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
BEST

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

Disease or Use	Patient Population	Surrogate endpoint	Type of approval appropriate for	Drug mechanism of action	Age range
Lipodystrophy	Patients with congenital or acquired generalized lipodystrophy	Serum hemoglobin A1C , fasting glucose and triglycerides	Traditional	Leptin analog	

NASH ?

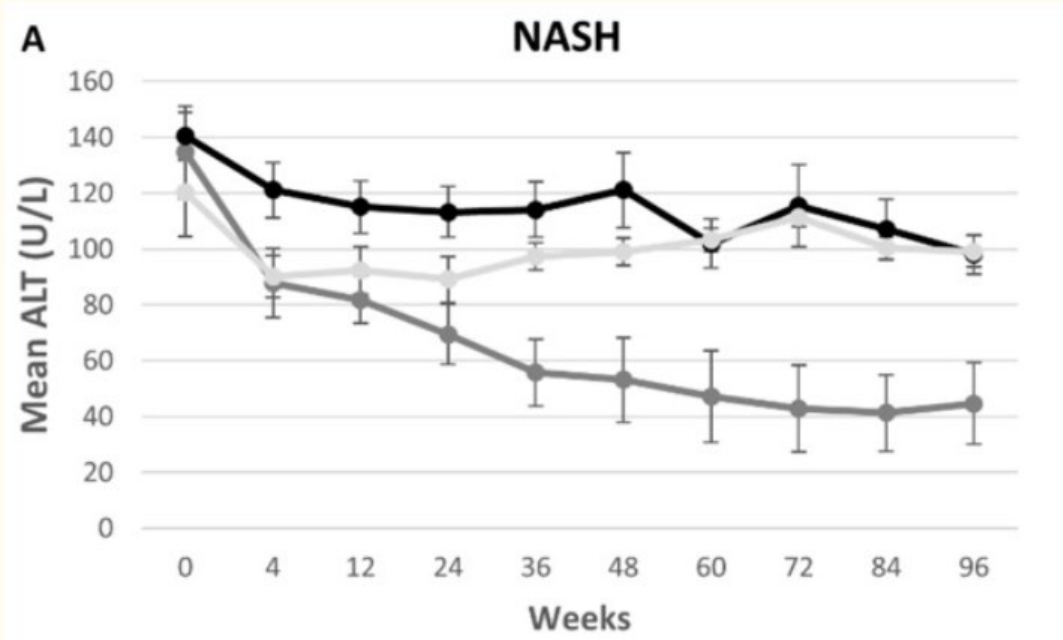
https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

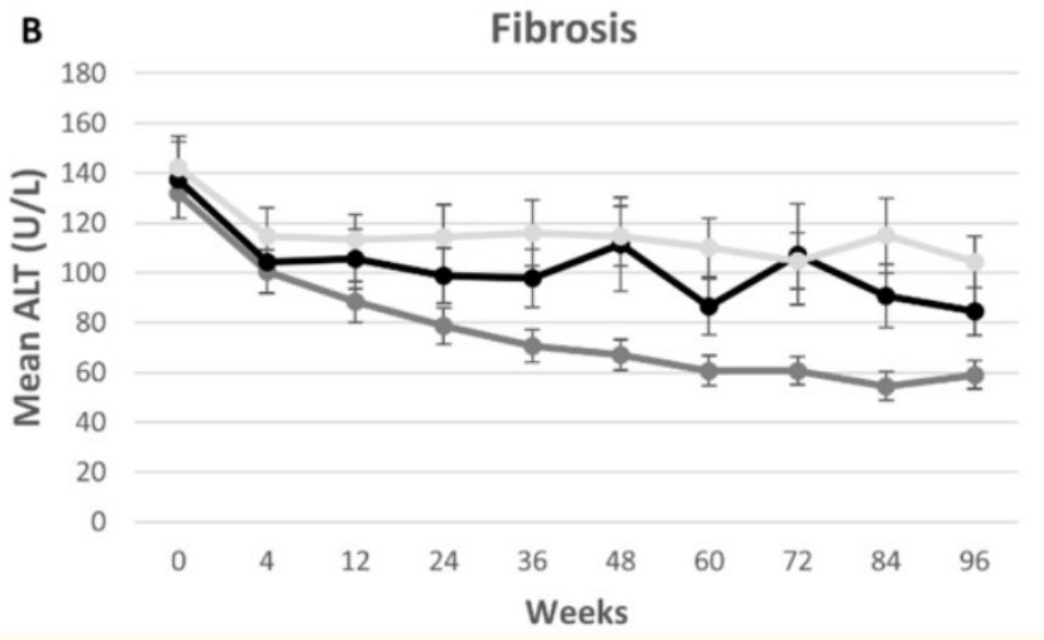
CURRENT GUIDANCE

- "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.

