The ability to predict histological response from MR parameters: lessons learned from phase 2 trials

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International Think Tank
Paris NASH Meeting

Disclosures

- **Consultant:** Arrowhead, Kowa, Median, Novo Nordisk
- **Stockholder:** General Electric, Pfizer
- **Lab services agreements through UCSD** (current and prior)**:**

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Background

- **UCSD Liver Imaging Group:** development, validation, and implementation of quantitative imaging biomarkers in clinical trials
- **NASH-CRN:** FLINT and CyNCh Trials
- **QIBA:** PDFF and MRE committees
- **Academic Research Organization (ARO)**:
  - started our ARO at UCSD in 2008
  - 32 starting, ongoing, or completed drug-development clinical trials to date
  - MRI-PDFF, MRS-PDFF, MRE liver stiffness
  - > 5,000 imaging exams evaluated to date at over 300 sites worldwide

Rationale for PDFF as biomarker of liver fat

Accuracy

- MRI accurate compared to MRS as reference-standard[1-5]
- MRI accurate compared to histology as reference-standard[6,7]

Precision

- MRI precise[8-11] (repeatability, reproducibility)

Meta-analysis

- In an analysis of 23 studies[12]:

  "*Excellent linearity, bias, and precision across different field strengths, imager manufacturers, and reconstruction methods*"

1 - Liu et al, *Magn Reson Med* **2007**; 58:354
2 - Haufe et al, *JMRI* **2017**; 1641
3 - Hernando et al, *Magn Reson Med* **2017**; 77:1516
4 - Heba et al, *JMRI* **2016**; 43:398
5 - Zand et al, *JMRI* **2015**; 42:1223
6 - Middleton et al, *Gastroenterology* **2017**; 153:753
7 - Middleton et al, *Hepatology* **2018**; 67:858
8 - Negrete et al, *JMRI* **2014**; 39:1265
9 - Kang et al, *JMRI* **2011**; 34:928
10- Mashhood et al, *JMRI* **2013**; 37:1359
11 - Artz et al, *JMRI* **2015**; 42:811
12 - Yokoo et al, *Radiology* **2018**; 286:486

Rationale for MRE as biomarker of liver stiffness

- Liver fibrosis increases shear stiffness and other parameters[13-15]
- Accurate using histologic steatosis grade as reference standard[16]
- Repeatable and reproducible[17-20], predicts NASH[21] and advanced fibrosis[22]
- Precision in large meta-analysis study supports the claim[23]:

  "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

13 - Singh et al, *Clin Gastroenterol Hepatol* **2015**; 13:440
14 - Asbach et al, *Radiology* **2010**; 257:80
15 - Huwart et al, *Radiology* **2007**; 245:456
16 - Morisaka et al, *JMRI* **2017**; 47:1268
17 - Zhang et al, *JMRI* **2016**; 43:704
18 - Shi et al, *JMRI* **2014**; 32:665
19 - Serai et al, *Abdom Imaging* **2015**; 40:789
20 - Lee et al, *JMRI* **2014**; 39:326
21 - Chen et al, *Radiology* **2011**; 259:749
22 - Loomba et al, *Hepatology* **2014**; 60:1920
23 - Serai et al, *Radiology* **2017**; 285:92

Long-term goal - full biomarker validation

- All quantitative imaging biomarkers being developed at this time are as yet **only partially validated**
- **Full validation** for given **contexts of use** requires acceptance by regulators as endpoint surrogates in drug development clinical trials and clinical care
- Close involvement of and cooperation between regulatory agencies, academia, and industry is needed for this to happen
- The **NIMBLE** and **LITMUS** trials, both in their planning/start-up phases, will contribute significantly to this effort
- **Adequate accuracy** is important, but probably **adequate precision i**s more important

Technical lessons learned from drug trials

- **Current MRI-PDFF analyzability across all imaging sites, MR scanners, and clinical trials currently is at ~ 99%**
- **Current MRE analyzability across all imaging sites, MR scanners, and clinical trials currently is at ~ 97-98%**
- **These rates of successful analysis depend on** (all *sine qua non* status)**:**
  - Rigorous prior biomarker (preliminary) validation
  - Central site qualification and training
  - Central intake QC and image analysis
  - Real-time case-by-case feedback to clinical sites
  - Strong support by CROs

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Quantitative metrics of analyzability

- **Just as** validation requires quantitative imaging biomarkers to demonstrate appropriate accuracy and precision for defined contexts of use,

  So also the translation of those biomarkers to clinical trials and eventually to clinical care requires development of **quantitative metrics of analyzability** so that users of that data can be reassured that the promised and necessary accuracy and precision are being delivered.

