SCSG 2015 POST-AASLD SYMPOSIUM

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Innovations in Clinical Trials and NASH Update

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- Participation in advisory committees for Galmed, Nimbus, Gilead, BMS, Arrowhead Research, Conatus, Tobira;
- Consultant for Gilead, BMS, Merck, Pfizer, Fibrogen, NGM, Alnylam, DeuteRx, Zafgen, RuiYi, Shire, Scholar Rock, Metacrine, Viking, Receptos, Isis, Enanta, Celgene, Receptos, CNI, Metacrine, Viking, Boehringer Ingelheim, Eli Lily, Conatus and Janssen Inc
- Co-founder of Liponexus Inc
- No “off-label” discussion

Outline: 2015

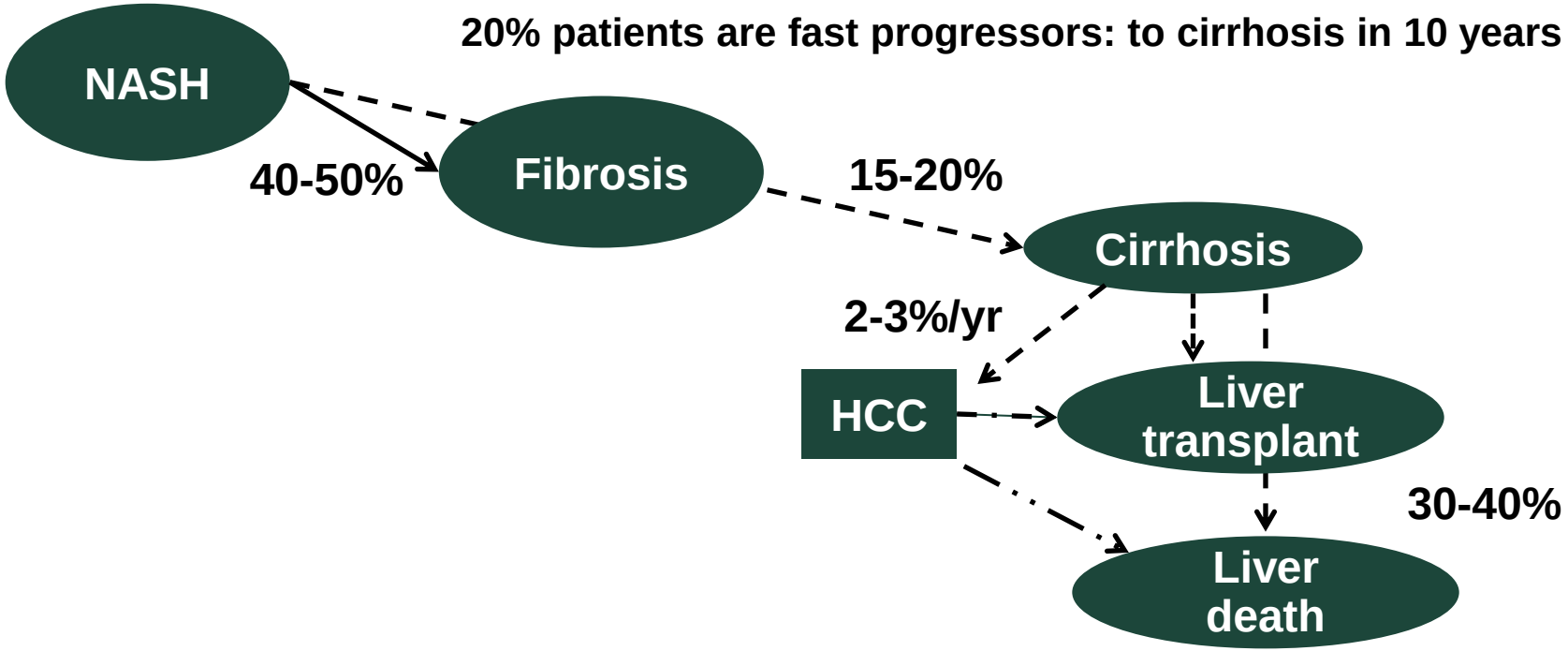
- Natural history of NAFLD
- Key studies on clinical trial design
- Innovations in MRI-based biomarkers
- AASLD Abstract