Liver Forum Pediatric Paper, Gastro 2019

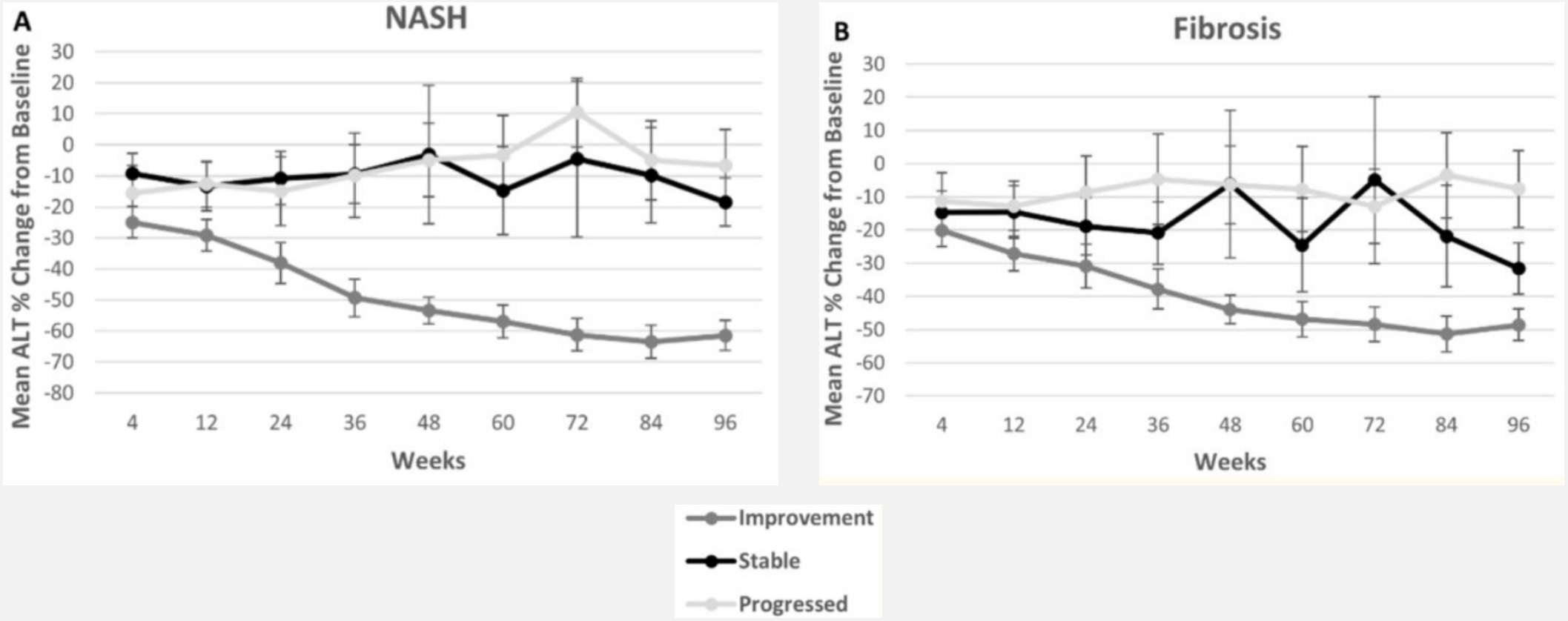
MEAN ALT BY HISTOLOGY CHANGE





Arsik et al, Children 2018

% CHANGE IN ALT BY HISTOLOGY CHANGE



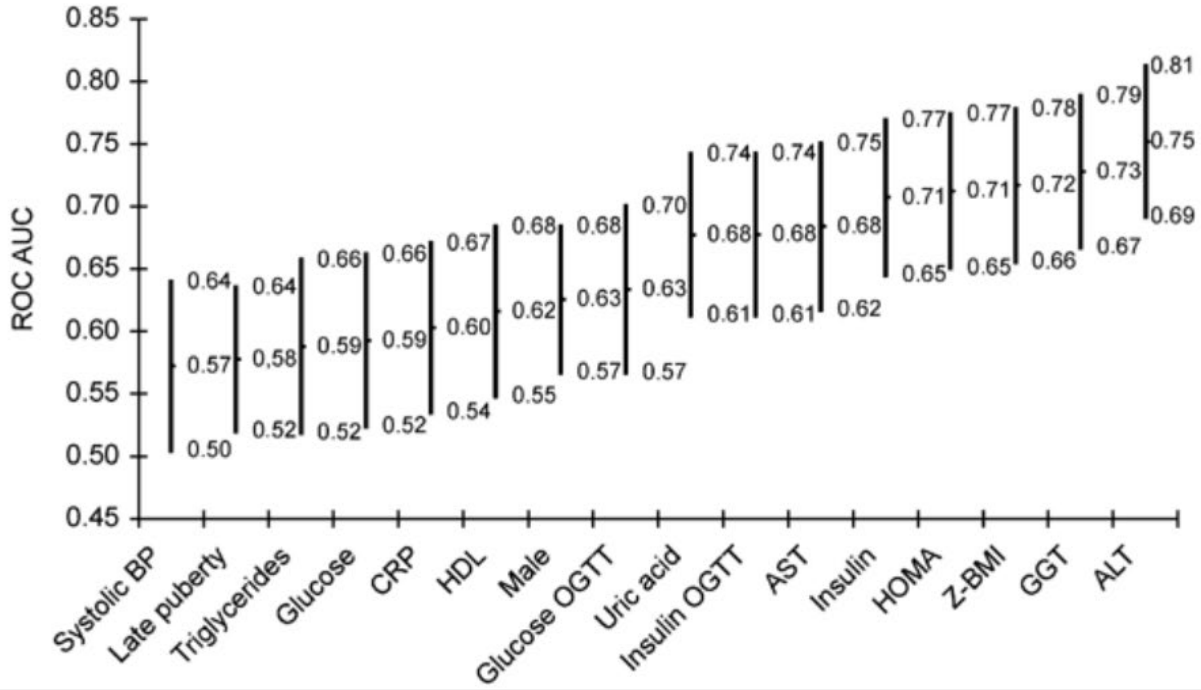
CYNCH DATA SUPPORTS IMPROVEMENT IN ALT AND GGT LINKS TO HISTOLOGY

