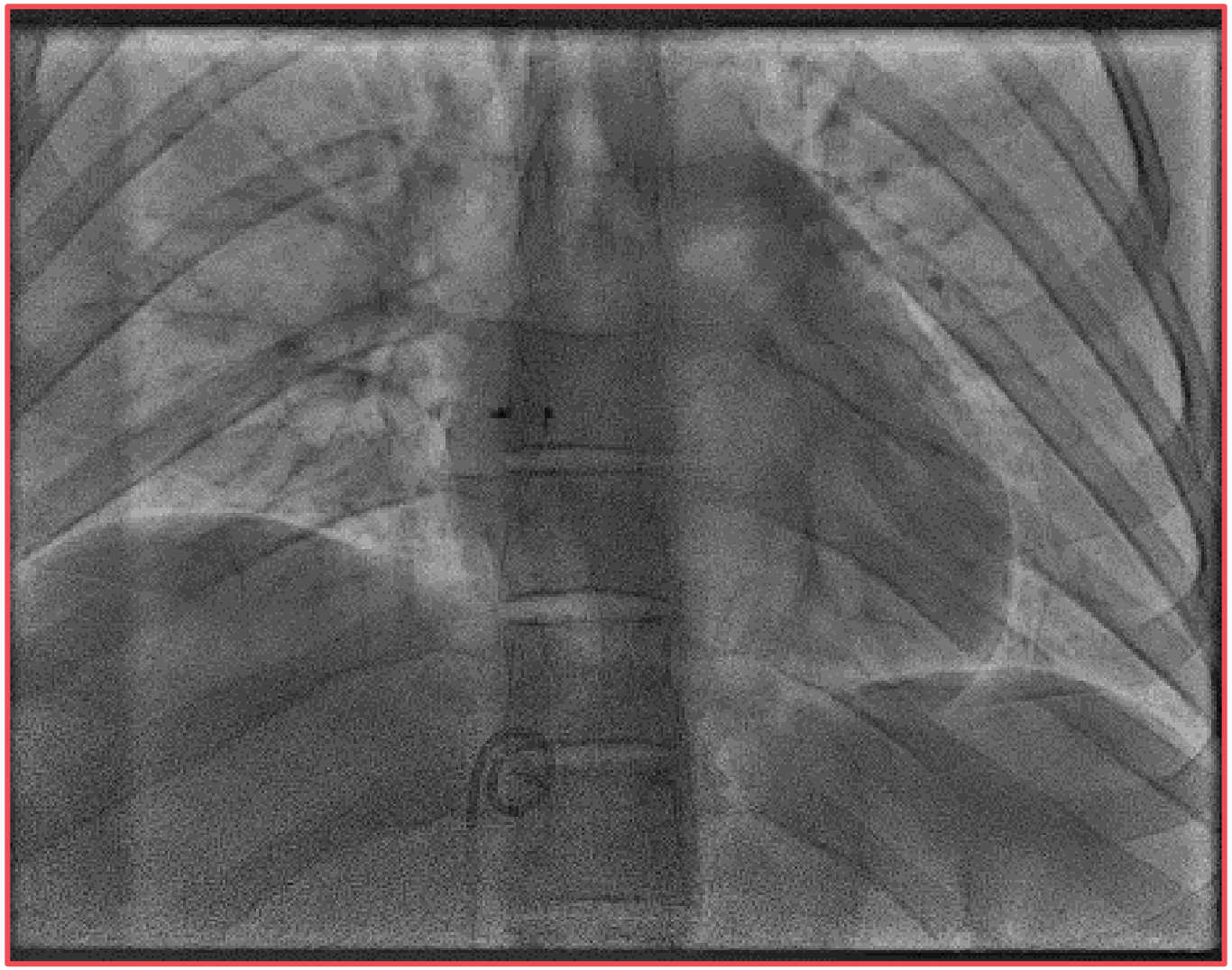
Liver MRI (2018)



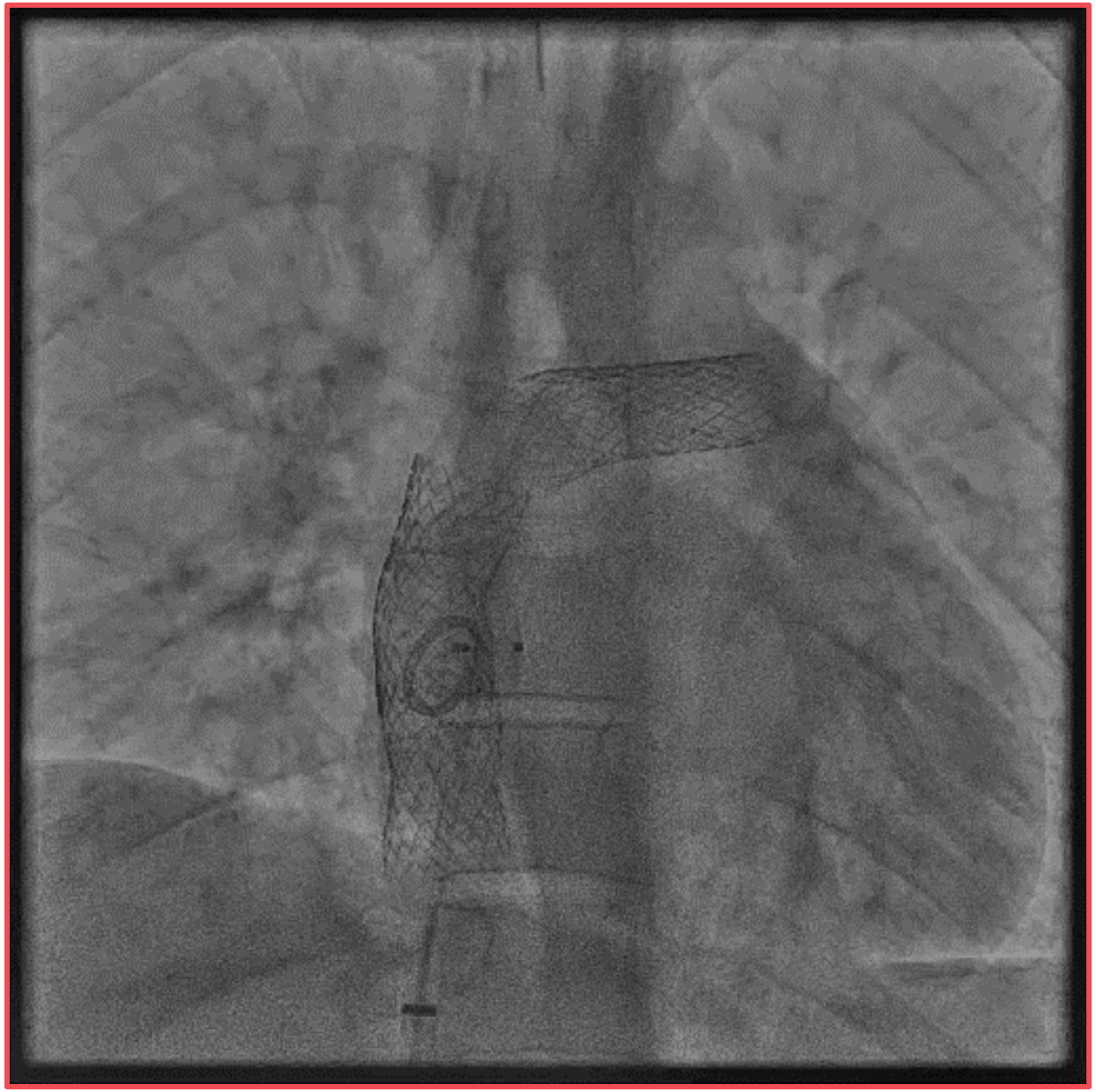
Liver MRI (2018)