- Two such metrics of analyzability that are under development are:
  - *a cutoff* ***r^2 fitting parameter*** *for PDFF that indicates how well multi-echo data is fitted by triglyceride-model analysis algorithms; 0.97 has been reported to be a useful value for this cutoff*
  - *a* ***minimum MRE ROI area*** *of 500-700 pixels across 4 slices through the widest part of the liver as a cutoff for acceptable liver stiffness results*

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How much change in PDFF is clinically meaningful?

- In a post-study secondary analysis by Patel et al (2016) of 36 patients from the MOZART study (ezetimibe), the 10 who showed histologic response of ≥ 2 point decrease in NAS had a *relative* MRI-PDFF decrease of 29.3% (-4.1% PDFF compared to -0.6% PDFF).
- On the basis of that finding, they suggested that, pending external independent validation by other groups, these results could be incorporated into designing future clinical trials.
- Since NAS includes PDFF, however, a large drop in PDFF can drive a large drop in NAS. Adding a requirement for NASH resolution would probably help.
- Validation of this finding should be in a prospective study with a placebo group.

How much change in MRE is clinically meaningful?

- In a 2017 poster[24] for the GS-4997 study of selonsertib entitled "*Longitudinal changes in liver stiffness by magnetic resonance elastography (MRE), liver fibrosis, and serum markers of fibrosis in a multi-center clinical trial in nonalcoholic steatohepatitis (NASH)*", a 15% reduction in MRE liver stiffness is suggested as being a clinically meaningful response by the following statement:

  "Relative reductions of liver stiffness by MRE ≥ 15% at W24 were significantly associated with reductions in serum markers of fibrosis, high sensitivity C-reactive protein (hsCRP), and HbA1c."

- This poster is referenced in a review by Connolly et al (2018)[25]
- This suggestion also would probably benefit from prospective validation in external independent studies that include a placebo arm.

24 - Loomba et al, *J Hepatology* (***2017***); *66:S543*
25 - Connolly et al, *J Clin Translat Hepatol* (***2018***); *6:264*

Phase 2 clinical trials

- **Reviewed 25 published papers reporting Phase 2 clinical trials:**
  - 16 assessed MRI-PDFF
  - 8 assessed MRS-PDFF
  - 5 assessed MRI-PDFF and MRE
  - 1 assessed MRE alone

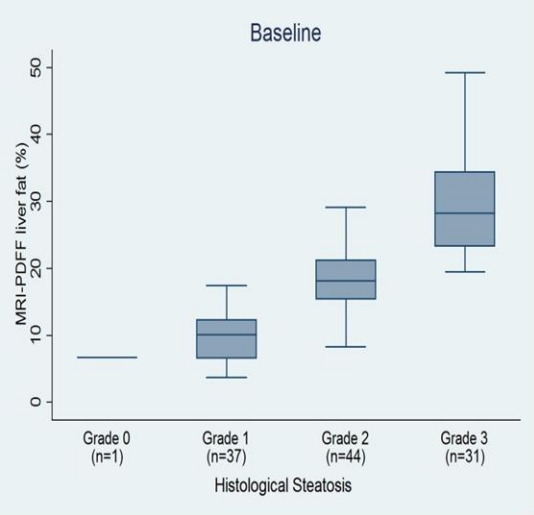
- **Lessons learned:**
  - MRI-PDFF vs. MRS-PDFF
  - Discriminatory PDFF cutoffs for histologic steatosis grades
  - Discriminatory MRE cutoffs for histologic fibrosis stages
  - Longitudinal change of PDFF with pathology
  - Longitudinal change of MRE liver stiffness with histology