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

Histology	ALT	AST	GGT
Responders	-81	-42	-20
Non-responders	-36	-24	-5
P for difference	.002	.03	.001

GGT

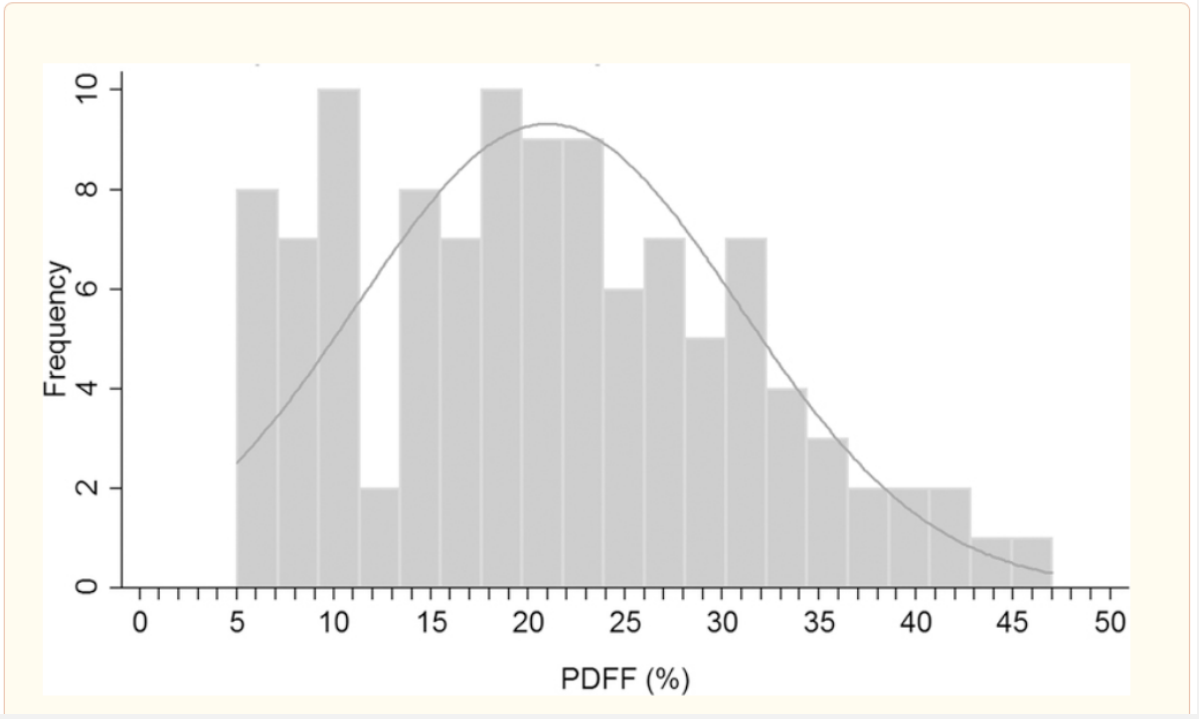
Predictors of non-alcoholic fatty liver disease in obese children