Other information

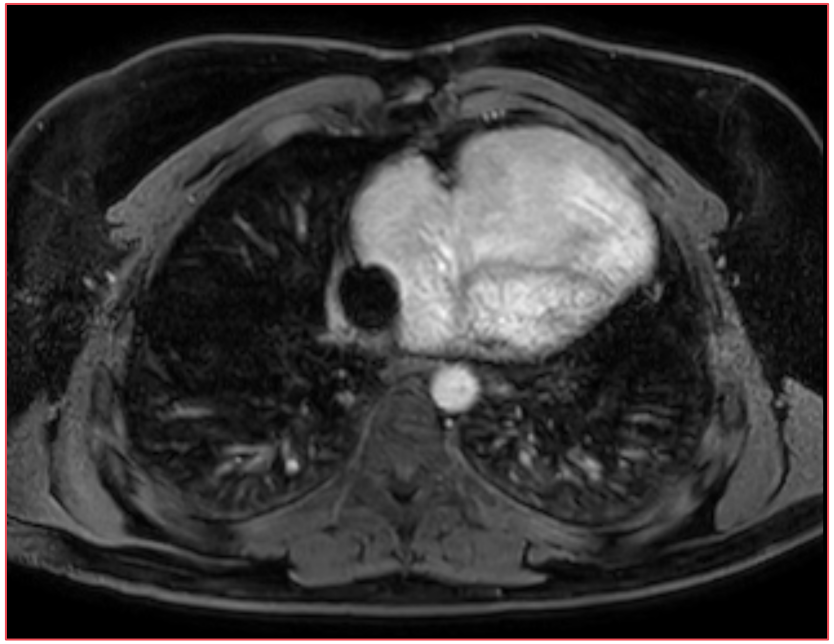
- No heart catheterization since Fontan
- No prior liver biopsy

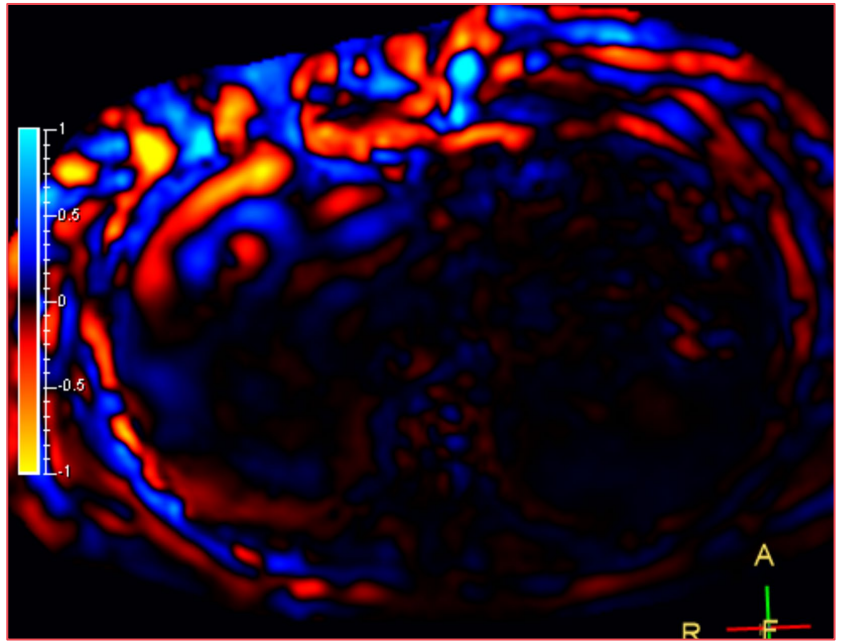


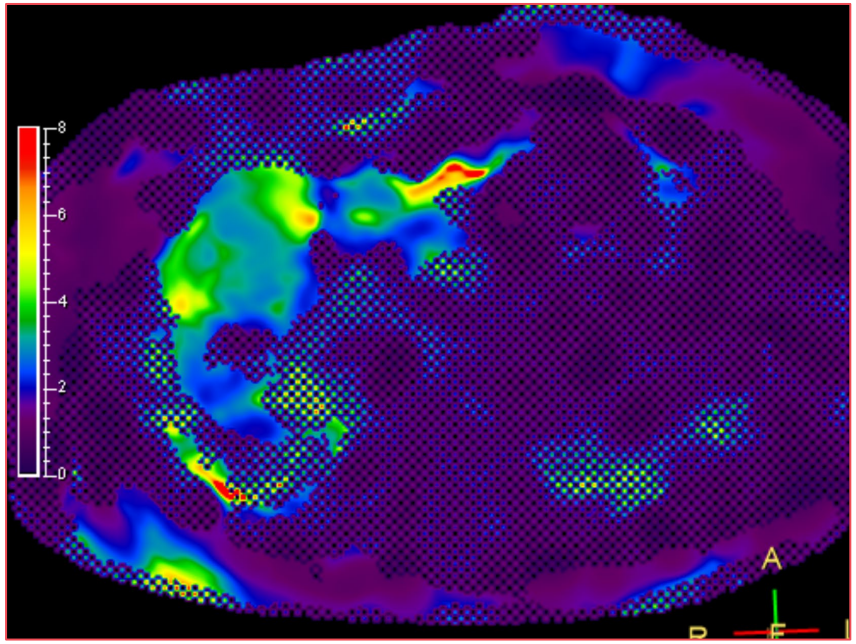
Heart Catheterization



Heart Catheterization







Liver MRI (2019)
3.4 kPa (was 4.9 kPa)

FONTAN OUTCOMES NETWORK

	Ultrasound Shear Wave Elastography	Magnetic Resonance Elastography
What does it measure?	SHEAR WAVE SPEED (m/s) Often converted to YOUNG'S MODULUS *(SWS^2 x 3, if tissue density = 1; also kPa)* Reported by transient elastography (Fibroscan)	SHEAR MODULUS (Stiffness) (kPa)
Availability	+++	+
Reproducibility	More variability	Good reproducibility / repeatability More standardized across vendors

How Reliable is MRE?

Radiology

ORIGINAL RESEARCH ■ GASTROINTESTINAL IMAGING

Liver Stiffness Measurements with MR Elastography: Agreement and Repeatability across Imaging Systems, Field Strengths, and Pulse Sequences[1]

Andrew T. Trout, MD
Suraj Serai, PhD
Alana D. Mahley, BS
Hui Wang, PhD
Yue Zhang, MS
Bin Zhang, PhD
Jonathan R. Dillman, MD, MSc

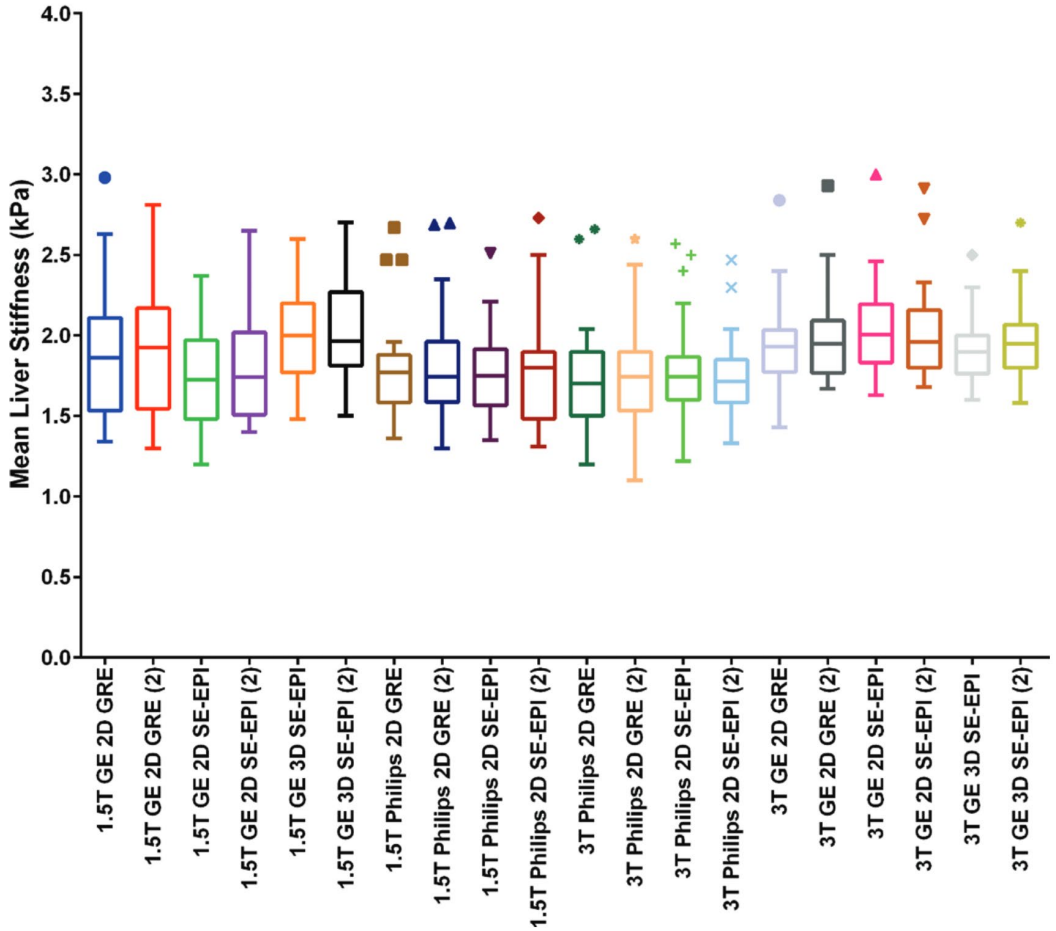
Purpose: To prospectively assess agreement and repeatability of magnetic resonance (MR) elastography liver stiffness measurements across imager manufacturers, field strengths, and pulse sequences.