Natural History of NASH

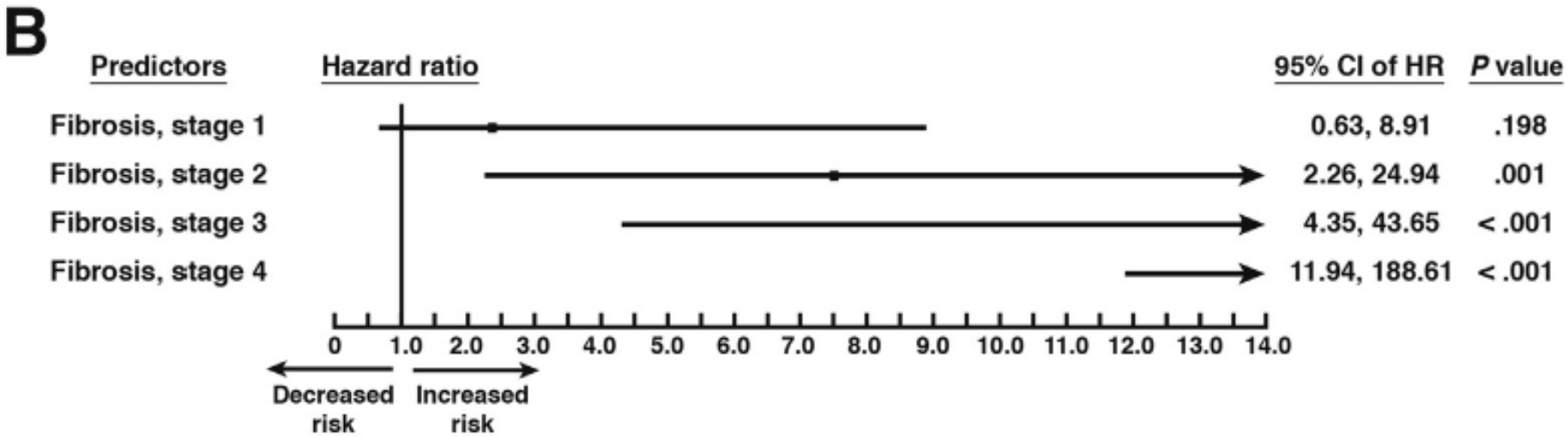
18 million Americans

Fibrosis progression rate in NASH: 1 stage per 7 year

20% patients are fast progressors: to cirrhosis in 10 years

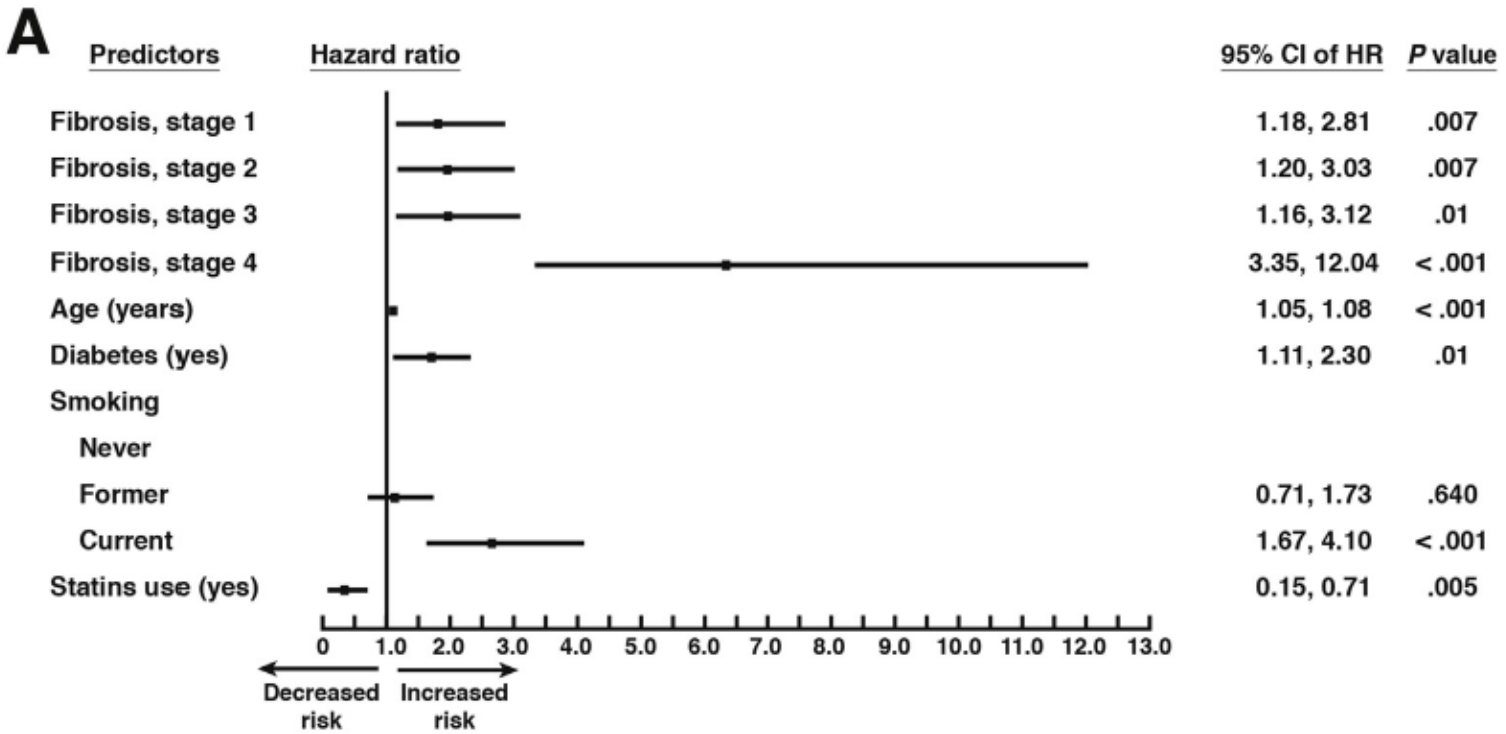


Predictors of Liver Events



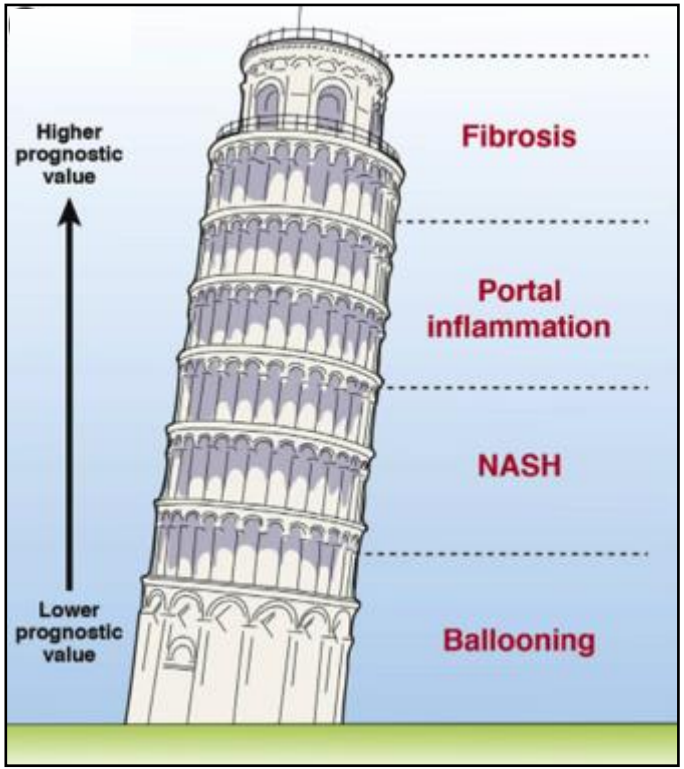
Angulo, et al. *Gastroenterology* 2015; Loomba, Chalasani. *Gastroenterology* 2015.

Predictors of Mortality or Liver Transplantation in NAFLD



Angulo, et al. *Gastroenterology* 2015; Loomba, Chalasani. *Gastroenterology* 2015.

Key Histologic Predictors of Mortality in NAFLD



Loomba, et al. *Gastroenterology.* 2015.

THE LANCET

Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial

*Brent A Neuschwander-Tetri, Rohit Loomba, Arun J Sanyal, Joel E Lavine, Mark L Van Natta, Manal F Abdelmalek, Naga Chalasani, Srinivasan Dasarathy, Anna Mae Diehl, Bilal Hameed, Kris V Kowdley, Arthur McCullough, Norah Terrault, Jeanne M Clark, James Tonascia, Elizabeth M Brunt, David E Kleiner, Edward Doo, for the NASH Clinical Research Network**

NIH National Institute of Diabetes and Digestive and Kidney Diseases

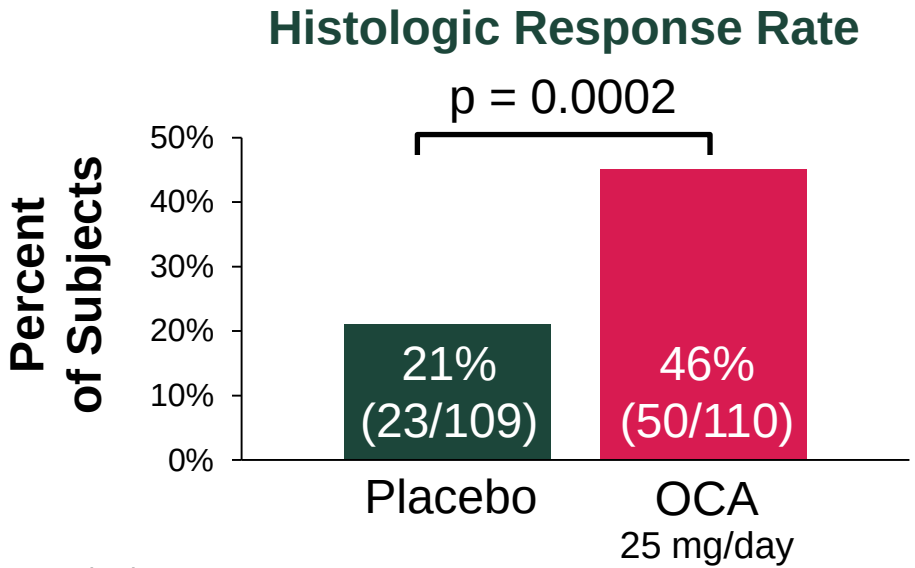
NATIONAL CANCER INSTITUTE

Partial funding for the trial, obeticholic acid, and placebo were provided by Intercept Pharmaceuticals under a Collaborative Research and Development Agreement with the NIDDK.

Published Online November 7, 2014, http://dx.doi.org/10.1016/S0140-6736(14)61933-4.

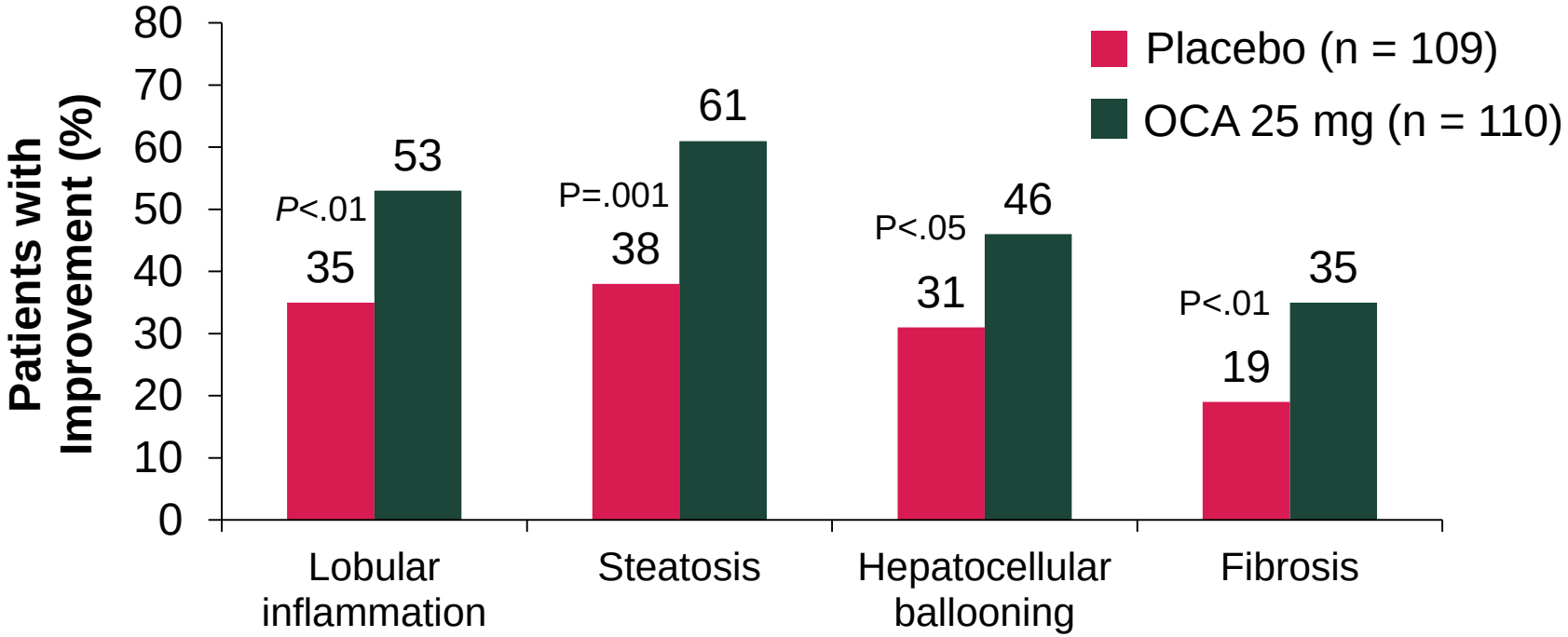
FLINT Primary Endpoint

- Improvement in NAFLD activity score* (NAS) ≥ 2 pts
  - * NAS = steatosis grade (0-3) + inflammation grade (0-3) + ballooning grade (0-2)
- No worsening of fibrosis



Neuschwander-Tetri BA, Loomba R, et al. *The Lancet.* 2015.

FLINT – Improved Secondary Histologic Outcomes at Week 72



Abbreviation: OCA, obeticholic acid.