Sartorio et al, EJCN 2006

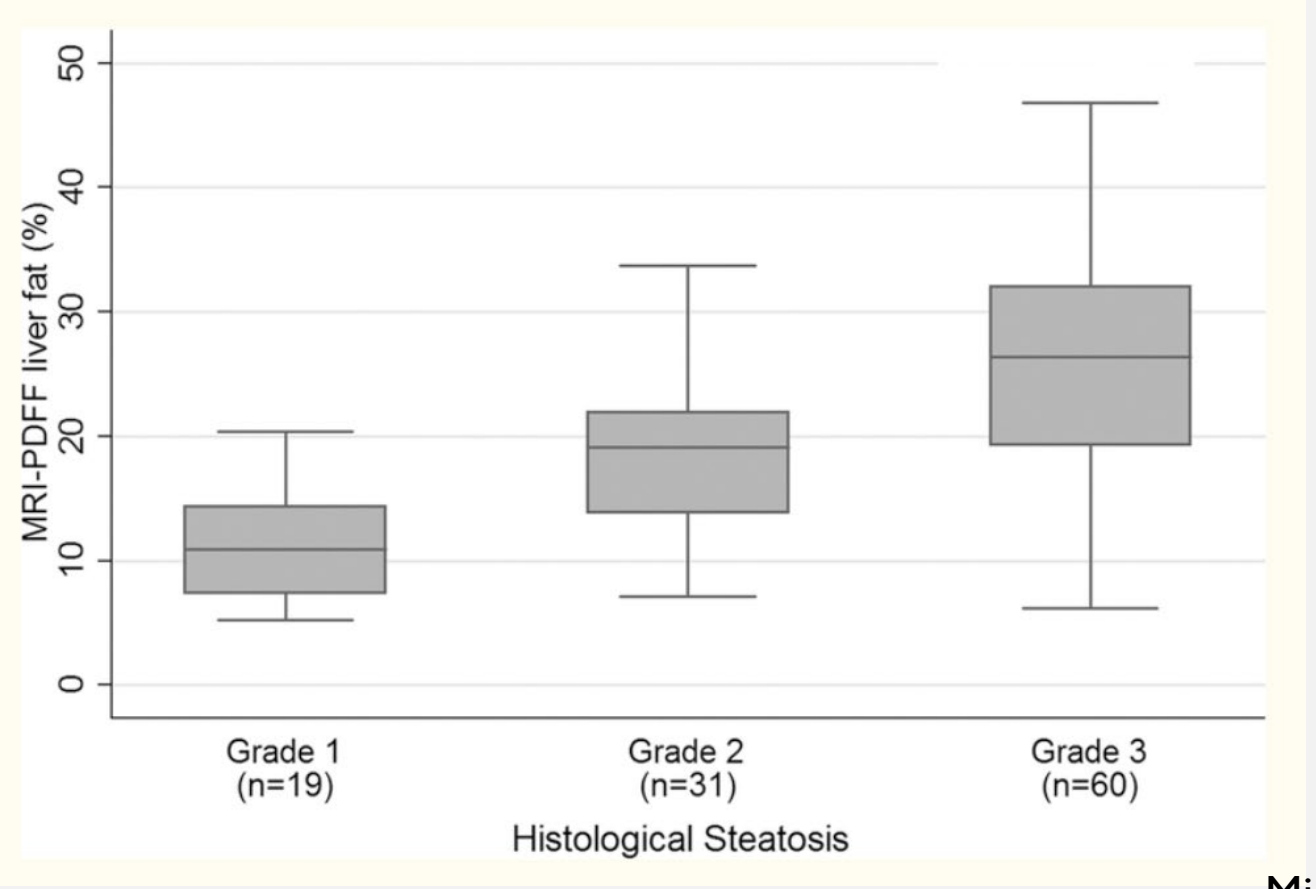
HEPATIC FAT

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%.



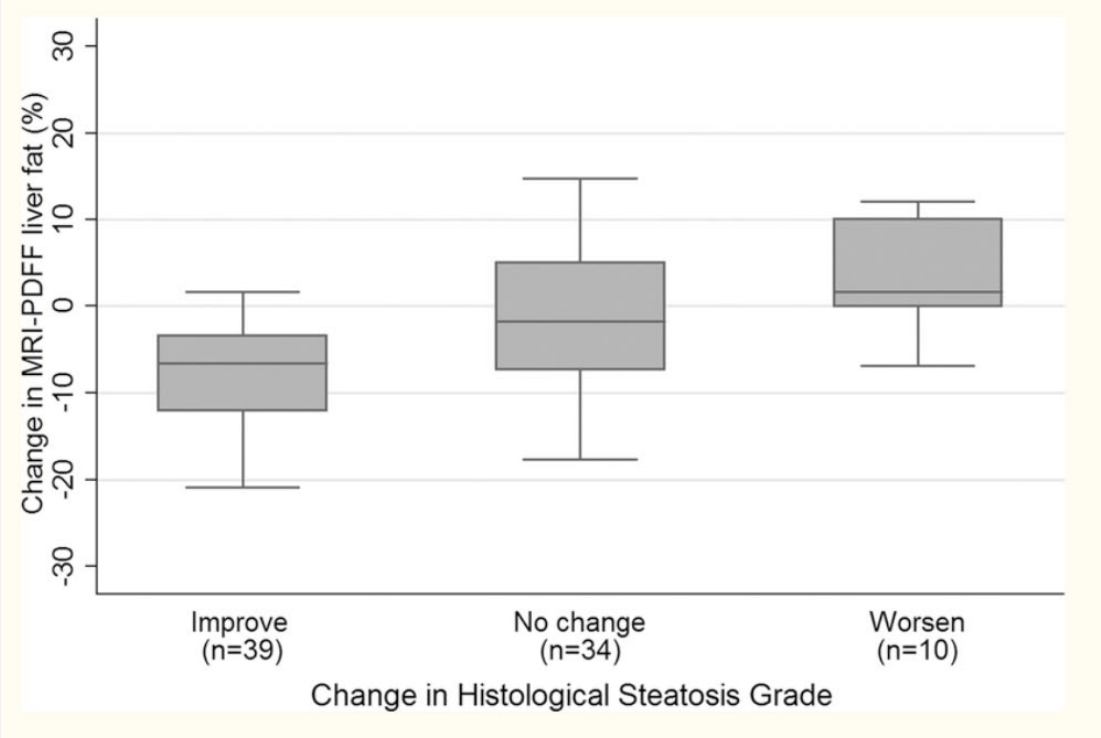
Middleton et al, Hepatology 2018

COMPARISON OF MR TO HISTOLOGY



Middleton et al, Hepatology 2018

CHANGE IN MR FAT FRACTION PREDICTS HISTOLOGIC CHANGE IN STEATOSIS



"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).."