Materials and Methods: This prospective cross-sectional study was approved by the institutional review board; informed consent was obtained from all subjects. On the basis of an a priori power calculation, 24 volunteer adult subjects underwent MR

Table 3

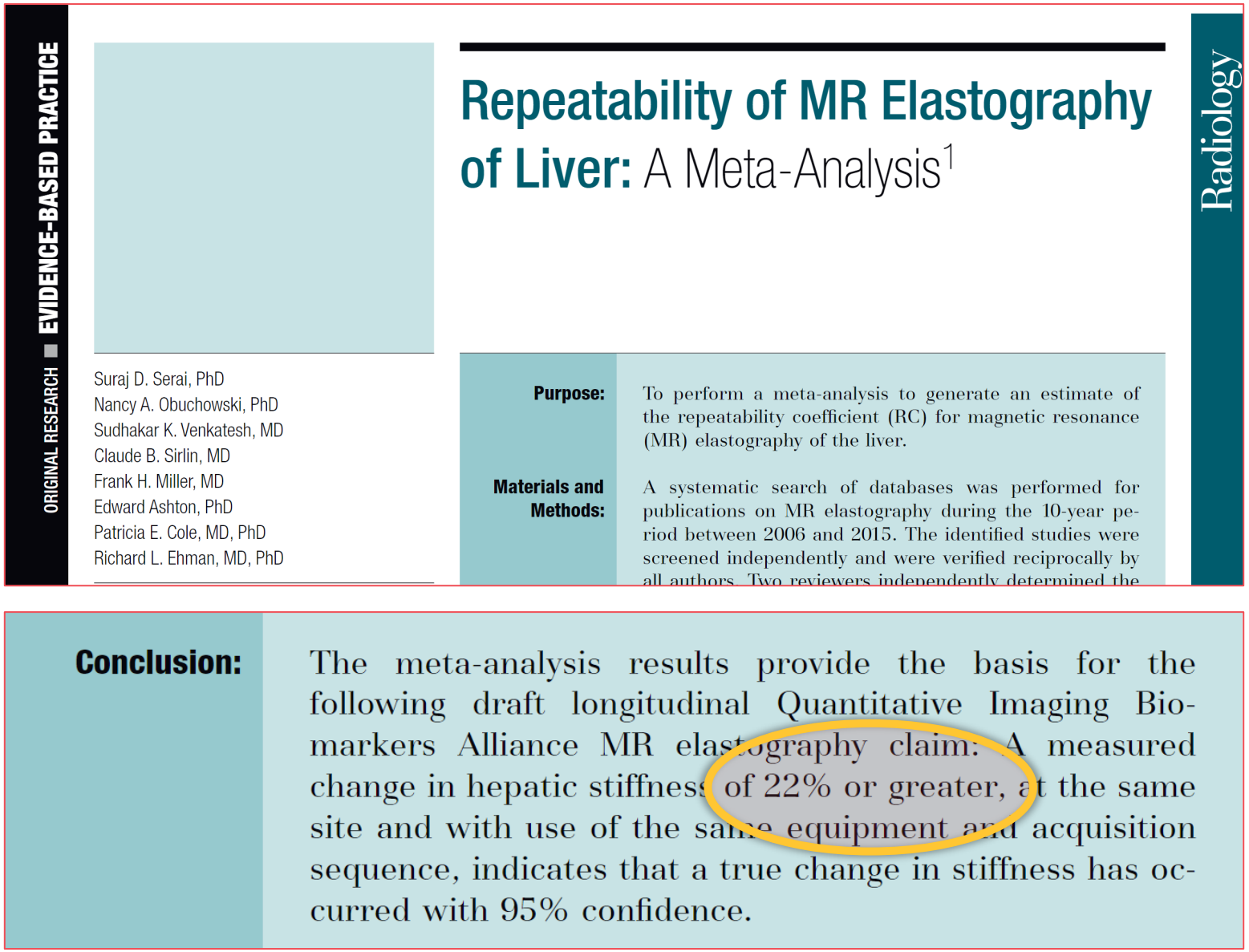
MR Elastography Pairwise Reproducibility across Pulse Sequences

	Mean Stiffness (kPa)*					
Fixed Variable	2D GRE	2D SE EPI	3D SE EPI	ICC†	*P* Value†	Pearson *r*‡
2D GRE vs 2D SE EPI						
GE 1.5 T	1.90 ± 0.41	1.74 ± 0.31	…	0.73 (0.47, 0.87)	.0094 (0.16)	0.76 (0.5, 0.89)
Philips 1.5 T	1.81 ± 0.36	1.78 ± 0.27	…	0.9 (0.78, 0.95)	.28	0.91 (0.79, 0.96)
GE 3.0 T	1.95 ± 0.27	2.05 ± 0.29	…	0.82 (0.64, 0.92)	.012 (0.093)	0.83 (0.62, 0.92)
Philips 3.0 T	1.79 ± 0.33	1.75 ± 0.33	…	0.76 (0.52, 0.89)	.45	0.76 (0.5, 0.89)
2D GRE vs 3D SE EPI						
GE 1.5 T	1.90 ± 0.41	…	2.01 ± 0.28	0.8 (0.59, 0.91)	.027 (−0.11)	0.85 (0.68, 0.93)
GE 3.0 T	1.95 ± 0.27	…	1.92 ± 0.2	0.66 (0.35, 0.83)	.36	0.68 (0.37, 0.85)
2D SE EPI vs 3D SE EPI						
GE 1.5 T	…	1.74 ± 0.31	2.01 ± 0.28	0.76 (0.52, 0.89)	<.0001 (−0.27)	0.76 (0.51, 0.89)
GE 3.0 T	…	2.05 ± 0.29	1.92 ± 0.2	0.45 (0.06, 0.72)	.025 (0.13)	0.51 (0.075, 0.73)



FONTAN OUTCOMES NETWORK

How small of a difference between tests is likely to indicate a true change?



ORIGINAL RESEARCH ■ EVIDENCE-BASED PRACTICE

Repeatability of MR Elastography of Liver: A Meta-Analysis[1]

Radiology

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Frank H. Miller, MD
Edward Ashton, PhD
Patricia E. Cole, MD, PhD
Richard L. Ehman, MD, PhD

Purpose: To perform a meta-analysis to generate an estimate of the repeatability coefficient (RC) for magnetic resonance (MR) elastography of the liver.

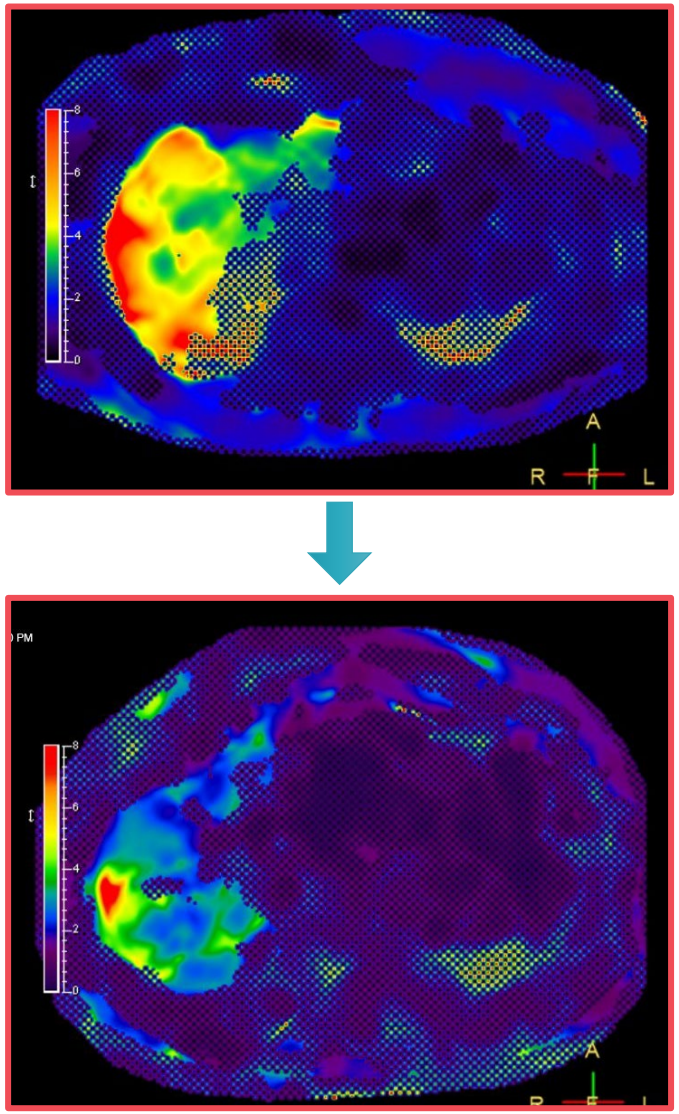
Materials and Methods: A systematic search of databases was performed for publications on MR elastography during the 10-year period between 2006 and 2015. The identified studies were screened independently and were verified reciprocally by all authors. Two reviewers independently determined the