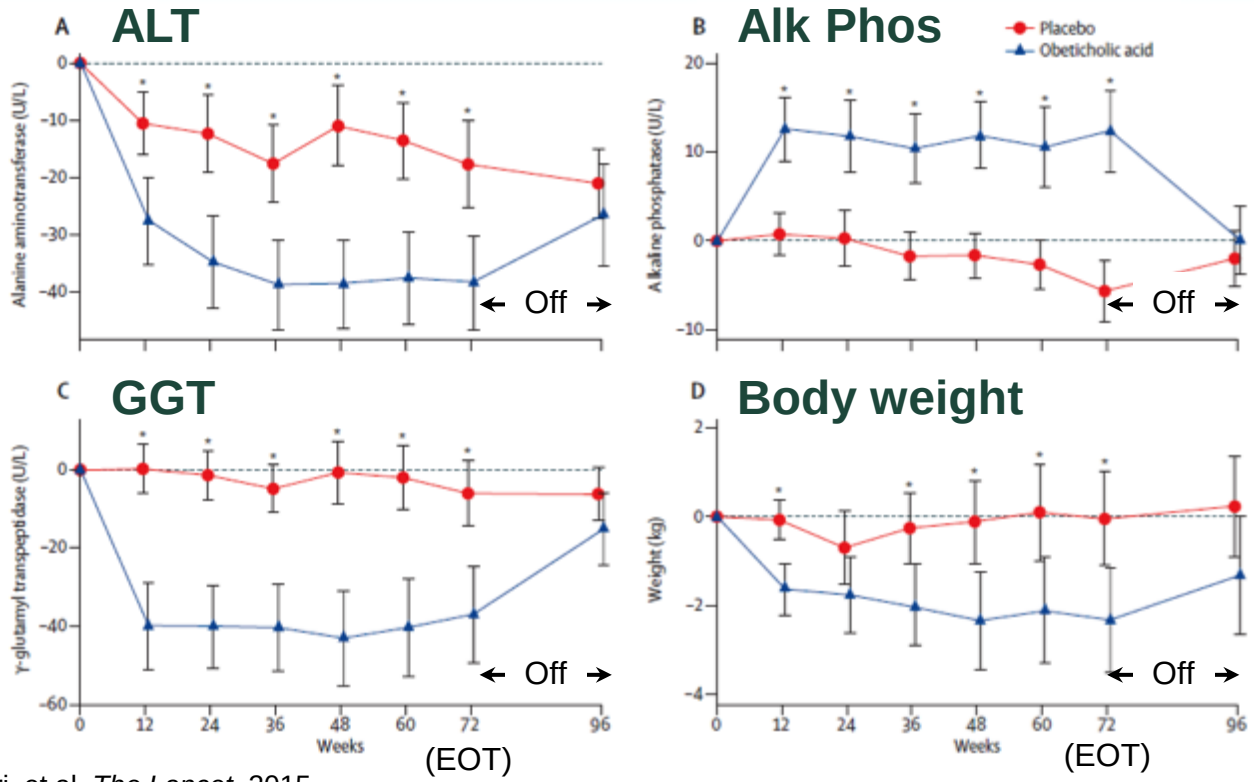
Neuschwander-Tetri BA, et al. *The Lancet*. 2015;385:956-965.

Summary: Efficacy

- Obeticholic acid (25 mg orally daily) improves liver histology in NASH
- Obeticholic acid may improve NASH-related fibrosis
- Obeticholic acid improves all features of NASH
  - Steatosis
  - Lobular inflammation
  - Ballooning

Neuschwander-Tetri BA, Loomba R, et al. *The Lancet.* 2015.

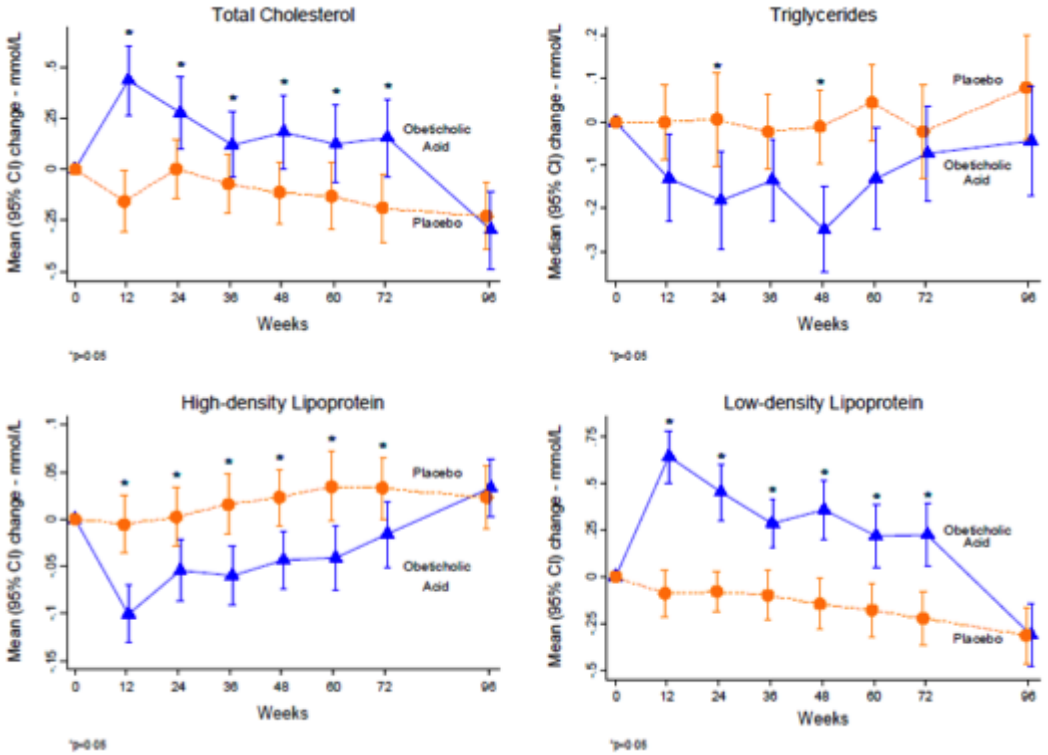
Enzymes and Body Weight



Neuschwander-Tetri, et al. *The Lancet.* 2015.

Risks, Benefits, and Alternatives

Increase in LDL and Decrease in HDL

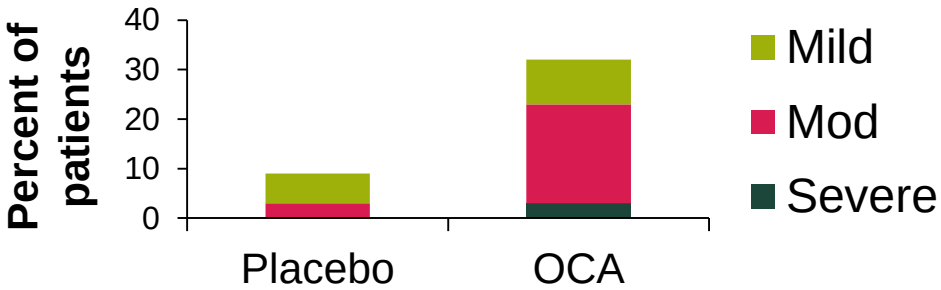


Neuschwander-Tetri BA, Loomba R, et al. *The Lancet.* 2015.

Pruritus

- 6 severe adverse events in obeticholic acid group
  - 4 severe pruritus (1 stopped treatment)
  - 1 hypoglycemia
  - 1 possible cerebral ischemia (dysarthria and dizziness)
- Moderate or severe pruritus
  - 23% in obeticholic acid
  - 6% in placebo

} P<0.0001

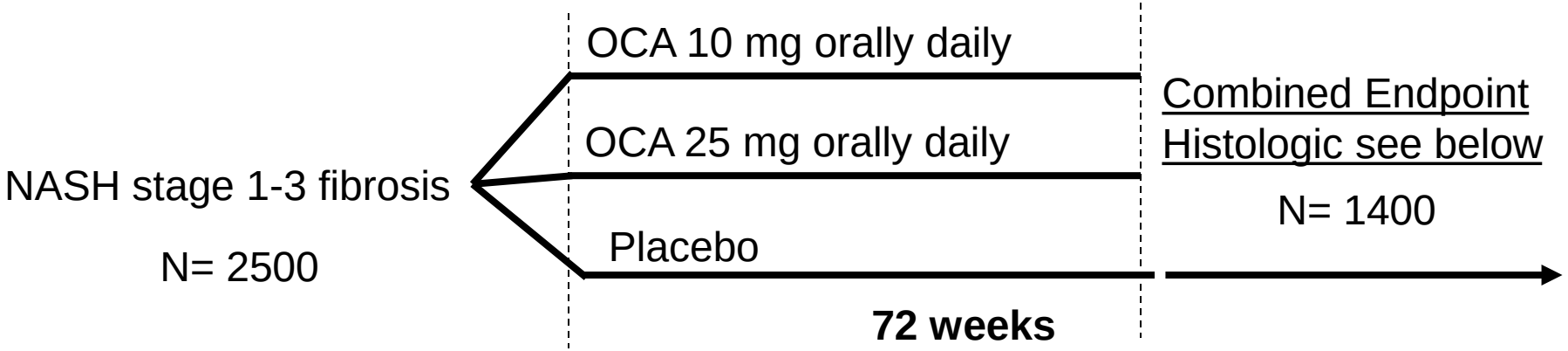


Neuschwander-Tetri, et al. *The Lancet*. http://dx.doi.org/10.1016/S0140-6736(14)61933-4.