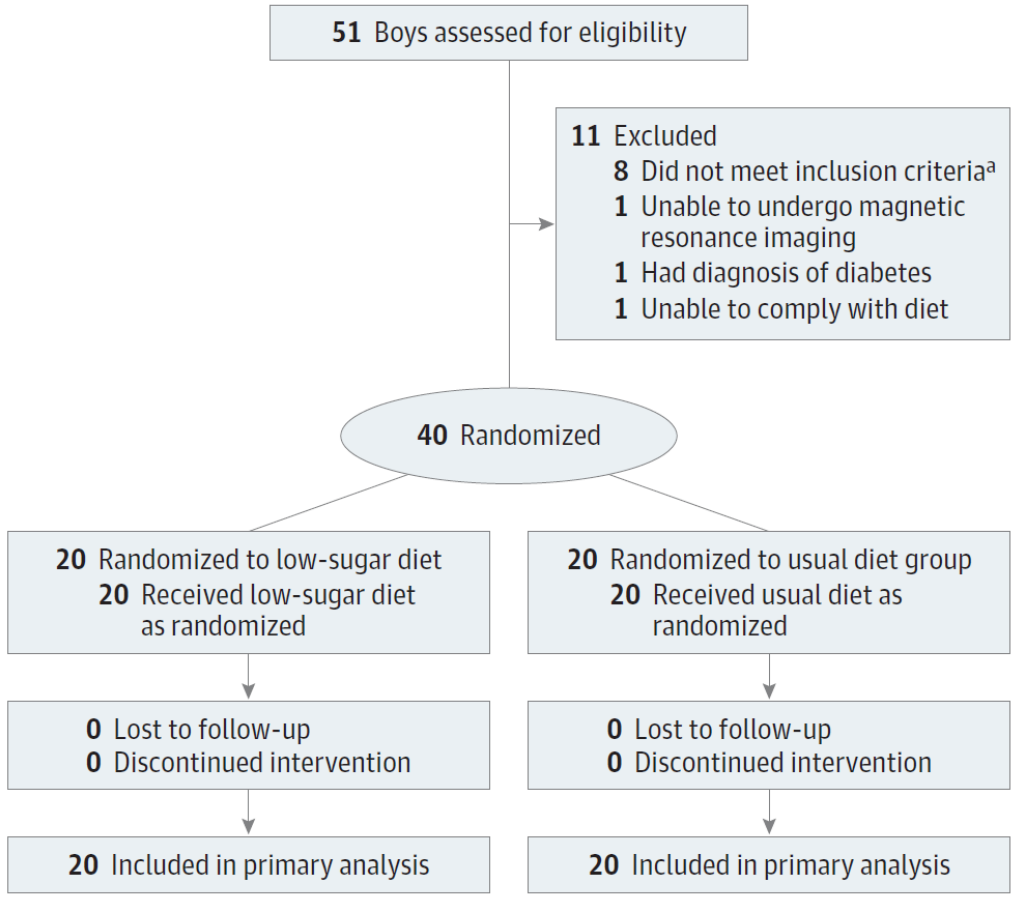
Middleton et al, Hepatology 2018

JAMA | Preliminary Communication

Effect of a Low Fre on Nonalcoholic Fatty Liver Disease: A Randomized Clir

Jeffrey B. Schwimmer, MD; Patricia Ugalde-N Maria Cordero; Kathryn E. Harlow, MD; Adina Alazraki, MD; J ebecca Cleeton, MPH; Cynthia Knott, RDN; Juna Konomi, PhD; Mich MD; Albert Hernandez; Ahlia Sekkarie, MPH; Cou