Conclusion: The meta-analysis results provide the basis for the following draft longitudinal Quantitative Imaging Biomarkers Alliance MR elastography claim: A measured change in hepatic stiffness of 22% or greater, at the same site and with use of the same equipment and acquisition sequence, indicates that a true change in stiffness has occurred with 95% confidence.

FONTAN OUTCOMES NETWORK

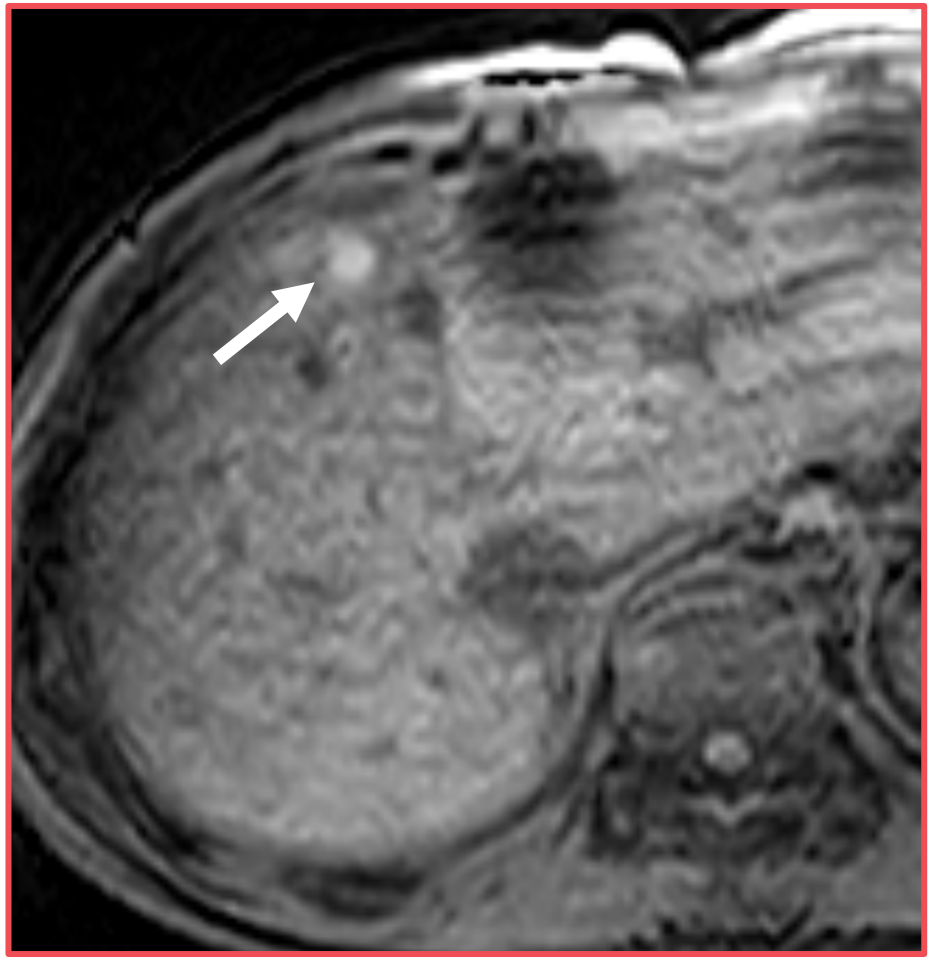
Case 1 Summary

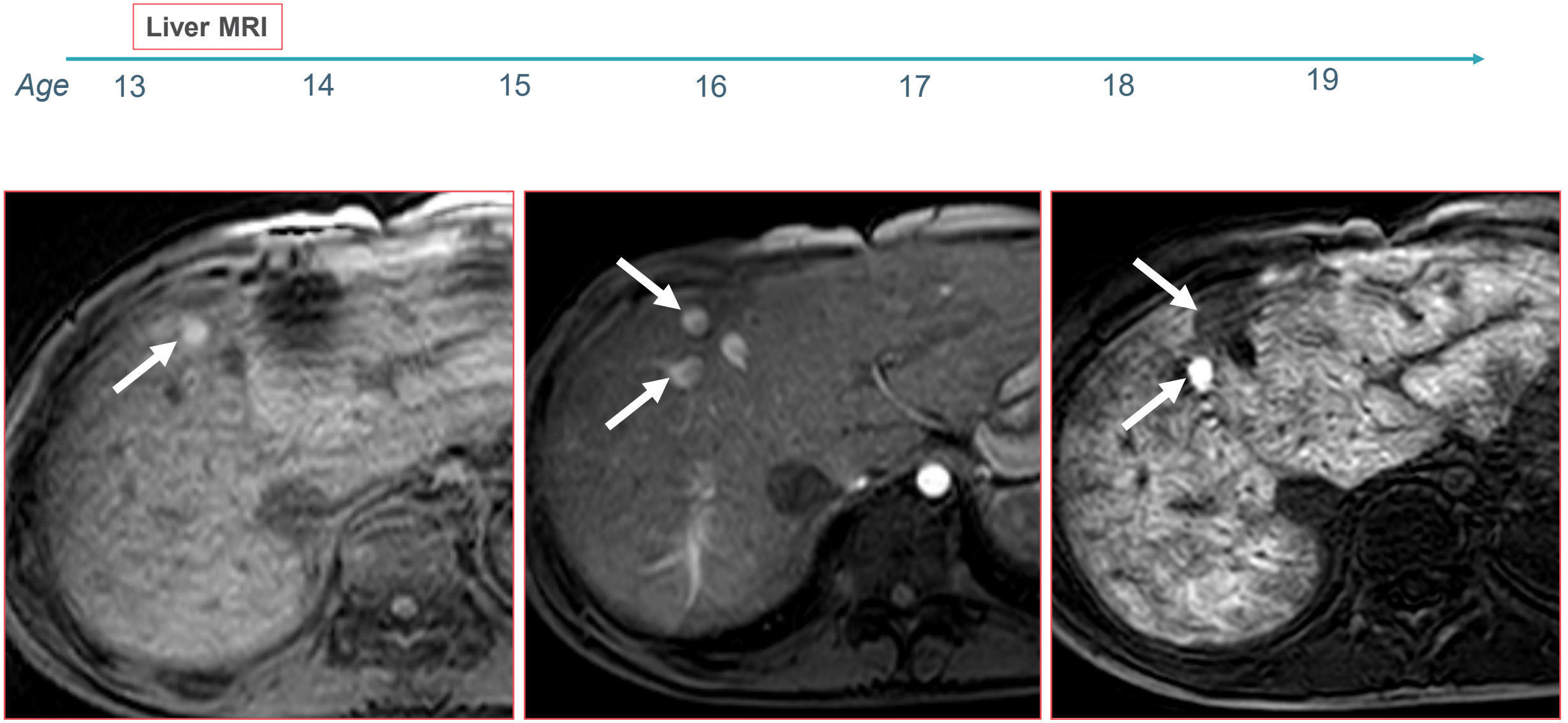
- Liver stiffness is a function of liver histology (e.g., fibrosis) + congestion.
- A finding of elevated stiffness raised suspicion for Fontan pathway obstruction, in the context of limited cardiovascular imaging.
- Alleviating Fontan pathway impedance to flow may facilitate hepatic decongestion, and thereby delay progression of liver disease.