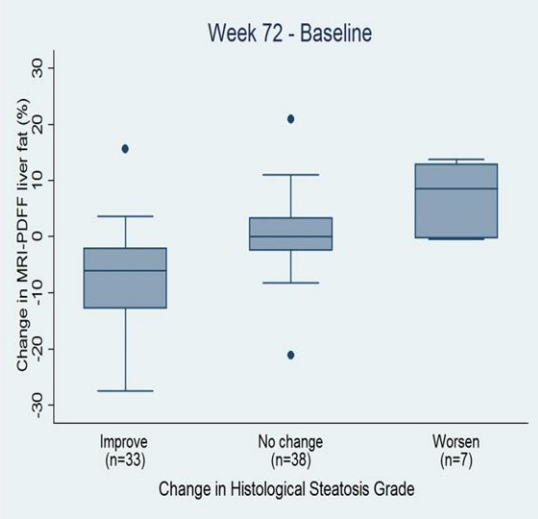
MRI-PDFF vs. MRS-PDFF

- **The selected MRS papers were limited in one way or another:**
  - 5/8 studies were single center
  - 6/8 studies used the PRESS sequence (not optimal; STEAM is better)
  - only 2/8 evaluated a drug (the others evaluated lifestyle, exercise, diet, etc.)
  - mostly smaller papers than the ones reporting major clinical trials
- Because of these and other factors (mainly, increased difficulty implementing MRS in large multi-center clinical trials), **using MRI-PDFF is strongly recommended over MRS-PDFF in drug development clinical trials**

PDFF histology cutoffs

- In the FLINT Trial, 113 adults with NASH at 8 sites were enrolled, dosed with obeticholic acid vs. placebo, and scanned at baseline and 72 weeks. Histology was compared to PDFF, and cutoffs were determined to distinguish histology grades[6].





At baseline for FLINT Trial:

16.3% PDFF distinguished grades 0,1 from 2,3 at 90% specificity

21.7% PDFF distinguished grades 0,1,2 from 3 at 90% specificity

(Similar values were obtained for CyNCh Trial[7]: **17.5%** and **23.3%** PDFF, respectively.)

6 - Middleton et al, *Gastroenterology* **2017**; 153:753
7 - Middleton et al, *Hepatology* **2018**; 67:858

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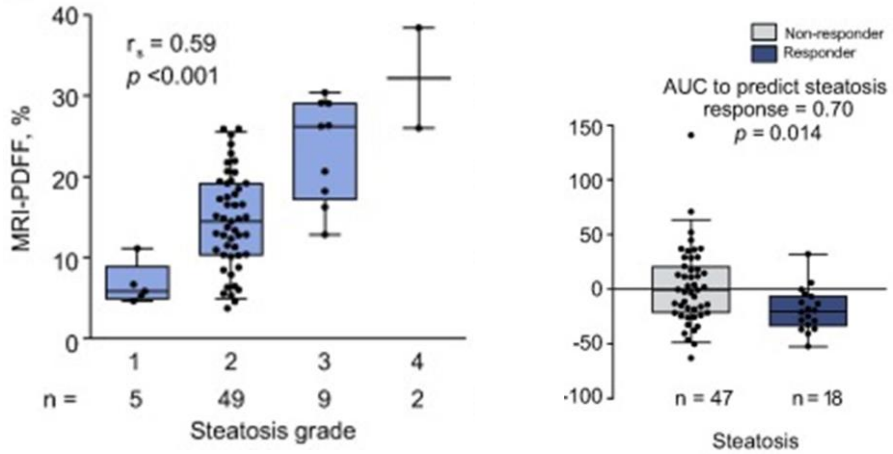
MRE histology cutoffs

- Not a Phase 2 clinical trial, but to address this question, Singh et al (2016) reported the following cutoffs for pooled data from 9 carefully selected studies that used similar MRE technique[26]:
  - Stage ≥1 fibrosis cutoff reported as **2.88** kPa
  - Stage ≥2 fibrosis cutoff reported as **3.54** kPa
  - Stage ≥3 fibrosis cutoff reported as **3.77** kPa
  - Stage 4 fibrosis cutoff reported as **4.09** kPa
- The best cutoff at each level will depend, amongst other things, on the context of use to which it is intended to be used.
- **Take-home message for PDFF and MRE:** cutoff values exist that can be used to inform clinical trial design.