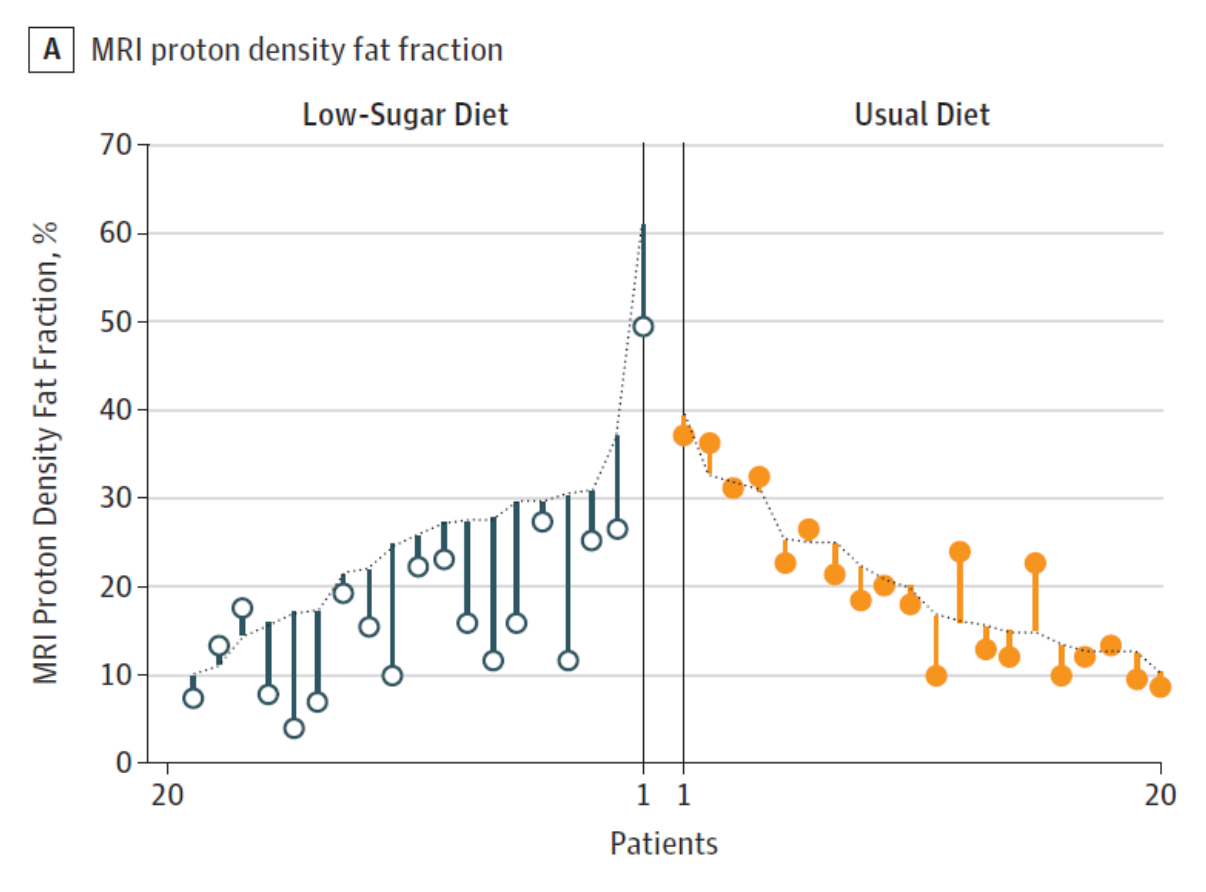
Figure 1. Consort Flow Diagram of Dietary Treatment Study Participants

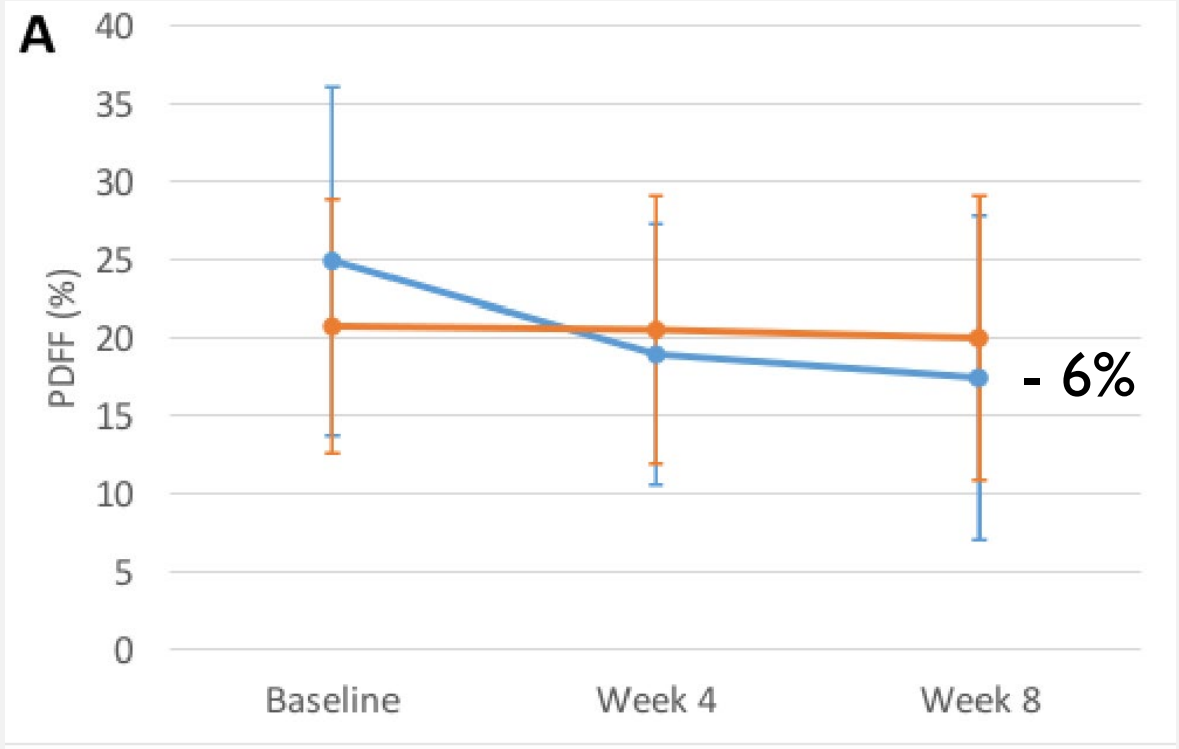


[a] Based on either the alanine aminotransferase level or the magnetic resonance imaging proton density fat fraction percentage measurement.