Case 2

- 13-year-old girl with DILV + left AVV atresia, s/p 20 mm extracardiac fenestrated Fontan
- H/o protein losing enteropathy
  - Resolved after surgical enlargement of restrictive ASD
- Normal ventricular function and excellent hemodynamics
- First liver imaging at age 13 years





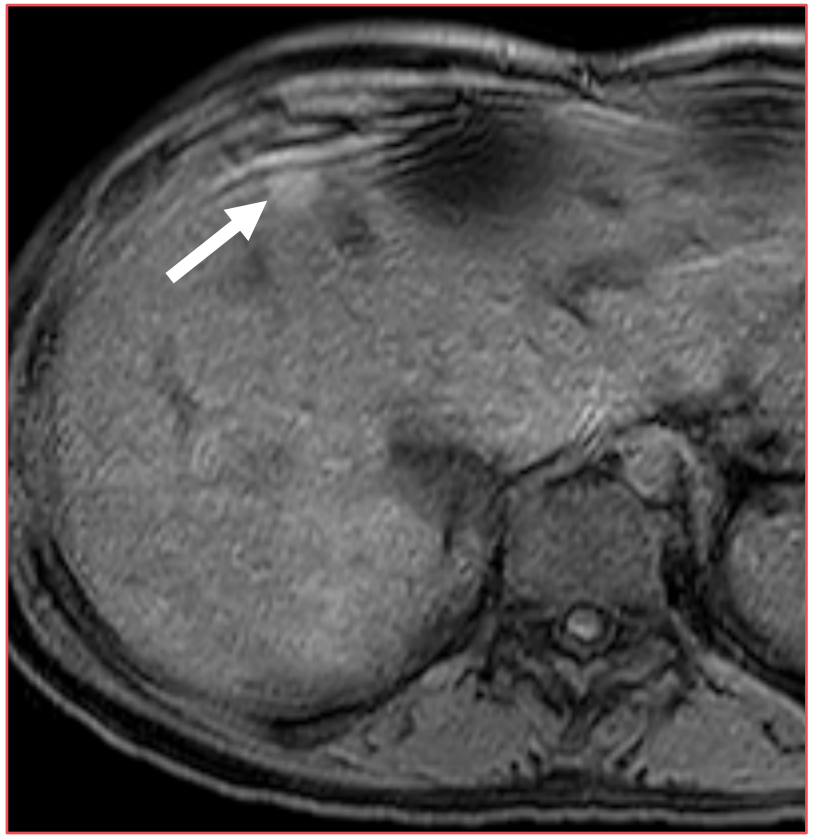
Liver MRI (baseline)

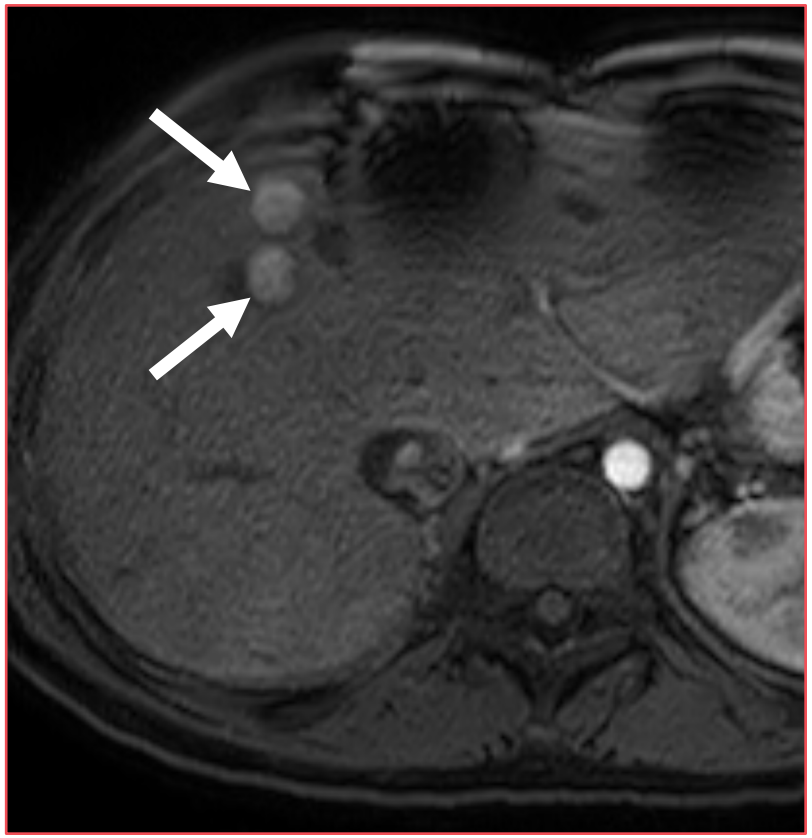
(2) 1 cm lesions – appear different

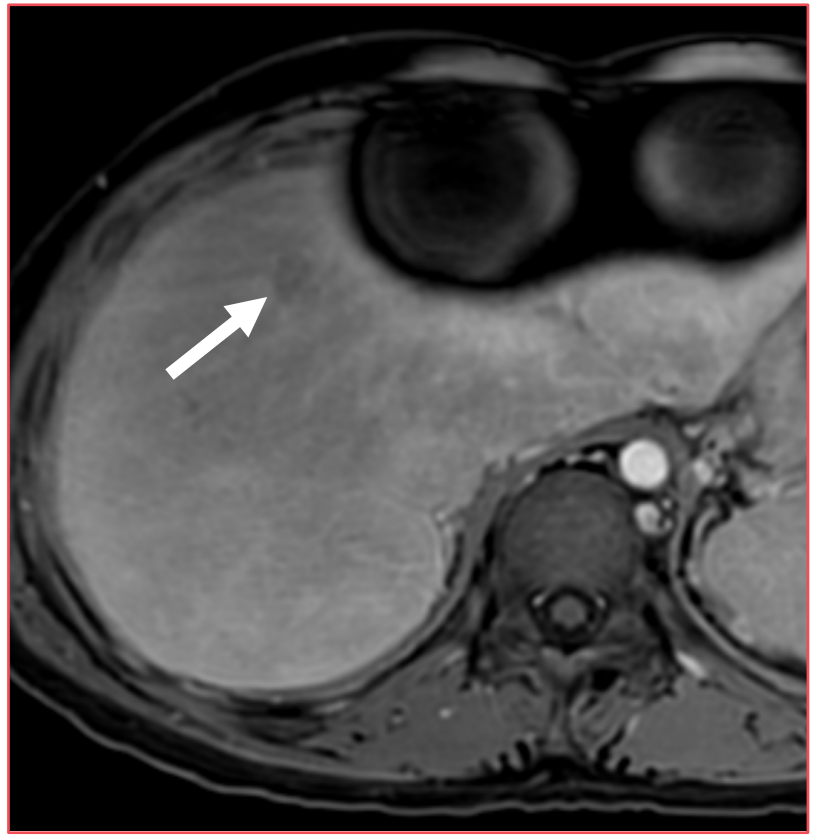
FONTAN OUTCOMES NETWORK

Liver MRI | **Liver MRI**

Age 13 14 15 16 17 18 19







Liver MRI (7 months later)