FLINT Trial Summary

- Obeticholic acid improved histological features of NASH including fibrosis
- Obeticholic acid treatment was associated with pruritus that was severe in 3%
- Elevated total and LDL cholesterol and decreased HDL cholesterol warrant further scrutiny in future trials
- Large phase 3 trials are being planned to assess it’s efficacy in NASH

REGENERATE Trial Design: OCA vs. Placebo



Combined Endpoint

i. The proportion of OCA-treated patients relative to placebo achieving at least one stage of liver fibrosis improvement with no worsening NASH; and

ii. The proportion of OCA-treated patients relative to placebo achieving NASH resolution with no worsening of liver fibrosis

GFT505—Phase IIb GOLDEN Trial

Design

Phase IIb, 1-year, international, multicenter, randomized, double-blind, placebo-controlled trial to assess the safety and efficacy of GFT505 in noncirrhotic patients with NASH

Arms

1. GFT505 80 mg
2. GFT505 120 mg
3. Placebo

Patients

270 patients ≥18 years of age

Histologic evidence of NASH based on a liver biopsy; treatment with vitamin E, polyunsaturated fatty acids, or ursodeoxycholic acid discontinued 3 months prior to biopsy

Endpoints

Primary

Resolution of NASH with no worsening of fibrosis

Secondary

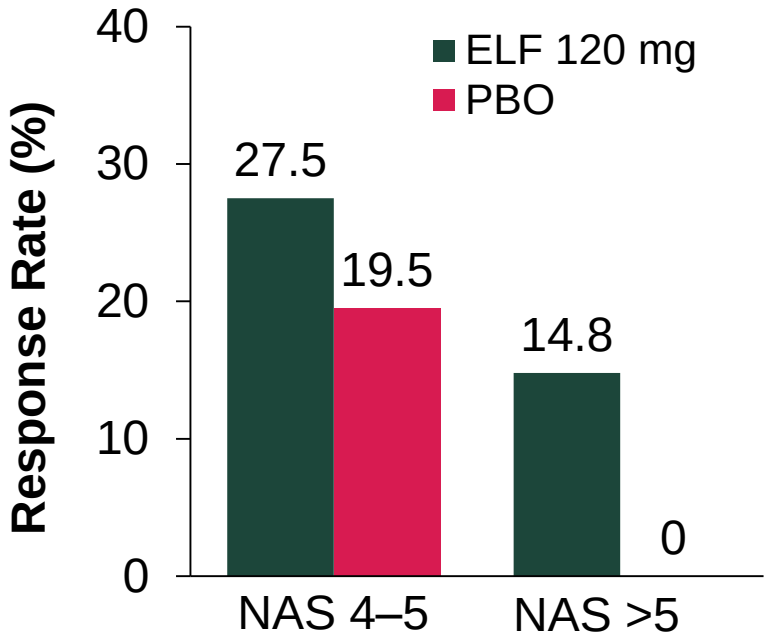
Change in NAS, fibrosis, liver enzymes, lipid parameters, metabolic markers, safety markers

Abbreviations: NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis.

ClinicalTrials.gov. NCT01694849. https://clinicaltrials.gov/ct2/show/NCT01694849.

GOLDEN – Preliminary Findings

- **Primary endpoint was not met in initial assessment**
  - Elafibranor was not better than placebo in resolving NASH
  - After controlling for baseline heterogeneity of severity and center effect, the primary endpoint was met
- **Main caveats**
  - High placebo response due to inclusion of milder disease
  - Sub-set analysis: NAS >5 shows significant improvement in elafibranor 120 mg group versus placebo



Abbreviation: ELF, elafibranor; NAS, NAFLD Activity Score; PBO, placebo.

Ratziu V, et al. *Hepatology.* 2015;62(suppl 1):262A.

Summary 1

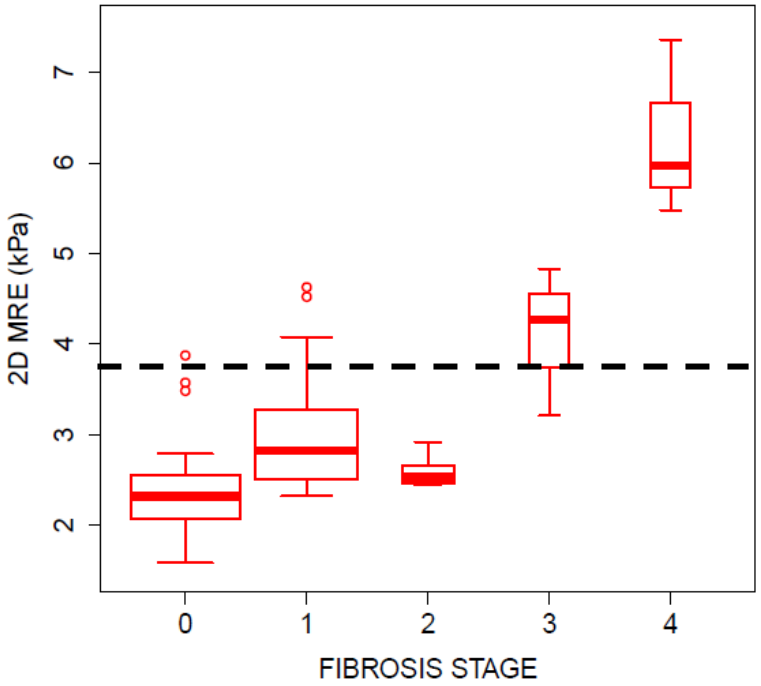
- We discussed new data on natural history of NAFLD
- We discussed two major trials
  - FLINT Trial
    - OCA versus placebo
  - GOLDEN Trial
    - Elafibranor versus placebo

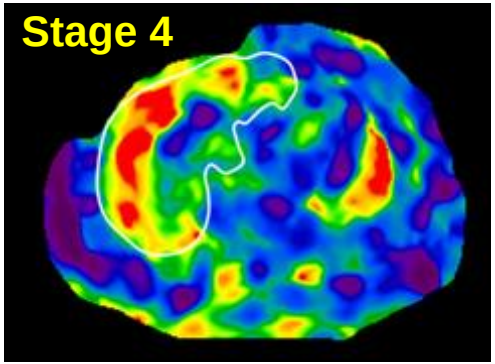
Innovations in Clinical Trial Design

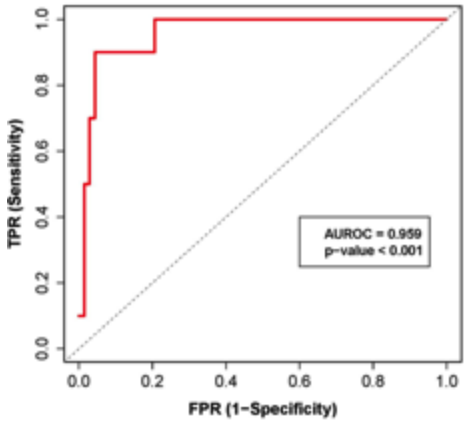
How Will Future Clinical Trials Assess NASH?

Accuracy of MRE in Non-invasive Diagnosis of Advanced Fibrosis in NAFLD

A Threshold of 3.63 Kpa Descriminates Advanced Fibrosis







Loomba, et al. *Hepatology.* 2014.

Novel MRI and MRE Assessment of Ezetimibe versus Placebo for the Treatment of Nonalcoholic Steatohepatitis: A Randomized-Controlled Trial MOZART Trial

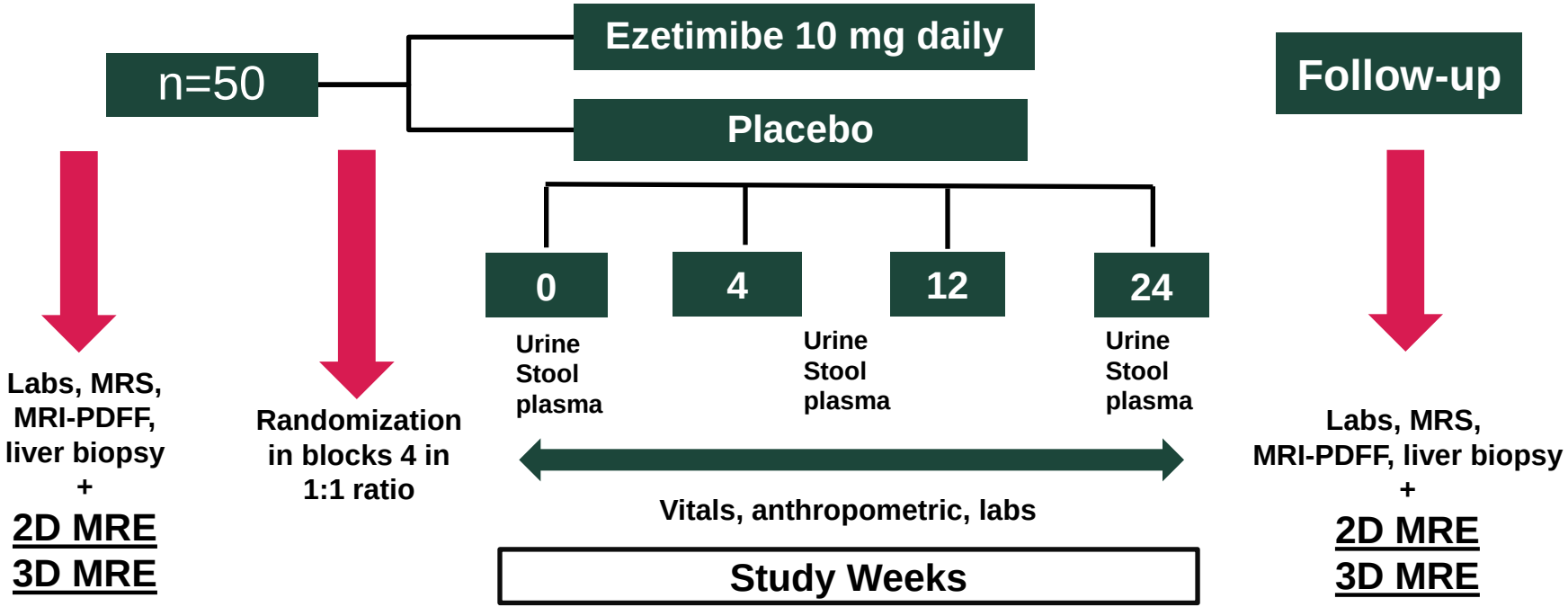
An Example of Innovation in Clinical Trials

Loomba, et al. *Hepatology*. 2015.