Study Funded by Nutrition Science Initiative

PRIMARY OUTCOME: LIVER FAT





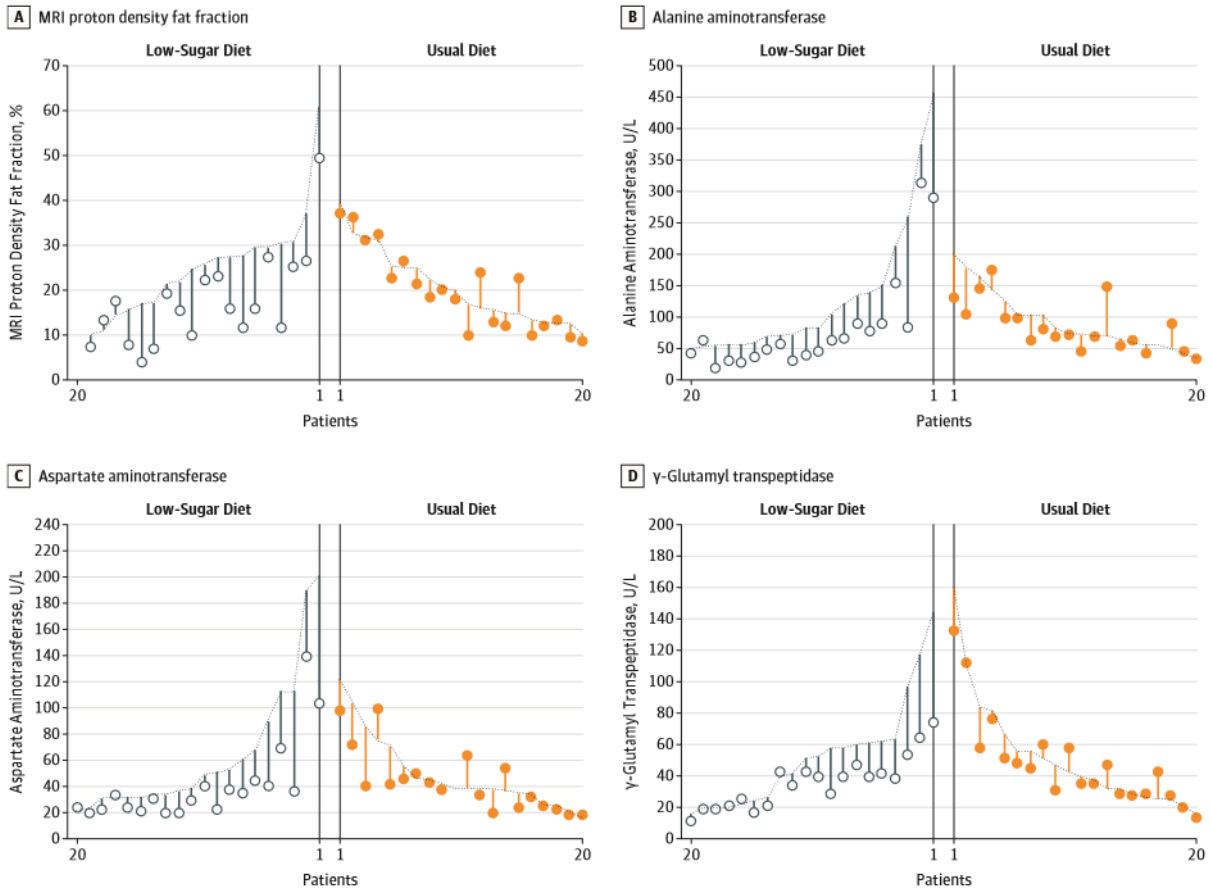
Individual data

8 week study

Adjusted means

Schwimmer, Vos et al, JAMA 2019

LIVER BIOMARKERS TRACKED TOGETHER



FIBROSIS - IMAGING

- This is the future but insufficient longitudinal data correlated with histology exists at this time.