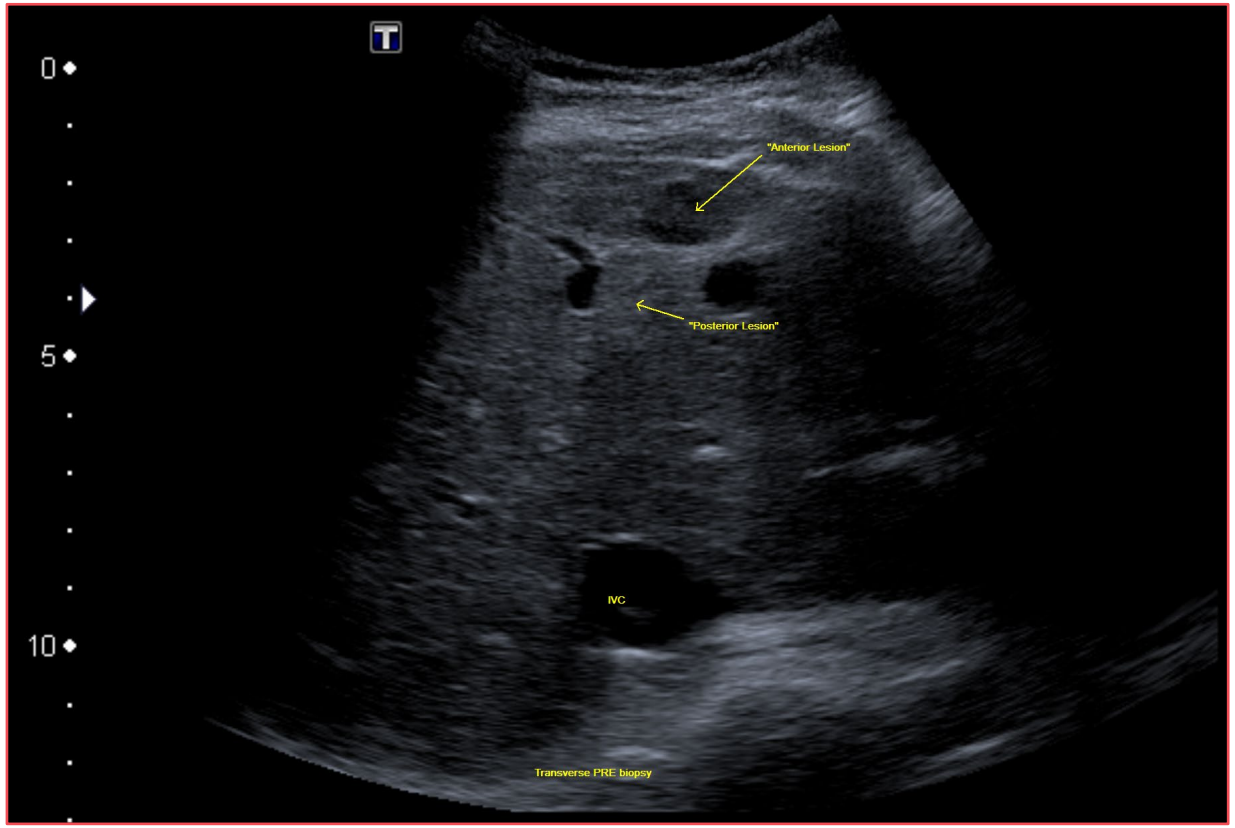
Lesions larger (1.5 cm)

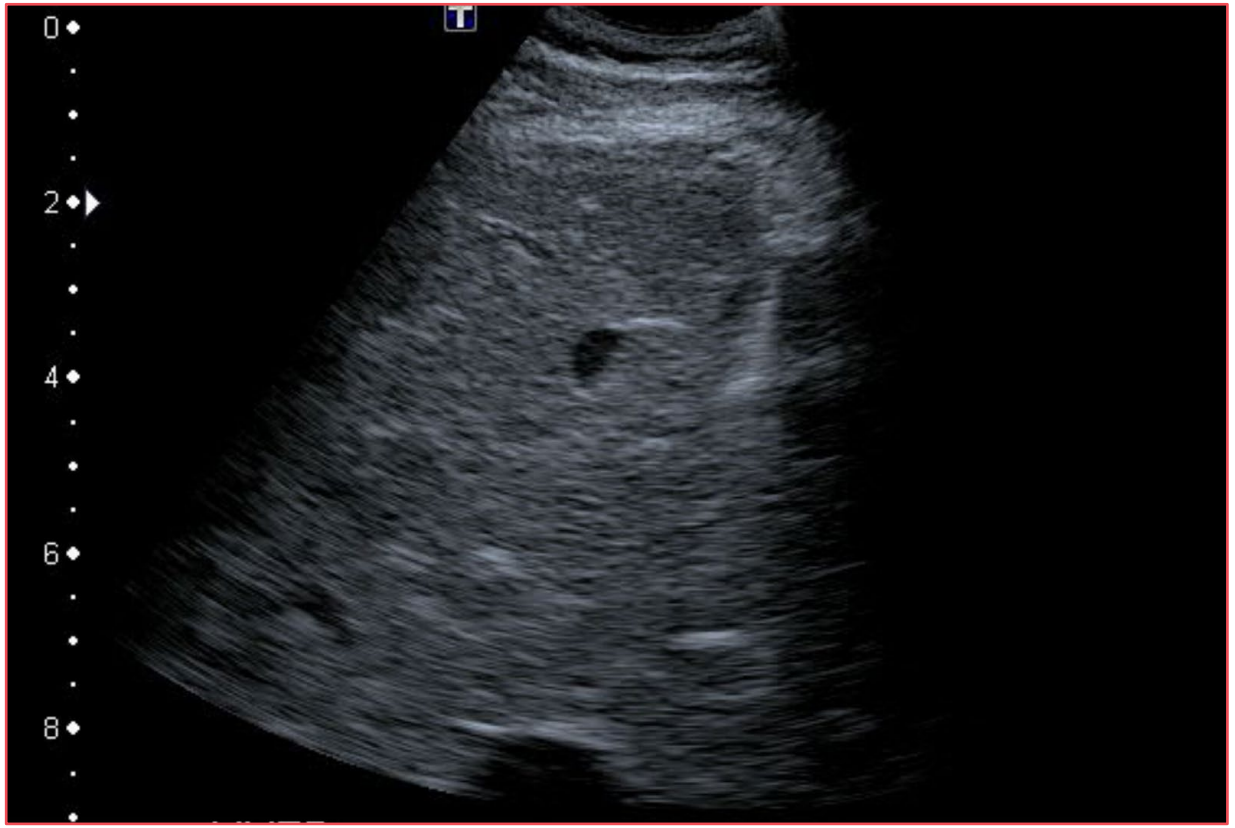
FONTAN OUTCOMES NETWORK

Liver MRI | Liver MRI | Liver MRI

Age 13 14 15 16 17 18 19

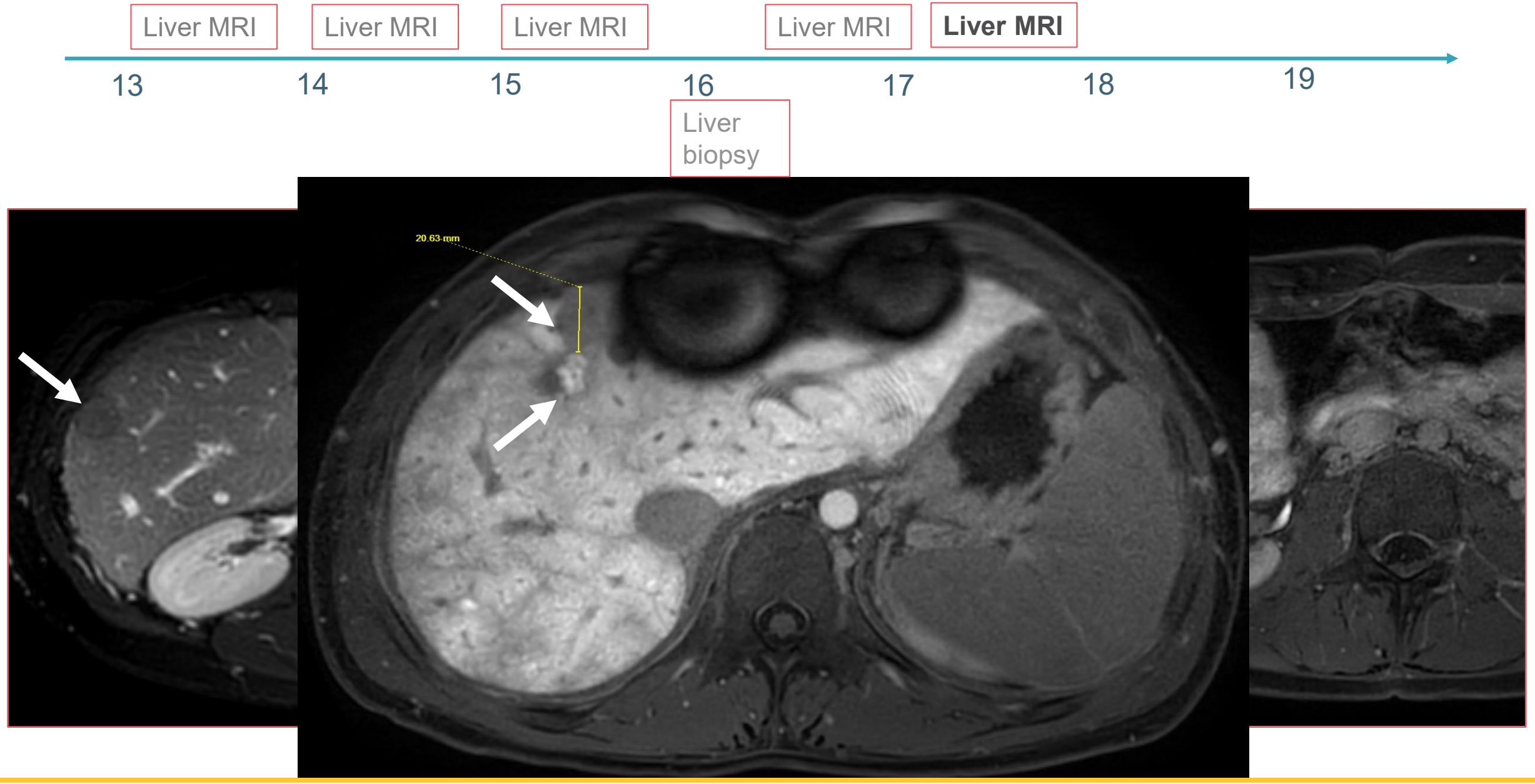
Liver biopsy





Liver Biopsy (age 16)

