DEFINING RESPONSE IN PEDIATRIC NAFLD – SURROGATE BIOMARKERS
## DISCLOSURES

### Research Funding and In-kind Research Services:
- NIH
- Nutrition Science Foundation (NuSI)
- Mason Foundation
- Resonance Health
- AMRA
- Siemens
- Perspectum
- Immuron
- Labcorp
- Gemphire
- Target Pharmasolutions
- Shire

### Advisory Boards:
- AMRA
- Target Pharmasolutions

### Consultant:
- Allergan
- Axcella Health
- Shire
- Boehringer Ingelheim
- Bristol Myers Squibb
- Immuron
- Intercept
- Novo Nordisk
DEFINITIONS

• “A surrogate endpoint is a clinical trial endpoint used as a substitute for a direct measure of how a patient feels, functions, or survives. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather is expected to predict that clinical benefit.”

• Biomarker: 1.) A defined characteristic that is measured as an indicator of normal or pathogenic biological processes or 2.) response to an intervention

https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development
FOCUS ON RESPONSE

• Non-progression = response
• Reversal = response
• “A biomarker used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent.”

https://www.ncbi.nlm.nih.gov/books/NBK402286/
CRITICAL QUESTIONS

• Are biomarkers approved/validated/qualified for adults with NASH applicable to children?
• What are the most important needs for biomarkers? Diagnostic? Response?
# Example of Pediatric Surrogate

**Pediatric Surrogate Endpoint Table**

<table>
<thead>
<tr>
<th>Disease or Use</th>
<th>Patient Population</th>
<th>Surrogate endpoint</th>
<th>Type of approval appropriate for</th>
<th>Drug mechanism of action</th>
<th>Age range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipodystrophy</td>
<td>Patients with congenital or acquired generalized lipodystrophy</td>
<td>Serum hemoglobin A1C, fasting glucose and triglycerides</td>
<td>Traditional</td>
<td>Leptin analog</td>
<td>?</td>
</tr>
</tbody>
</table>

NASH

https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure
CURRENT GUIDANCE

• “For early phase studies, reduction of elevated serum ALT is a reasonable primary outcome.”

• “While steatosis can be measured accurately with MRI, there is inadequate data to support that steatosis reduction will lead to clinically meaningful benefit or changes in other pertinent features related to NASH.“

• Endpoints “reasonably likely to predict clinical outcomes” by the regulatory authorities for adults are as follows, and pediatric trials may use similar endpoints in those with NASH:
  • -FDA: Biopsy based resolution of steatohepatitis and no worsening of fibrosis OR at least one-point improvement in fibrosis with no worsening of steatosis, ballooning or inflammation.
  • -EMA: Biopsy based resolution of steatohepatitis and no worsening of fibrosis AND at least one-point improvement in fibrosis with no worsening of steatosis, ballooning or inflammation.
MEAN ALT BY HISTOLOGY CHANGE

A

NASH

B

Fibrosis

Arsik et al, Children 2018
% CHANGE IN ALT BY HISTOLOGY CHANGE

A. NASH

B. Fibrosis

Mean ALT % Change from Baseline

Improvement
Stable
Progressed

Weeks

4 12 24 36 48 60 72 84 96
CYNCH DATA SUPPORTS IMPROVEMENT IN ALT AND GGT LINKS TO HISTOLOGY

- Abstract presentation AASLD 2017
- Liver histology improved in 35% of cysteamine and 24% of placebo
  - Response defined at decrease in NAS of $\geq 2$ at 52 weeks

<table>
<thead>
<tr>
<th>Histology</th>
<th>ALT</th>
<th>AST</th>
<th>GGT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>-81</td>
<td>-42</td>
<td>-20</td>
</tr>
<tr>
<td>Non-responders</td>
<td>-36</td>
<td>-24</td>
<td>-5</td>
</tr>
<tr>
<td>P for difference</td>
<td>.002</td>
<td>.03</td>
<td>.001</td>
</tr>
</tbody>
</table>
Predictors of non-alcoholic fatty liver disease in obese children
The distribution of PDFF in the 110 children at baseline, all of whom were diagnosed with NAFLD is shown in Figure 1: PDFF mean ± SD was 21.1 ± 9.8%, and ranged from 5.3% to 46.8%.
COMPARISON OF MR TO HISTOLOGY

Middleton et al, Hepatology 2018
“No associations with change in PDFF were found for changes in lobular or portal inflammation scores, hepatocellular ballooning score, or fibrosis score (p-values 0.40 to 0.80).”

Middleton et al, Hepatology 2018
Effect of a Low-Fructose, Low-Sugar Diet on Nonalcoholic Fatty Liver Disease: A Randomized Clinical Trial

Jeffrey B. Schwimmer, MD; Patricia Ugalde-Hernandez, MD; Kathryn E. Harlow, MD; Adina Alazraki, MD; Michael Alpern, MD; Cynthia Knott, RDN; Juna Konomi, PhD; Michele L. Mark, RN; Victoria M. Morgan; Albert Hernandez; Ahlia Sekkarie, MPH; Coula C. M. Chow; Maria Cordero; and Rebecca Cleeton, MPH; MD;

Study Funded by Nutrition Science Initiative
PRIMARY OUTCOME: LIVER FAT

8 week study

Individual data

Adjusted means

Schwimmer, Vos et al, JAMA 2019
LIVER BIOMARKERS TRACKED TOGETHER

A) MRI proton density fat fraction

B) Alanine aminotransferase

C) Aspartate aminotransferase

D) γ-Glutamyl transpeptidase

Graphs showing changes in biomarkers under Low-Sugar Diet and Usual Diet conditions.
• This is the future but insufficient longitudinal data correlated with histology exists at this time.
- Response in histology
  - Current based on NAS
  - However, lack of ballooning in peds an issue
  - Unclear if NAS captures pediatric pattern sufficiently
- Needs:
  - Studies comparing histology to pediatric clinical status
  - ~10 year natural history studies with baseline surrogates/biomarkers and 10 year clinical outcomes
  - Phenotypes of NAFLD and response within each phenotype
PHENOTYPING CHILDREN WITH NAFLD

- Prepubertal, pubertal and post pubertal (adult)
- Insulin resistant, prediabetic, diabetic
- Dyslipidemic, normolipidemic
- Lean, overweight, obese
- Low ALT, mid-range and very high (>250)
- No fibrosis, early fibrosis, advanced fibrosis

- What is the relationship of progression to these phenotypes?
FUTURE BIOMARKERS
HFF COMMUNITY

Cioffi et al, unpublished data