HISTOLOGY

- 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

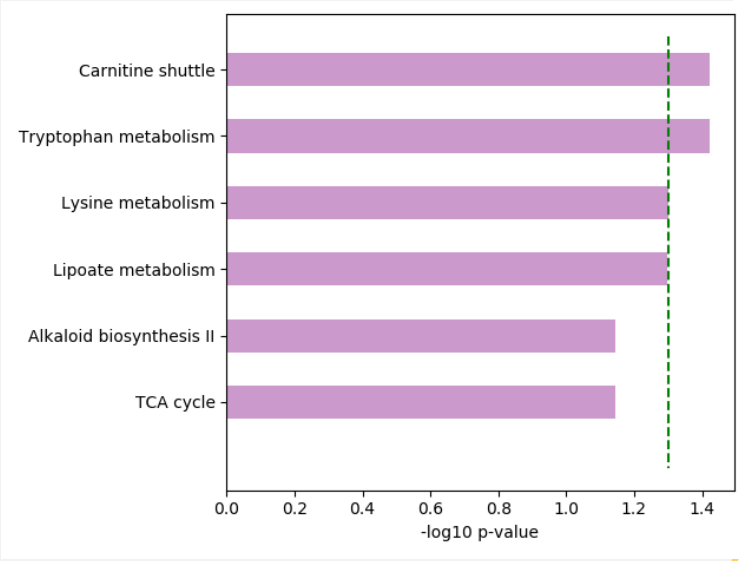
PHENOTYPING CHILDREN WITH NAFLD

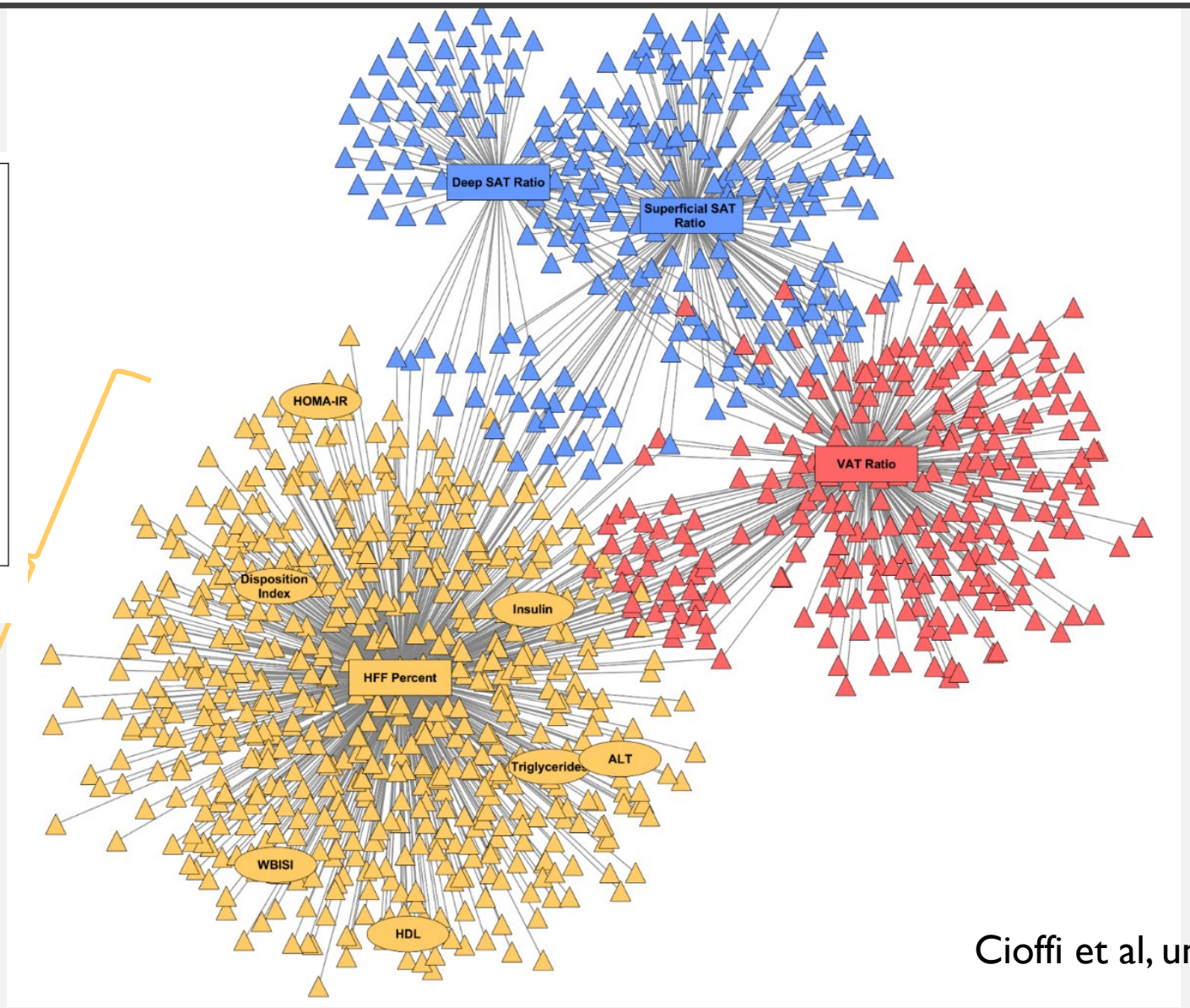
- Prepubertal, pubertal and post pubertal (adult)
- Insulin resistant, prediabetic, diabetic
- Dyslipidemic, normolipidemic
- Lean, overweight, obese
- Low ALT, mid-range and very high (>250)
- No fibrosis, early fibrosis, advanced fibrosis

- What is the relationship of progression to these phenotypes?

FUTURE BIOMARKERS

HFF COMMUNITY





Cioffi et al, unpublished data