MOZART Trial Design: Ezetimibe vs Placebo

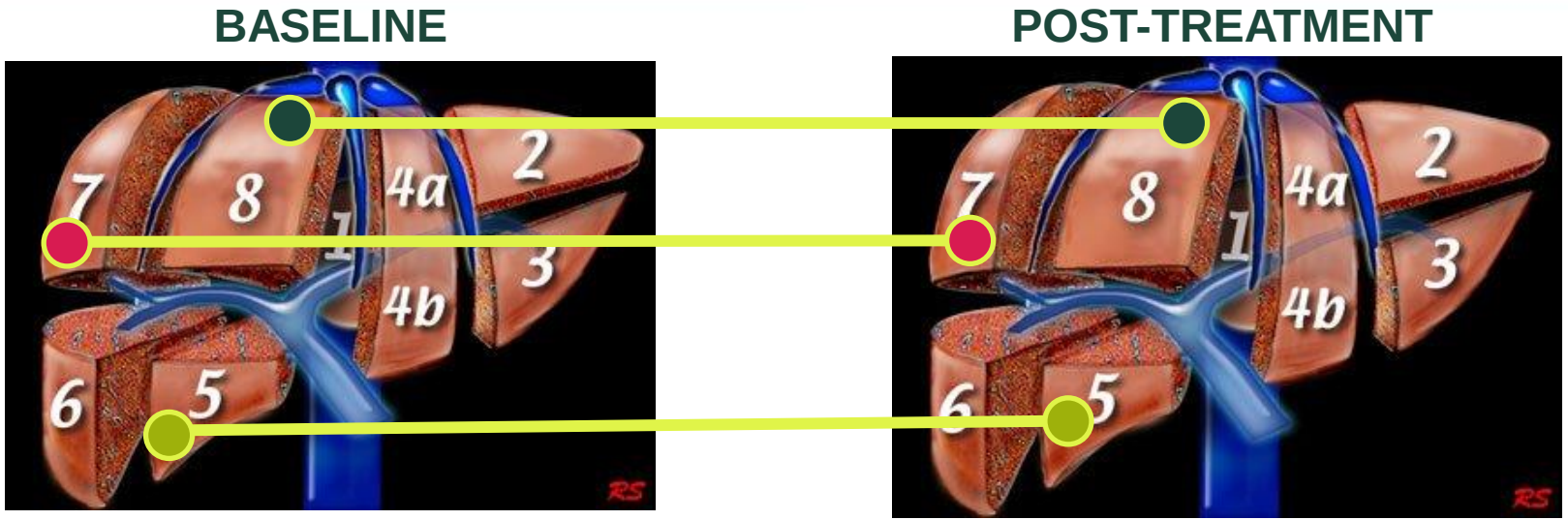
Design: Randomized, double-blind, allocation-concealed, placebo-controlled, clinical trial

First Trial to Assess 2D and 3D MRE in NASH



Co-localized MRI-PDFF and Cross-validated with MRS

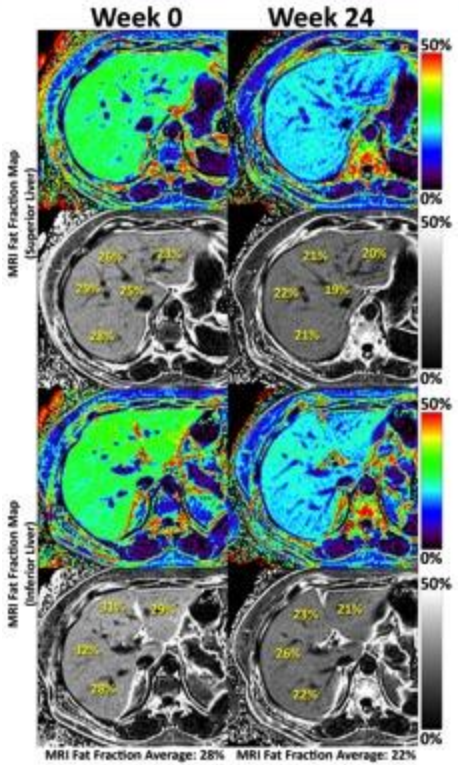
BASELINE **POST-TREATMENT**



- PDFF recorded in regions of interests (ROI)s ~300-400mm^2
- The same ROIs in each of the 9 liver segments measured at baseline and post-treatment
- Each segment fat fraction = 1 ROIs
- Total liver fat fraction = average 9 ROIs

Loomba, et al. *Hepatology.* 2015.

Fat-mapping Before and After Treatment



Loomba, et al. *Hepatology.* 2015.

Fat distribution:

- Heterogenous
- Predictable

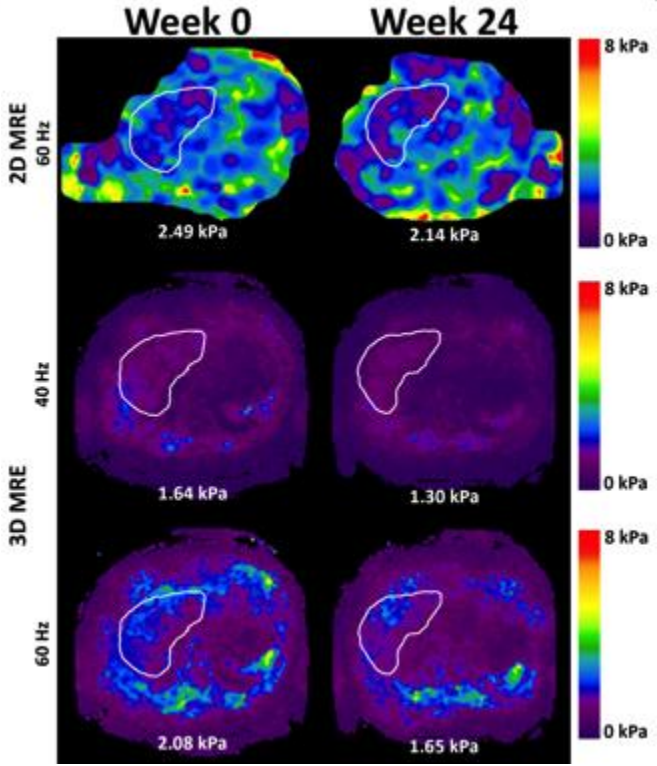
- **Why do we need to co-localize?**
  - Heterogeneity
  - Need for precision

Higher precision and accuracy

↓

Efficiency in clinical trial

Stiffness-mapping Before and After Treatment



2D and 3D MRE is feasible

2D and 3D MRE may change in 24 wks

<u>Larger area of the liver:</u>

- More comprehensive assessment

- **Why do we need to co-localize?**
  - Need for precision

Higher precision and accuracy

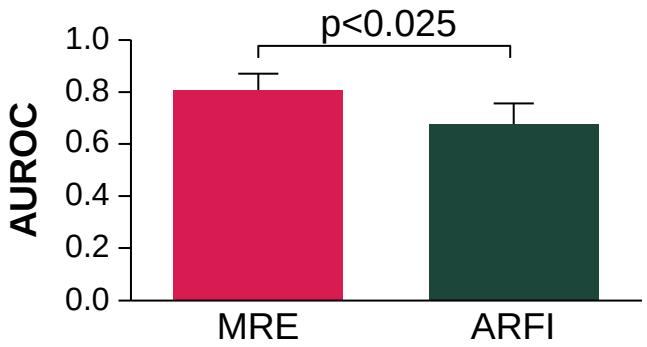
↓

Efficiency in clinical trial

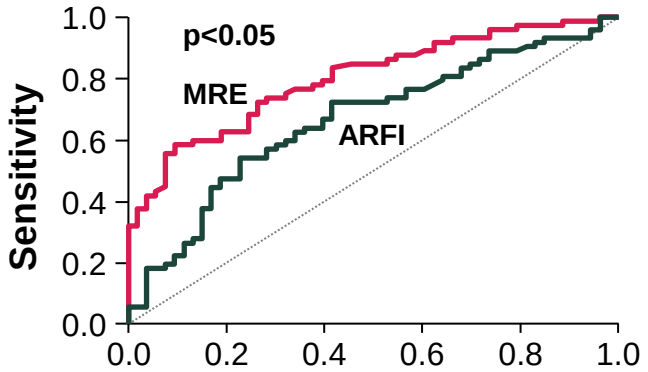
Loomba, et al. *Hepatology.* 2015.

Magnetic Resonance Elastography (MRE) is Superior to Acoustic Radiation Force Impulse (ARFI) for the Diagnosis of Fibrosis in Patients with Biopsy-proven NAFLD: A Prospective Study

- All patients underwent MRE and ARFI within 1 year of contemporaneous liver biopsy
- Liver biopsies scored using the NASH CRN histological system



ROC Curves for 125 Consecutive Patients with Biopsy-Proven NAFLD with Contemporaneous MRE and ARFI



Diagnostic Test Parameters of MRE vs ARFI for Diagnosing Fibrosis

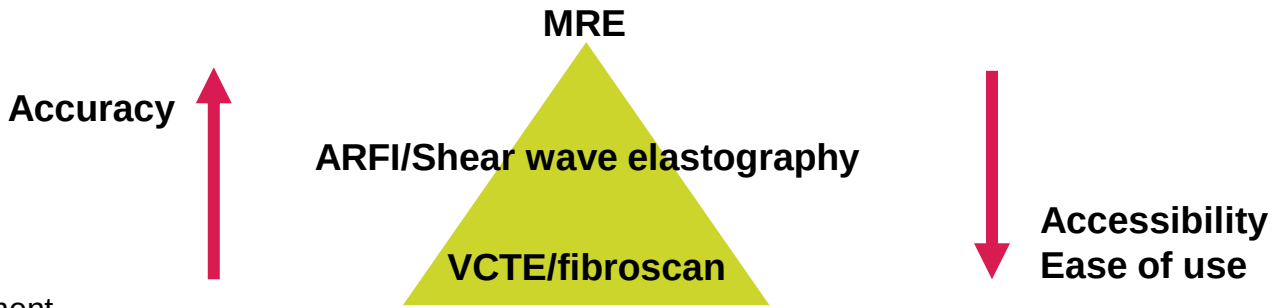
	NAFLD fibrosis	No fibrosis	AUROC (95% CI)	Cut-off	Sens	Spec	PPV	NPV
MRE	72	53	0.80 (0.72, 0.88)	2.99	58%	91%	89%	62%
ARFI			0.66 (0.57, 0.76)	1.29	54%	77%	77%	55%

- In patients with BMI <30 kg/m^2, ultrasound may be used; for those ≥30 kg/m^2, MRE should be used

Cui JY, et al. AASLD 2015, San Francisco. #45.