FONTAN OUTCOMES NETWORK



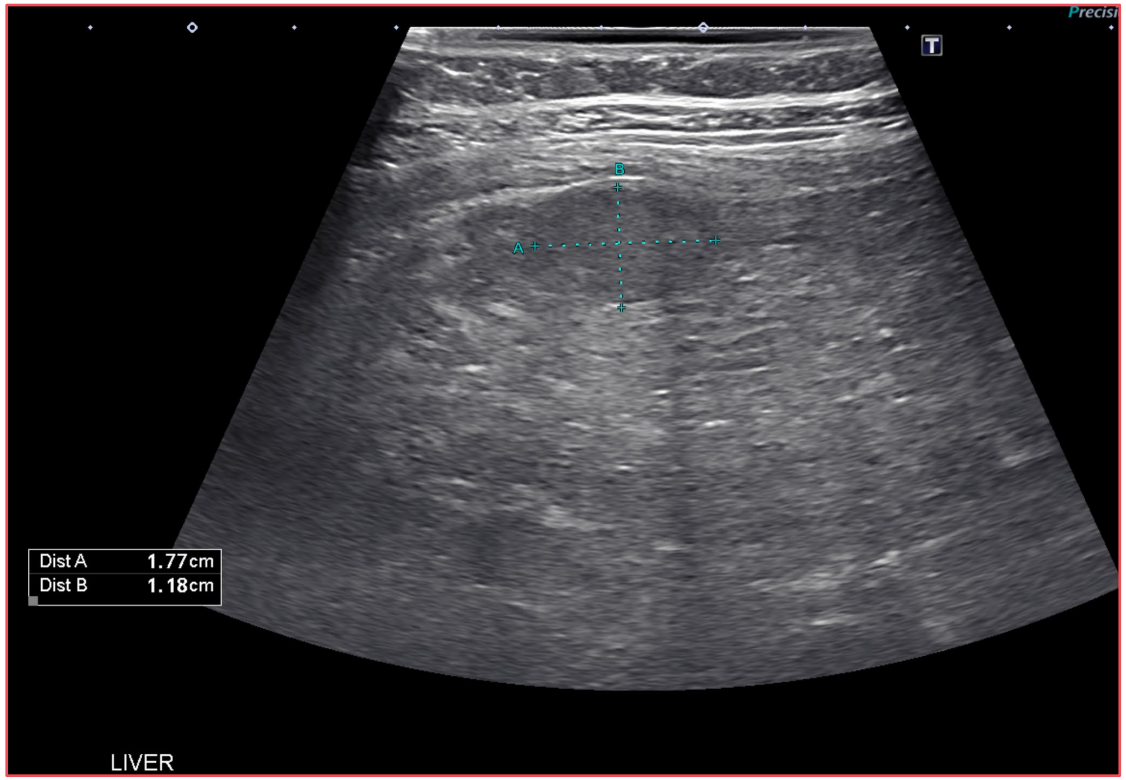
Liver MRI (age 17) New 1.5 cm lesion, old lesion growing

Liver MRI | Liver MRI | Liver MRI | Liver MRI | Liver MRI

Age 13 14 15 16 17 18 19

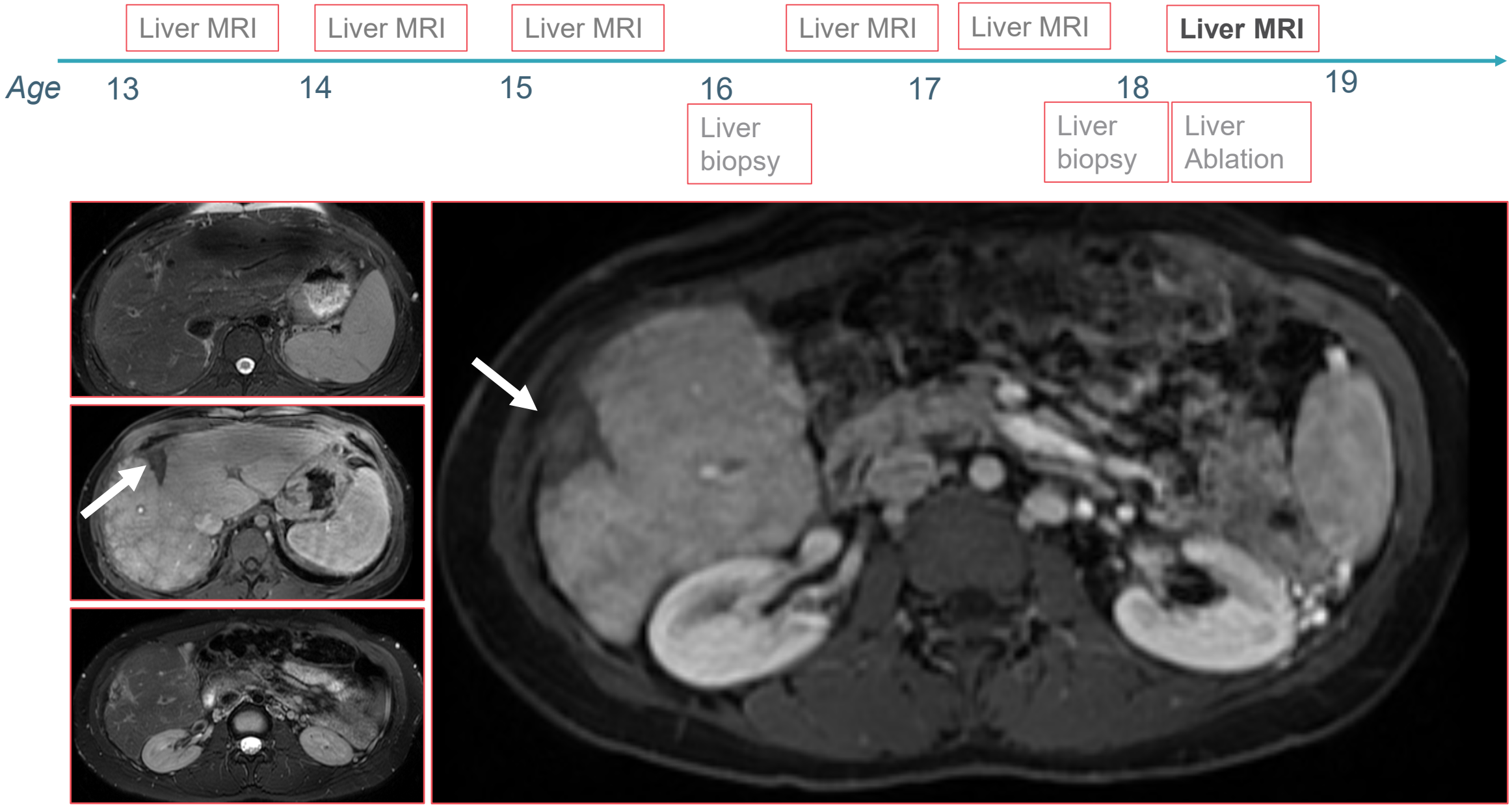
Liver biopsy

Liver biopsy | **Liver Ablation**



Liver Ablation (age 17)