26 - Singh et al, *European Radiology* (**2016**); 26:1431

Longitudinal change of PDFF with histology

- Phase 2 multi-center trial (GS-US-384-1497)[27], NASH and stage 2-3 fibrosis, MRI-PDFF and MRE liver stiffness evaluated compared to biopsy at baseline and at week 24 of treatment with selonsertib (selective inhibitor of apoptosis signal-regulating kinase 1.
- Steatosis grade was seen to correlate with MRI-PDFF (**left**), and histologic steatosis responders were seen to show decreases in MRI-PDFF (**right**):



27 - Jayakumar et al, *Journal of Hepatology* (**2019**); 70:133

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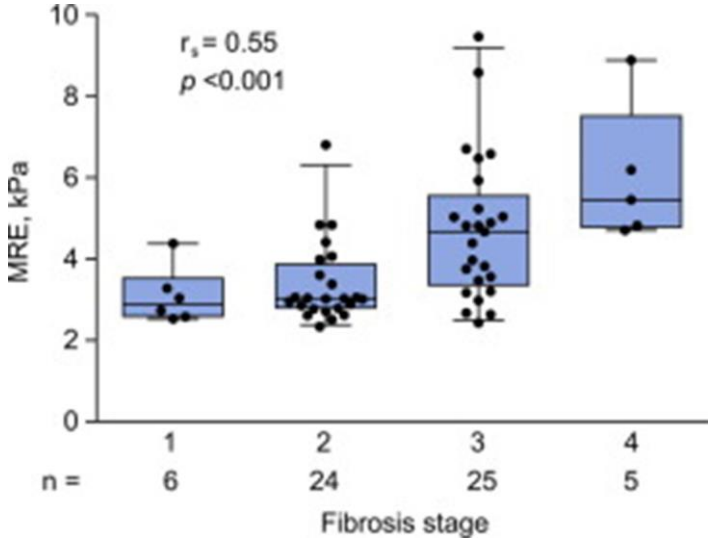
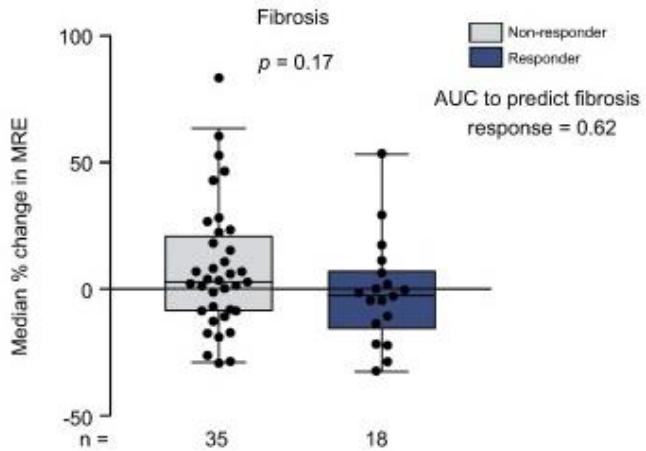
Longitudinal change of MRE liver stiffness with histology

- Same study (Jayakumar et al, 2019)[27]
- Fibrosis stage was seen to correlate with MRE liver stiffness (**left**), and histologic fibrosis responders were seen to show decreases in MRE liver stiffness (**right**):





Opportunities and conclusions

- Drug development clinical trials, in addition to helping develop new drugs, also provide invaluable opportunities to:
  - *test and validate quantitative imaging biomarkers*
  - *create, test, and validate artificial intelligence applications*
  - *advance medical science when those biomarkers are adequately validated*
- The upcoming **NIMBLE** and **LITMUS Trials** will allow several selected mature imaging (MRI and ultrasound) NASH-related biomarkers to be rigorously tested with the aim of being found acceptable for use in drug development clinical trials in Europe and the United States

Thank you

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