Caveats Associated with Available Modalities

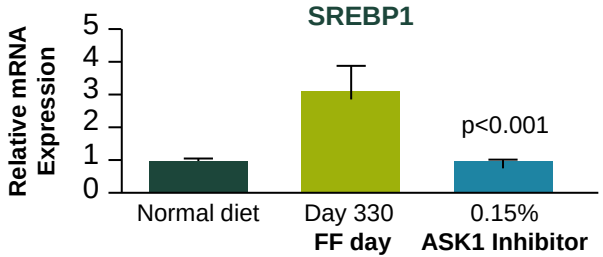
- Transient elastography or ARFI or other ultrasound-based test have following limitations:
  - Obesity
  - Ascites
  - Acute Inflammation
  - Cirrhosis
- MRE improves upon all except
  - Iron Overload
  - Acute Inflammation



- Depth of assessment
- Total volume or surface area of the liver covered
- MRE is more precise, accurate, reproducible not affected by obesity, ascites
- US-based and fibroscan point-of-care, ease of use, more access

Efficacy of an ASK1 Inhibitor to Reduce Fibrosis and Steatosis in a Murine Model of NASH is Associated with Normalization of Lipids and Hepatic Gene Expression and a Reduction in Serum Biomarkers of Inflammation and Fibrosis

- Mice received a high fat, high cholesterol, high sugar diet for 330 days
- ASK1 inhibition:
  - Corrected alterations in fatty-acid metabolism mediated by D5D, D6D and D9D
  - Decreased hepatic steatosis
  - Altered expression of SREBP1 (↓68%), and genes involved in fatty acid synthesis

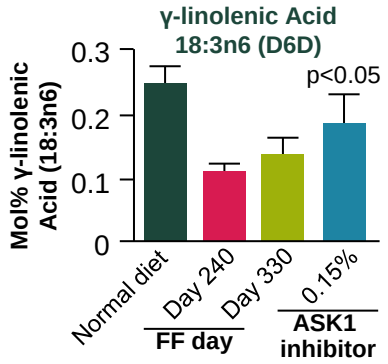


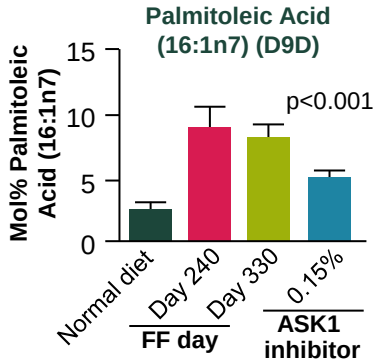
- ASK-1 inhibition reduces hepatic steatosis by shutting down SREBP1, and reverses NASH towards NAFL
- ASK-1 inhibition also improves fibrosis

EOT, end of treatment; SOT, start of treatment.

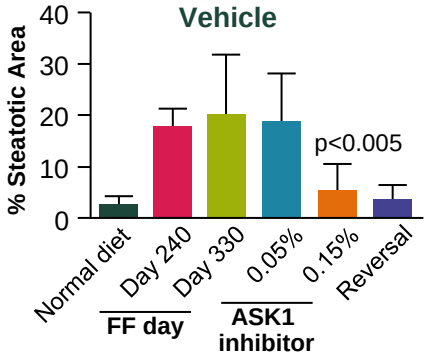
Karnik S, et al. AASLD 2015, San Francisco. #1359.

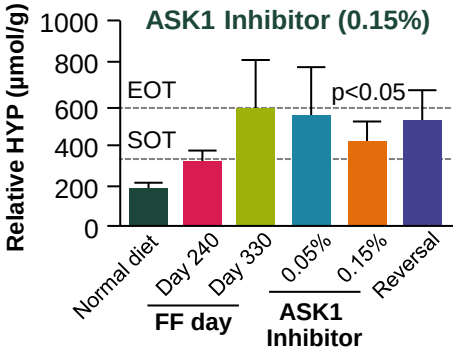
Fatty Acid Metabolism





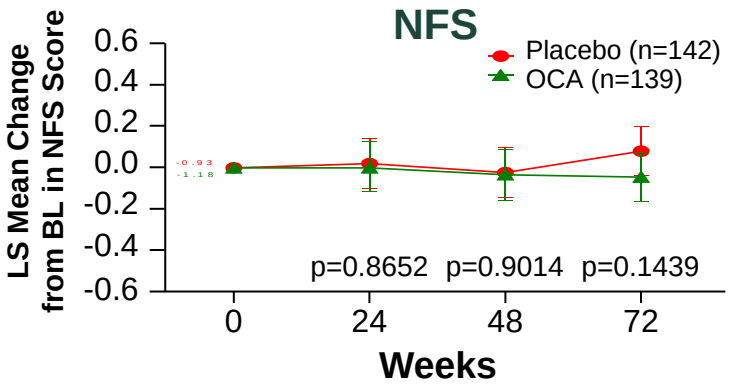
Hepatic Steatosis and Fibrosis

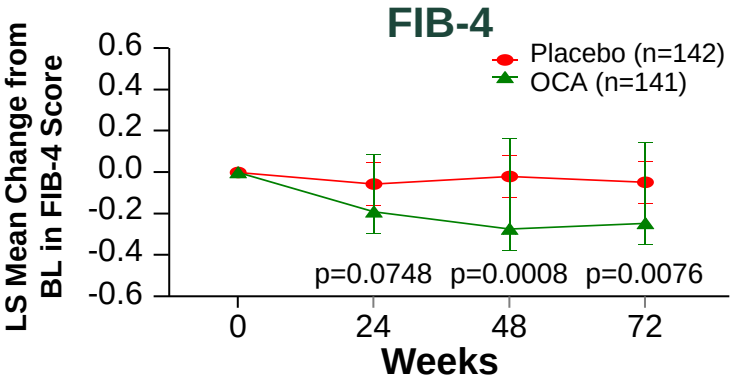


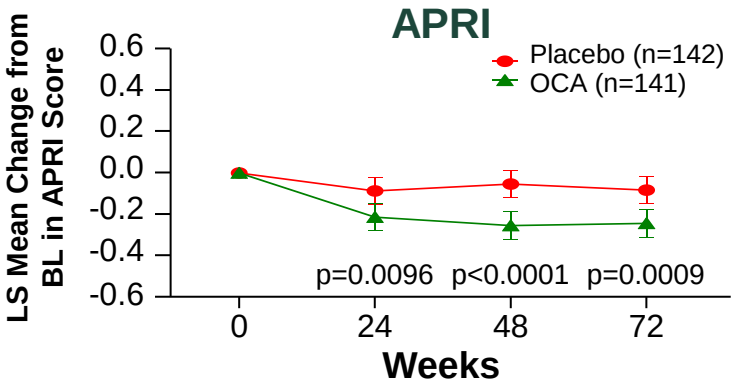


Longitudinal Changes in FIB-4 and Improvement in Fibrosis Stage with Obeticholic Acid: A Secondary Analysis of the FLINT Trial

- 72-week, multicenter, double-blind trial in patients with non-cirrhotic NASH
- 2° analysis in 200 patients with baseline and end of treatment biopsies: 32% stage 3, 29% stage 2 and 26% stage 1 fibrosis (biopsy)
- Baseline APRI was 0.7 in both treatment groups; baseline FIB-4 was 1.7 (OCA) and 1.5 (placebo)



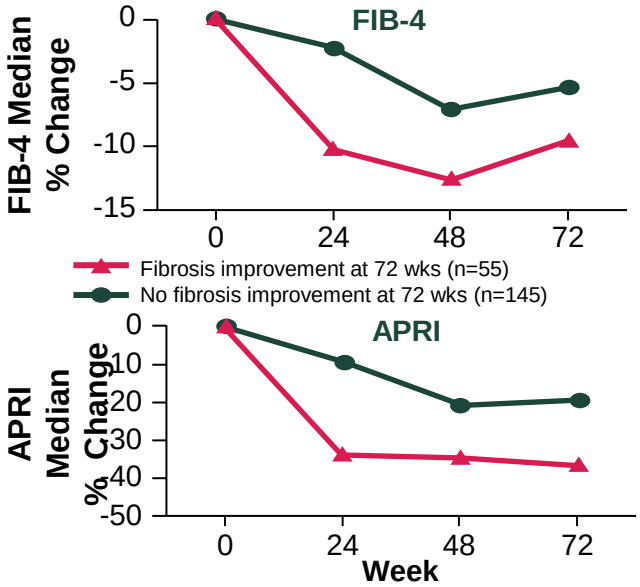




Chalasani NP, et al. AASLD 2015, San Francisco. #239.