FONTAN OUTCOMES NETWORK

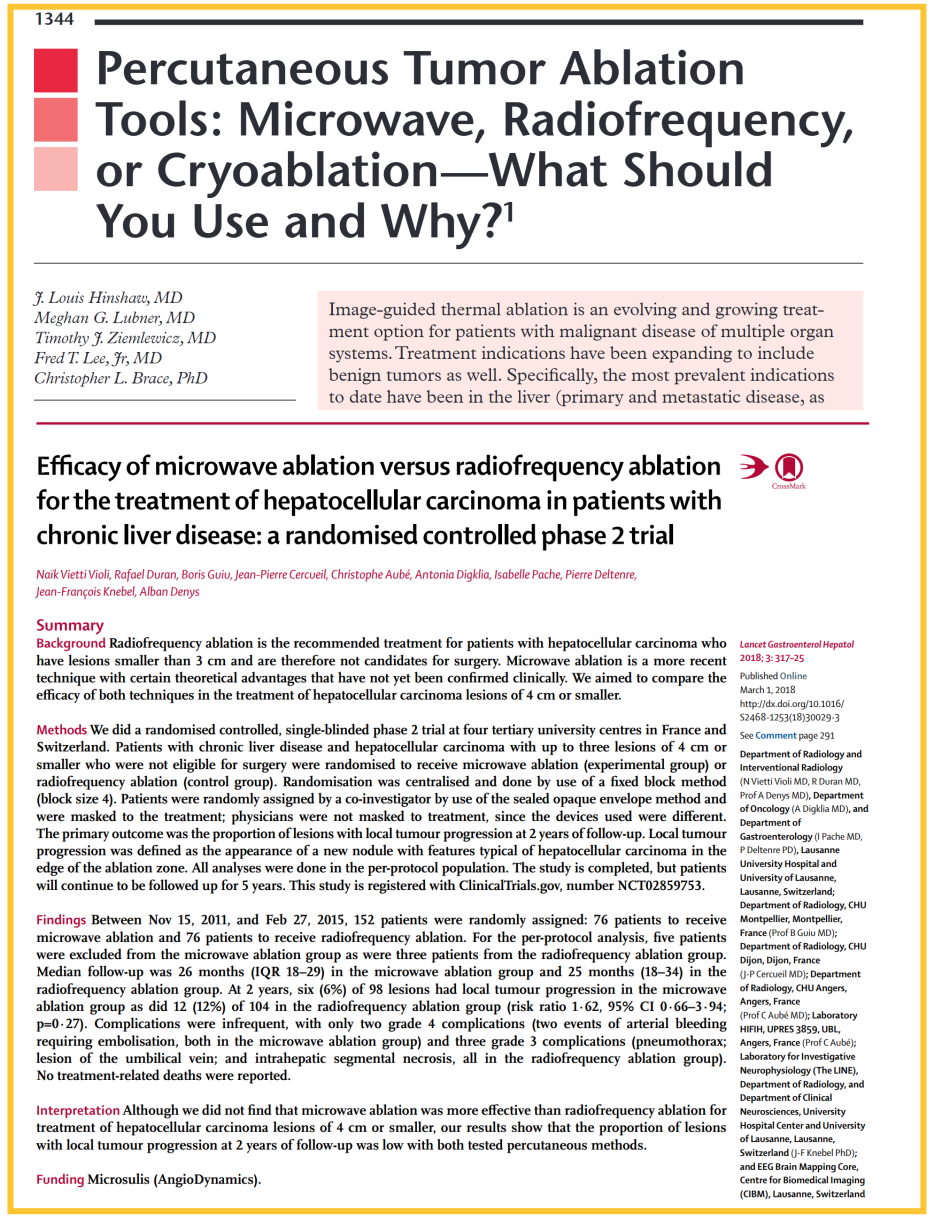


Liver MRI Post-Ablation

FONTAN OUTCOMES NETWORK

Percutaneous Options for Liver Ablation

- Cryoablation (cold)
- Radiofrequency (heat)
- Microwave (heat)
  - ➢Increasingly preferred in adults
  - ➢Shorter ablation time, higher temperature
  - ➢Larger ablation zone than RFA
  - ➢No heatsink issues



1344

Percutaneous Tumor Ablation Tools: Microwave, Radiofrequency, or Cryoablation—What Should You Use and Why?[1]

J. Louis Hinshaw, MD
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Timothy J. Ziemlewicz, MD
Fred T. Lee, Jr, MD
Christopher L. Brace, PhD

Image-guided thermal ablation is an evolving and growing treatment option for patients with malignant disease of multiple organ systems. Treatment indications have been expanding to include benign tumors as well. Specifically, the most prevalent indications to date have been in the liver (primary and metastatic disease, as

Efficacy of microwave ablation versus radiofrequency ablation for the treatment of hepatocellular carcinoma in patients with chronic liver disease: a randomised controlled phase 2 trial

Naïk Vietti Violi, Rafael Duran, Boris Guiu, Jean-Pierre Cercueil, Christophe Aubé, Antonia Digklia, Isabelle Pache, Pierre Deltenre, Jean-François Knebel, Alban Denys

Summary

Background Radiofrequency ablation is the recommended treatment for patients with hepatocellular carcinoma who have lesions smaller than 3 cm and are therefore not candidates for surgery. Microwave ablation is a more recent technique with certain theoretical advantages that have not yet been confirmed clinically. We aimed to compare the efficacy of both techniques in the treatment of hepatocellular carcinoma lesions of 4 cm or smaller.

Methods We did a randomised controlled, single-blinded phase 2 trial at four tertiary university centres in France and Switzerland. Patients with chronic liver disease and hepatocellular carcinoma with up to three lesions of 4 cm or smaller who were not eligible for surgery were randomised to receive microwave ablation (experimental group) or radiofrequency ablation (control group). Randomisation was centralised and done by use of a fixed block method (block size 4). Patients were randomly assigned by a co-investigator by use of the sealed opaque envelope method and were masked to the treatment; physicians were not masked to treatment, since the devices used were different. The primary outcome was the proportion of lesions with local tumour progression at 2 years of follow-up. Local tumour progression was defined as the appearance of a new nodule with features typical of hepatocellular carcinoma in the edge of the ablation zone. All analyses were done in the per-protocol population. The study is completed, but patients will continue to be followed up for 5 years. This study is registered with ClinicalTrials.gov, number NCT02859753.

Findings Between Nov 15, 2011, and Feb 27, 2015, 152 patients were randomly assigned: 76 patients to receive microwave ablation and 76 patients to receive radiofrequency ablation. For the per-protocol analysis, five patients were excluded from the microwave ablation group as were three patients from the radiofrequency ablation group. Median follow-up was 26 months (IQR 18–29) in the microwave ablation group and 25 months (18–34) in the radiofrequency ablation group. At 2 years, six (6%) of 98 lesions had local tumour progression in the microwave ablation group as did 12 (12%) of 104 in the radiofrequency ablation group (risk ratio 1·62, 95% CI 0·66–3·94; p=0·27). Complications were infrequent, with only two grade 4 complications (two events of arterial bleeding requiring embolisation, both in the microwave ablation group) and three grade 3 complications (pneumothorax; lesion of the umbilical vein; and intrahepatic segmental necrosis, all in the radiofrequency ablation group). No treatment-related deaths were reported.

Interpretation Although we did not find that microwave ablation was more effective than radiofrequency ablation for treatment of hepatocellular carcinoma lesions of 4 cm or smaller, our results show that the proportion of lesions with local tumour progression at 2 years of follow-up was low with both tested percutaneous methods.

Funding Microsulis (AngioDynamics).

Lancet Gastroenterol Hepatol 2018; 3: 317–25
Published Online March 1, 2018 http://dx.doi.org/10.1016/S2468-1253(18)30029-3
See Comment page 291

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FONTAN OUTCOMES NETWORK

Combined heart liver transplant

Transplant evaluation initiated

Listed ~ 5 months later

Transplanted ~ 2 years after evaluation

Case Summary

Serial imaging, preferably with MRI, is essential to evaluate changes in liver lesions and determine timing for biopsy.

Extended transplant wait times emphasize the importance of early detection and temporizing treatment.

Combined heart and liver transplant is the only curative option for some individuals.

Take Home Thoughts

Liver assessment provides not only insight into liver disease, but also a noninvasive window into Fontan hemodynamic status.

HCC screening is an integral part of Fontan care. There is little evidence for benefit from other liver evaluation (e.g., biopsy).

The path from HCC diagnosis to transplant may not be straightforward.