Imaging as an Outcome and Endpoint for Clinical Trials of NASH

Michael S. Middleton, MD PhD
msm@ucsd.edu
UCSD Department of Radiology
San Diego, CA
Liver Imaging Group (LIG)

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Disclosures

- **Consultant:** Arrowhead, Kowa, Median, Novo Nordisk
- **Stockholder:** General Electric, Pfizer
- **Grants:** Guerbet

**Lab services agreements through UCSD (current and prior):**

- Alexion
- AstraZeneca
- Bristol-Myers Squibb
- Celgene
- Enanta
- Galmed
- Genzyme
- Gilead
- Guerbet
- Intercept
- Isis
- Janssen
- NuSirt
- Organovo
- Pfizer
- Roche
- Sanofi
- Shire
- Synageva
- Takeda
- Alexion
- AstraZeneca
- Bristol-Myers Squibb
- Celgene
- Enanta
- Galmed
- Genzyme
- Gilead
- Guerbet
- Intercept
- Isis
- Janssen
- NuSirt
- Organovo
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- Takeda
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- AMRA
Biomarker development

- Validation of a quantitative imaging biomarker (QIB) requires **feasibility, accuracy, and precision** that are all **fit for purpose** (i.e., aligned with a context of use [COU]).
  - Additional attributes should probably include: **acceptable percentages, and ratio of false positives and false negatives**

- FDA drug development qualification program defines 7 **categories**, and gives examples of 11 **contexts of use**\(^1\).

- FDA and NIH refer to their **BEST** (Biomarkers, EndpointS, and other Tools) resource to support this process\(^2\).

- RSNA currently sponsors QIB assessment programs as part of the Quantitative Imaging Biomarker Alliance (QIBA)\(^3\).

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3. RSNA QIBA website, accessed 09 May 2018; [https://www.rsna.org/QIBA/](https://www.rsna.org/QIBA/)
Aims of this talk

To address the aims of this talk, we therefore need to ask:

- What are some of the main quantitative imaging biomarkers (QIBs) that are mature enough for use in drug development clinical trials?
  - MRI PDFF
  - MRE liver stiffness and loss modulus
  - cT1
  - VCTE CAP and FAST scores
  - Body Composition Profiling
- What is the support that they are mature enough?
- What roles have they played thus far in clinical trials?
- How can we expect their roles to change in the future?
Currently MRI-PDFF most accurate and precise non-invasive imaging biomarker to assess hepatic steatosis

189 papers now in PubMed ("liver" + "PDFF")

Note that PDFF is ratio of corrected fat signal, to sum of corrected fat and water signals, whereas histologic steatosis grade is based on percentage of hepatocytes with visible fat globules
Rationale for MRI-PDFF as biomarker of hepatic steatosis

Accuracy
- MRI accurate compared to MRS as reference-standard\(^4\)-\(^8\)
- MRI accurate compared to histology as reference-standard\(^9,10\)

Precision
- MRI precise\(^11\)-\(^14\) (repeatability, reproducibility)

Meta-analysis
- In an analysis of 23 studies\(^15\):
  
  "Excellent linearity, bias, and precision across different field strengths, imager manufacturers, and reconstruction methods"

5 - Haufe et al, *JMRI* 2017; 1641
8 - Zand et al, *JMRI* 2015; 42:1223
10 - Middleton et al, *Hepatology* 2018; 67:858
11 - Negrete et al, *JMRI* 2014; 39:1265
12 - Kang et al, *JMRI* 2011; 34:928
MRI-PDFF imaging method

6 echoes acquired at successive out-of-phase and in-phase TE values
MRI PDFF accuracy - regression

506 adult subjects

7 - Heba et al, JMRI 2016; 43:398-406
Adult cross-sectional and longitudinal relationships between PDFF and histologic steatosis grade (113 subjects, 8 sites)

## PDFF cutoffs summary separating steatosis grades

<table>
<thead>
<tr>
<th>Study</th>
<th>(0) vs. (1,2,3)</th>
<th>(0,1) vs. (2,3)</th>
<th>(0,1,2 vs. 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLINT⁹</td>
<td>-</td>
<td><strong>16.3% PDFF</strong> at 90% specificity</td>
<td><strong>21.7% PDFF</strong> at 90% specificity</td>
</tr>
<tr>
<td>CyNCh¹⁰</td>
<td>-</td>
<td><strong>17.5% PDFF</strong> at 90% specificity</td>
<td><strong>23.3% PDFF</strong> at 90% specificity</td>
</tr>
<tr>
<td>Tang et al¹⁶</td>
<td><strong>6.4% PDFF</strong> at 100% specificity</td>
<td><strong>17.4% PDFF</strong> at 91% specificity</td>
<td><strong>22.1% PDFF</strong> at 90% specificity</td>
</tr>
</tbody>
</table>

¹⁰ - Middleton et al, *Hepatology* 2018; 67:858
2D MRE Background

- MRE has been extensively investigated
- 299 papers now in PubMed ("liver" + "MRE" + "Elastography")
- **2D MRE** is FDA approved - used to estimate liver stiffness
- Available at over 1,000 sites, worldwide
Rationale for **MRE** as biomarker of liver fibrosis