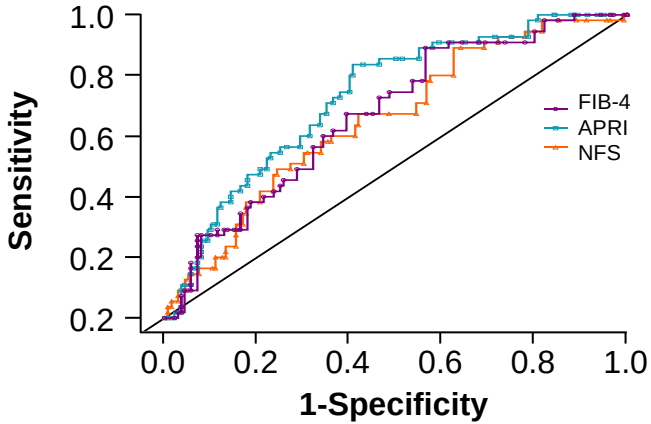
Longitudinal Changes in FIB-4 and Improvement in Fibrosis Stage with Obeticholic Acid: A Secondary Analysis of the FLINT Trial

Improvement in Histologic Fibrosis Stage at 72 Wks



- OCA led to a decrease in APRI and FIB-4 vs placebo
- This was related to improvement in fibrosis stage; a 10% (FIB-4) and 34% (APRI) decrease at 24 weeks was associated with a ≥1 stage- improvement in fibrosis at 72 weeks ($p<0.05$)

ROC Curves for Noninvasive Fibrosis Scores



Parameters

- Fibrosis stage at BL
- FIB-4/APRI at BL
- FIB-4/APRI change at 24 weeks
- Treatment

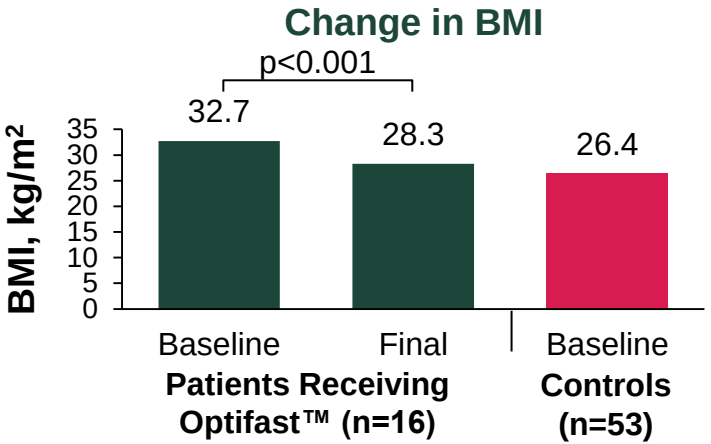
Name	Cutoff	AUROC	NPV	PPV	95% CI
FIB-4	0.29	0.6817	80.7%	40.7%	(0.6024, 0.7610)
APRI	0.34	0.7238	80.6%	47.5%	(0.6483, 0.7993)

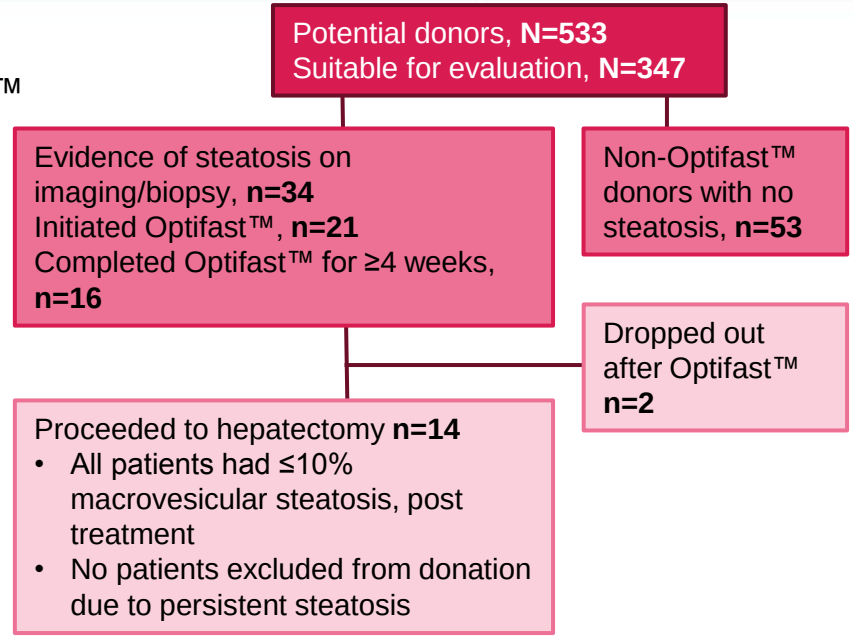
- OCA improves FIB-4 and APRI
- FIB-4 (10%) and APRI (34%) change at Week 24 predicts improvement in fibrosis at Week 72

Chalasani NP, et al. AASLD 2015, San Francisco. #239.

Treatment with Optifast™ Reduces Hepatic Steatosis and Safely Increases Candidacy Rates for Live Donor Liver Transplantation

- Retrospective study in large live donor program
- Reduction in BMI and hepatic steatosis with Optifast™
- Post-surgical donor and recipient outcomes comparable between Optifast™ and controls





- Optifast reduces liver fat by inducing weight loss and may increase donor pool for live donor liver transplant
- There are better and more accurate ways of studying this rather than serial biopsy

Doyle A, et al. AASLD 2015, San Francisco. #11.

Heritability of Hepatic Fibrosis and Hepatic Steatosis: A Prospective Twin Study

An Example of Innovative Application

Rohit Loomba, Nicholas Schork, Chi-Hua Chen, Ana Bhatt, Brandon Ang, Phirum Nguyen, Carolyn Hernandez, Lisa Richards, Joanie Salotti, Steven Lin, Karen E Nelson, Claude B Sirlin, David Brenner
for the Genetics of NAFLD in Twins Consortium

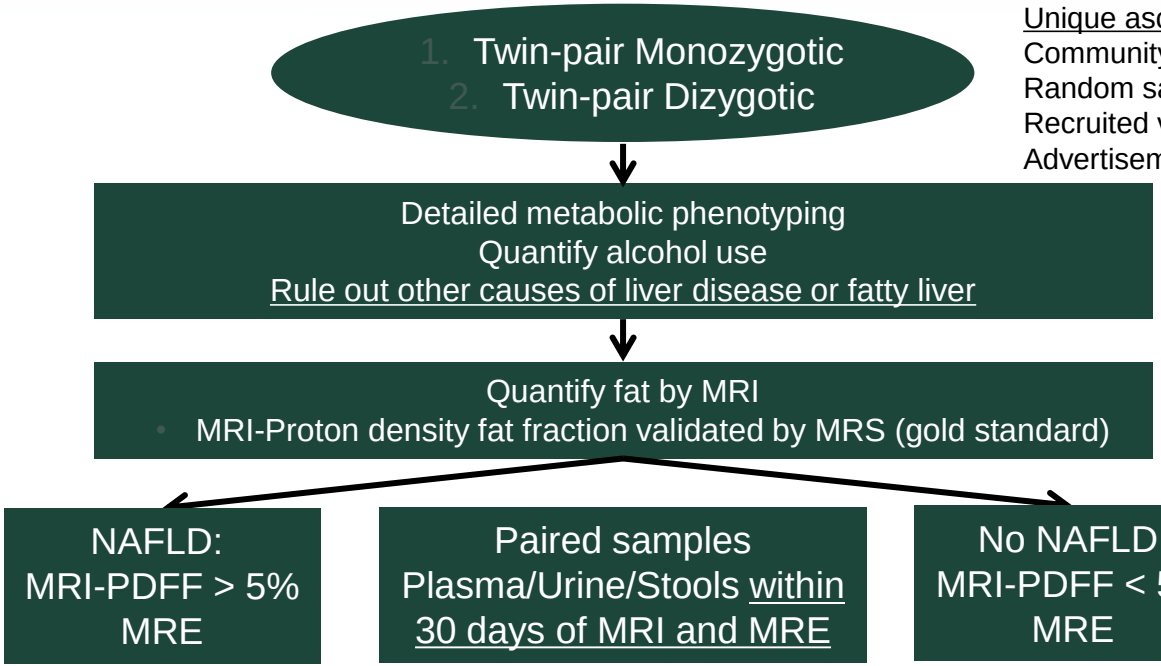
NAFLD Translational Research Unit, Division of Gastroenterology, Department of Medicine, Division of Epidemiology, Department of Family Medicine and Public Health, University of California, San Diego, La Jolla, CA 92093

Human Biology, J. Craig Venter Institute, La Jolla, CA 92037
Liver Imaging Group, Department of Radiology, University of California, San Diego, La Jolla, CA 92093

Email: roloomba@ucsd.edu

Loomba, et al. *Gastroenterology.* 2015.

UCSD Twin Study



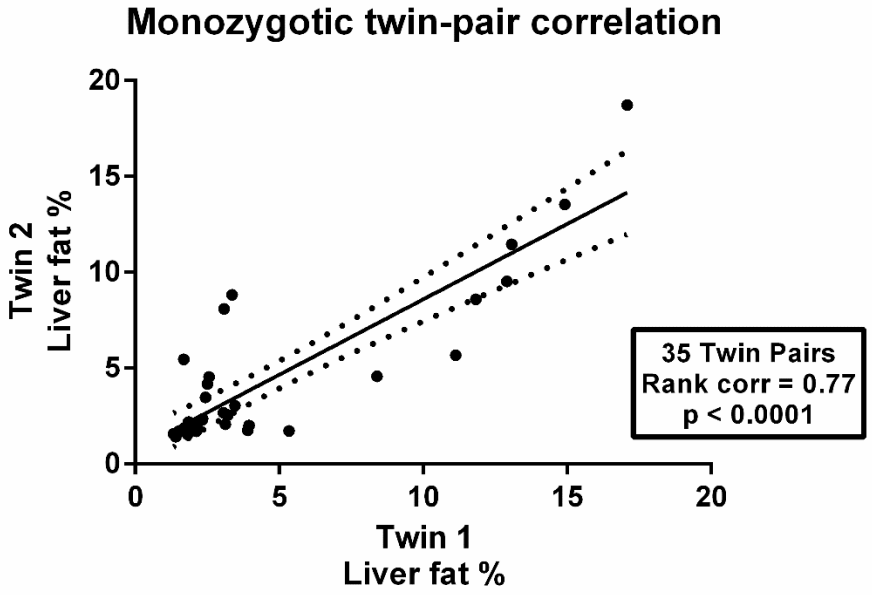
Unique ascertainment attributes
Community-dwelling
Random sample
Recruited via Newspaper Advertisement

