Imaging as an Outcome and Endpoint for Clinical Trials of NASH

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Disclosures

- **Consultant:** Arrowhead, Kowa, Median, Novo Nordisk
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  - Gilead
  - Pfizer
  - AstraZeneca
  - Guerbet
  - Roche
  - Bristol-Myers Squibb
  - Intercept
  - Sanofi
  - Celgene
  - Isis
  - Shire
  - Enanta
  - Janssen
  - Synageva
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  - NuSirt
  - 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, Endpoint\(S\), 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?
PDFF background

- 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
- MRI accurate compared to **histology** as reference-standard

**Precision**
- MRI precise (repeatability, reproducibility)

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

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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

1.15 msec
2.30 msec
3.45 msec
4.60 msec
5.75 msec
6.90 msec

3.0 Tesla
MRI PDFF accuracy - regression

506 adult subjects

7 - Heba et al, JMRI 2016; 43:398-406
NASH CRN FLINT trial results\textsuperscript{9}

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

\textsuperscript{9} - Middleton et al, \textit{Gastroenterology} 2017; 153:753-761
# 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>16.3% PDFF at 90% specificity</td>
<td>21.7% PDFF at 90% specificity</td>
</tr>
<tr>
<td>CyNCh¹⁰</td>
<td>-</td>
<td>17.5% PDFF at 90% specificity</td>
<td>23.3% PDFF at 90% specificity</td>
</tr>
<tr>
<td>Tang et al¹⁶</td>
<td>6.4% PDFF at 100% specificity</td>
<td>17.4% PDFF at 91% specificity</td>
<td>22.1% PDFF at 90% specificity</td>
</tr>
</tbody>
</table>

¹⁰ - Middleton et al, *Hepatology* 2018; 67:858  
Higher liver fat may be prognostic

Higher liver fat on MRI-PDFF is associated with fibrosis progression* in NAFLD

*Fibrosis progression defined as a transition from stage 0 fibrosis to stage 1 or greater on follow-up liver biopsy

Median follow up 1.75 years

Gastroenterology

this slide courtesy of Rohit Loomba, MD (UCSD) and Ajmani et al., Gastroenterology 2019; 155:307
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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18 - Asbach et al, *Radiology* 2010; 257:80  
20 - Morisaka et al, *JMRI* 2017; 47:1268  
22 - Shi et al, *JMRI* 2014; 32:665  
24 - Lee et al, *JMRI* 2014; 39:326  
26 - Loomba et al, *Hepatology* 2014; 60:1920  
MRE source images

Magnitude images

Phase images
MRE post-processed images

Wave images

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

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</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

Courtesy Claude Sirlin MD, UCSD, 07 Sep 2019
MRE histology cutoffs

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

\textsuperscript{28} - Singh et al, European Radiology 2016; 26:1431
\textsuperscript{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.\textsuperscript{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"
Corrected T1 (cT1)

- Correlation of cT1 with inflammation\textsuperscript{31} and ballooning\textsuperscript{32} have been reported

- In a Phase 2 clinical trial, cT1 has been reported to decrease in responders to NGM282\textsuperscript{33}

\textsuperscript{31} Banerjee et al, J Hepato\textit{i} 2014; 60:69
\textsuperscript{32} Adapted from Pavlides et al, Liver Int 2017; 37:1065
\textsuperscript{33} Harrison et al, Hepatology \textit{2019}; (DOI 10.1002/hep.30590)
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\(^{34}\)
  - S0 vs. S123: Cutoff of 302 → Se 0.80, Sp 0.83, NPV 0.37, PPV 0.97\(^{35}\)

\(^{34}\) Siddiqui et al, CGH 2019; 17:1877
\(^{35}\) Eddowes et al, Gastroenterology 2019; 156:1717
Body Composition Profile (BCP)

+ Liver PDFF

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

*Fatty Liver defined as Liver PDFF > 5%*

Linge J, et al. *Obesity* (Silver Spring) 2023;21(7):1230-99

* this slide provided for this talk, courtesy of AMRA
Future directions

- 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