- Liver fibrosis increases shear stiffness and other parameters\(^{17-19}\)
- **Accurate** using histologic fibrosis stage as reference standard\(^{20}\)
- **Repeatable and reproducible**\(^{21-24}\), predicts NASH\(^ {25}\) and advanced fibrosis\(^ {26}\)
- Precision in large meta-analysis study supports the claim\(^ {27}\):
  
  *A measured change in hepatic stiffness of 19% or greater, at the same site and with use of the same equipment and acquisition sequence, is inferred to indicate that a true change in stiffness has occurred with 95% confidence*

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MRE source images

Magnitude images

Phase images
MRE post-processed images

Wave images

Elastogram Images
As liver becomes more fibrotic, it becomes stiffer
As liver becomes more fibrotic, it becomes stiffer

<table>
<thead>
<tr>
<th>Stage 0</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.9 kPa</td>
<td>2.5 kPa</td>
<td>3.2 kPa</td>
<td>4.9 kPa</td>
<td>9.7 kPa</td>
</tr>
</tbody>
</table>

*Courtesy Claude Sirlin MD, UCSD, 07 Sep 2019*
As liver becomes more fibrotic, it becomes stiffer

Meta-analysis of MRE-stiffness in NAFLD
232 pts, 9 studies, 6 cohorts; Singh et al, 2016; Eur Rad 26:1431

“Advanced fibrosis”
MRE histology cutoffs

- Singh et al (2016) reported the following cutoffs for pooled data from nine carefully selected studies that used similar MRE technique\(^{28}\):
  - Stage $\geq 1$ cutoff: $2.88$ kPa
  - Stage $\geq 2$ cutoff: $3.54$ kPa
  - Stage $\geq 3$ cutoff: $3.77$ kPa
  - Stage 4 cutoff: $4.09$ kPa

- The best cutoff at each level will depend, amongst other things, on the COU to which it is intended to be used

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28 - Singh et al, European Radiology 2016; 26:1431
29 - Jayakumar et al, J Hepatology 2019; 70:133
3D MRE

- 3D MRE is currently investigational; used to estimate liver stiffness, and its real and imaginary component parts ($G'$ and $G''$). $G''$ (loss modulus) and damping ratio ($= G''/2G'$) correlate with liver inflammation in animals: 30

"Damping ratio and shear loss modulus can be used to distinguish inflammation from fibrosis at early stages of disease, even before the development of histologically detectable necroinflammation and fibrosis"

- Preliminary 3D MRE data in humans (24 obese and 10 controls) further supports a possible relationship between loss modulus and inflammation 31

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30 - Yin et al, 2017; Radiology 284:694
31 - Yin, 2019; preliminary unpublished data
Corrected T1 (cT1)

- Correlation of cT1 with inflammation\(^{32}\) and ballooning\(^{33}\) have been reported

- In a Phase 2 clinical trial, cT1 has been reported to decrease in responders to NGM282\(^{34}\)

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\(^{33}\) Adapted from Pavlides et al, *Liver Int* **2017**; 37:1065
Vibration-controlled transient elastography (VCTE)

- The **Controlled Attenuation Parameter** (CAP) score derived from VCTE measurements correlates with histologic steatosis
  - S0 vs. S123: Cutoff of 285 → Se 0.80, Sp 0.77, NPV 0.16, **PPV 0.99**
  - S0 vs. S123: Cutoff of 302 → Se 0.80, Sp 0.83, NPV 0.37, **PPV 0.97**

- The **FAST™** score, derived from the VCTE liver stiffness score, the VCTE CAP score, and AST, correlates with: **NASH diagnosis + NAS≥4 + F≥2**
  - Derived from UK Cohort (n=350): **AUROC 0.79** (0.74, 0.84)
  - Pooled external validation cohort (n=1026): **AUROC 0.86** (0.83, 0.89)

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35 - Siddiqui et al, CGH 2019; 17:1877
36 - Eddowes et al, Gastroenterology 2019; 156:1717
37 - Newsome et al, submitted for publication, 2019
Use of FAST™ score for pre-trial enrichment

UK Cohort:
- **SFR** = Screen Fail Rate
- **MCR** = Missed Case Rate
- **PLB** = Patients sent to liver biopsy

**FAST™ Score:**
- NASH diagnosis + NAS≥4 + F≥2

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37 - Newsome et al, submitted for publication, 2019
Body Composition Profile (BCP)

Weight-to-muscle ratio [kg/L]
Liver proton density fat fraction [%]
Muscle fat infiltration [%]
Fat ratio [%]
Total adipose tissue Index [L/m²]
Visceral adipose tissue Index [L/m²]

+ Liver PDFF

images in this slide provided for this talk, courtesy of AMRA (Sweden)
Identifying metabolic sub-phenotypes in NAFLD

T2D

CHD

*Fatty liver defined as Liver PDFF > 5%*

The precision of these biomarkers will be independently and rigorously tested in upcoming multi-center clinical trials.

Many of these biomarkers are included in ongoing and planned future drug development clinical trials.

MRI will probably be largely replaced in the future for clinical care by less expensive point-of-care modalities, like quantitative ultrasound.
Summary of topics covered

- We discussed quantitative imaging biomarker validation, and the need to consider it in light of actual contexts of use.
- We reviewed seven quantitative imaging biomarkers (MRI PDFF, MRE liver stiffness and loss modulus, VCTE CAP and FAST scores, cT1, and Body Composition Profiling) and their use in clinical trials.
- Finally, we speculated on directions and roles for imaging biomarkers in future clinical trials.
Thank you