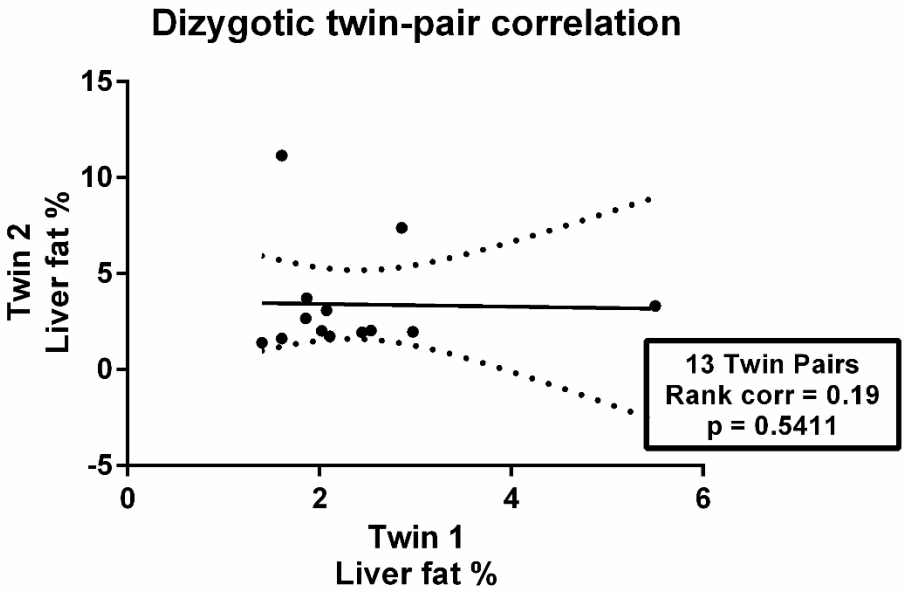
Unique phenotyping for normal (non-NAFLD) control
Resource for scientific community as ALT and ultrasound/CT are insensitive and liver biopsy is unethical

MRI-PDFF is the most accurate non-invasive method to quantify liver fat
MRE is the most accurate non-invasive method of quantify liver fibrosis

Loomba, et al. *Gastroenterology.* 2015.

Heritability of Hepatic Steatosis Content

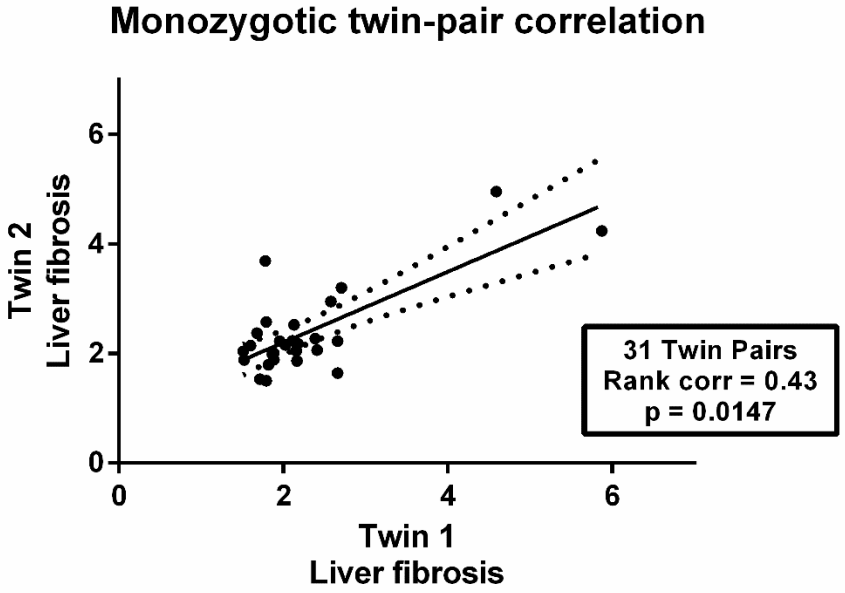


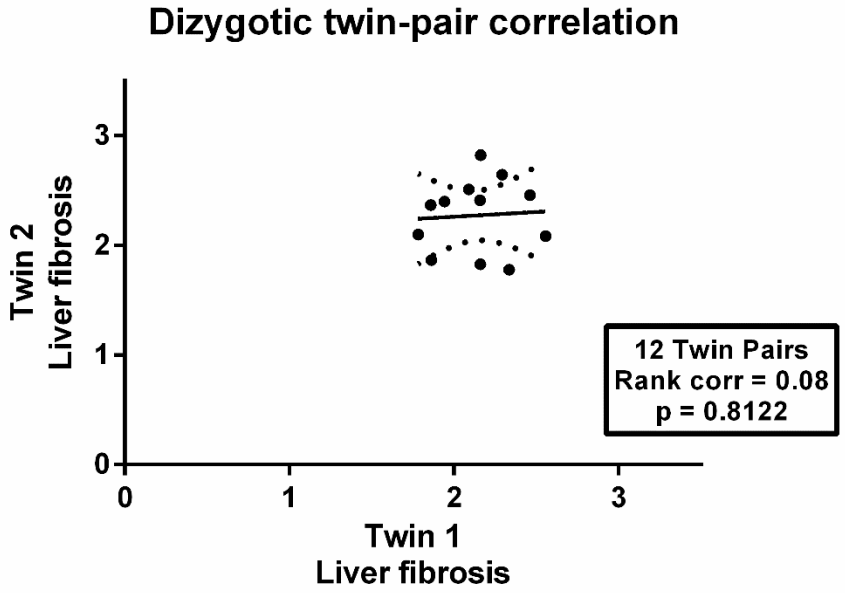


Heritability estimate of liver fat = 0.67, p-value < 1.1×10^{-15}

Loomba, et al. *Gastroenterology.* 2015.

Heritability of Hepatic Fibrosis Content





Heritability estimate of hepatic fibrosis = 0.66, p-value < 9.7×10^{-14}

Loomba, et al. *Gastroenterology.* 2015.

NASH: Final Summary

- NASH is one of the leading causes of progressive liver disease and cirrhosis in the United States
- There are several exciting molecules in clinical development for the treatment of NASH and hepatic fibrosis and cirrhosis
- Both liver fat and liver fibrosis are heritable traits
- MRI-PDFF is robust in quantitative assessment of liver fat especially in NASH trials
- MRE is robust in non-invasive quantification of liver fibrosis and can now be utilized in NASH trials

Thank You

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Acknowledgement:

1. R01, NIDDK, NIH
2. U01, NASH-CRN, NIDDK, NIH
3. K23, Genetic epidemiology of NAFLD, NIDDK, NIH
4. American Gastroenterology Association-Research Scholar Award
5. The T Franklin Williams Scholars Program
6. Investigator Initiated Research Grant Daiichi Sankyo Inc
7. Investigator Initiated Research Grant-1 Merck Inc
8. National Science Foundation
9. C-Treat, Digestive Disease Center, UCSD, NIDDK, NIH
10. Investigator Initiated Research Grant- 2 Merck Inc
11. Kinemed Inc

Advanced MRI Phenotyping in Diffuse Liver Disease

A one-stop shop for quantitative liver disease staging and phenotyping

A 15 minutes exam

- IDEAL liver fat quantification
- Whole body Dixon imaging with neck to knee coverage
- MR-Elastography

Clinical value

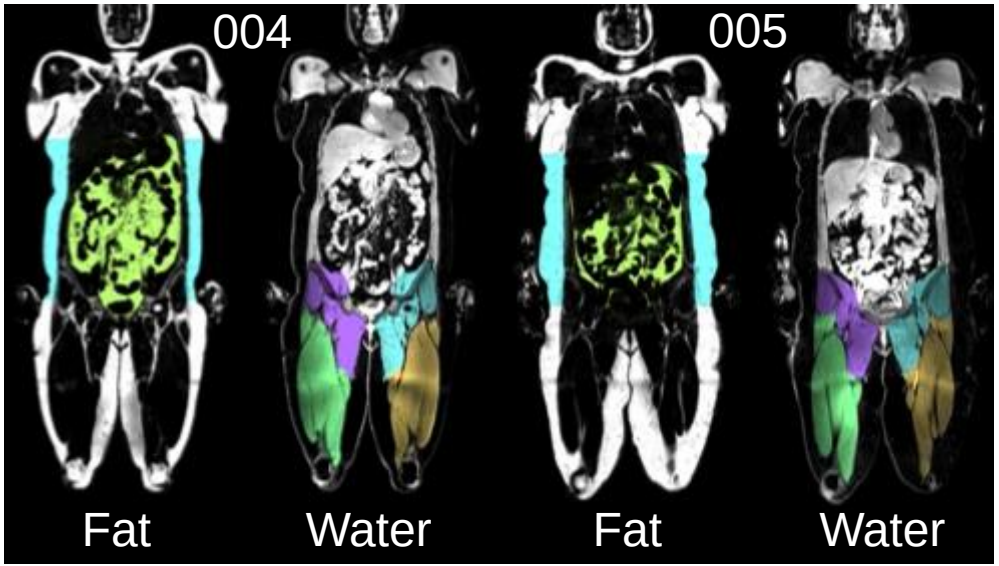
- Liver fat
- Visceral adipose tissue
- Abdominal subcutaneous adipose tissue (ASAT)
- Thigh muscle volume
- Fibrosis staging via liver stiffness

2017-03-15

Advanced Phenotyping Using Whole Body Fat-Water Separated MRI

Two female monozygotic twins, 43 years

	004	005
Weight	93.7 kg	108.6 kg
BMI	33.6 kg/m2	39.4 kg/m2
Waist circ.	103 cm	112 cm
Liver fat (PDFF)	5.2%	1.8%
MRE liver	2.00 kPa	2.53 kPa
Total thigh muscle	10.5 l	12.1 l
VAT	4.0 l	2.4 l
ASAT	12.4 l	17.5 l
VAT/(VAT+ASAT)	24%	12%
Thigh/weight	11%	11%



Subject 004 has

lower weight, BMI, and waist circumference

But…

higher liver fat and visceral adipose tissue volume.

2017-03-15

Novel Phenotyping Demonstrates Mono-zygotic Twin Pair with NAFLD Cirrhosis