Innovations in Non-invasive Imaging Assessment of Treatment Response in NASH

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- Advisory Committees: Gilead, Galmed, Intercept, Gemphire, Arrowhead Research, Tobira, NGM, Conatus, Octeta
- Consultant: Gilead, Novo Nordisk, Pfizer, BMS, Fibrogen, NGM, Alnylam, DeuteRx, Zafgen, RuiYi, Shire, Receptos, Enanta, Celgene, Boehringer Ingelheim, Eli Lilly, Ionis, Viking, Metacrine, Madrigal, CohBar, Scholar Rock, Bird rock bio, Intercept, GNI, GRI, Glympse bio, Conatus, Alergan and Janssen Inc.
- Co-founder: Liponexus Inc.

Outline

- Epidemiology
- Definition
  - NAFLD: NAFL versus NASH
- Natural history of NAFLD
- Advances in imaging assessment
- Pharmacologic treatment
- Novel therapies in NASH

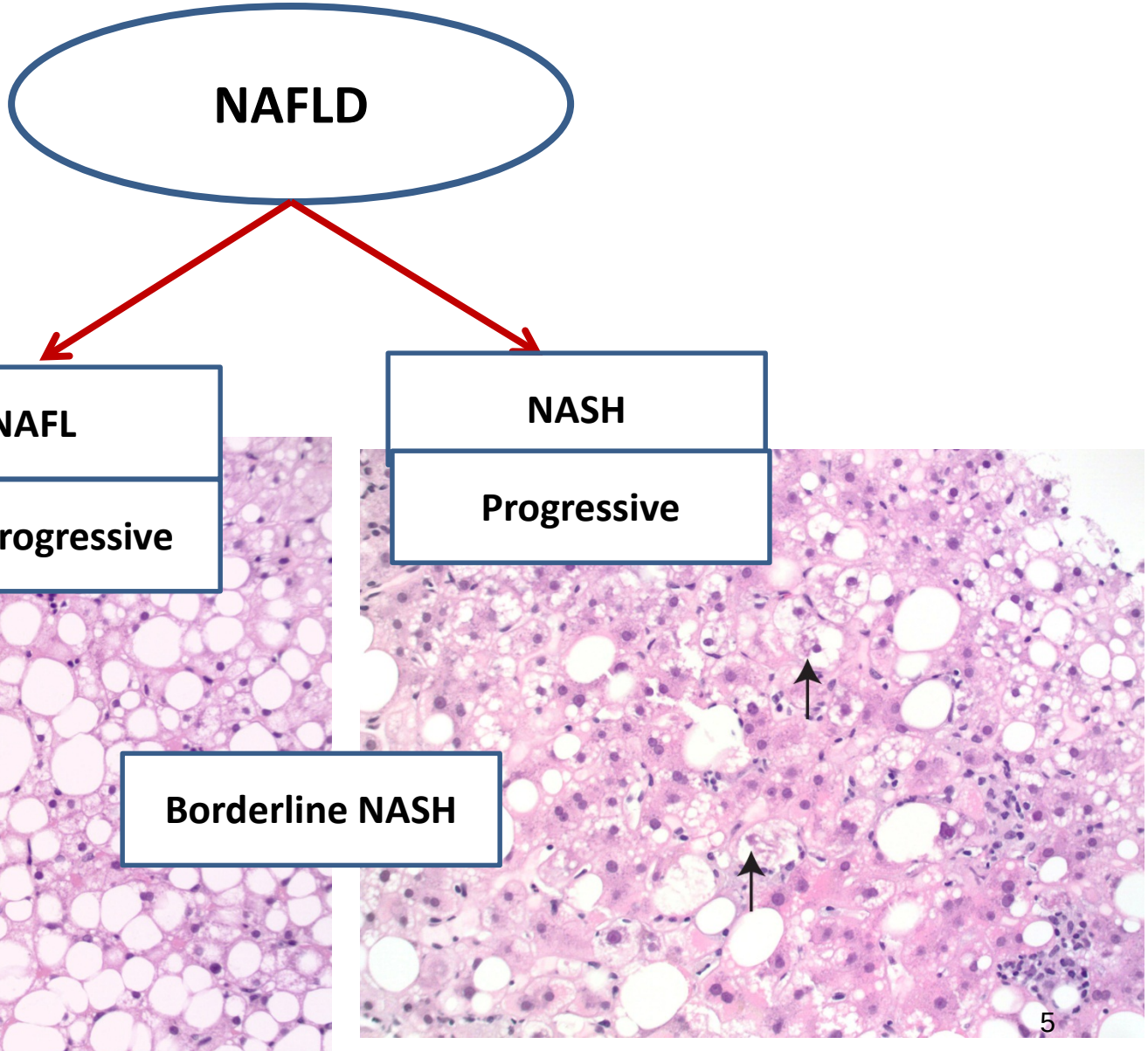
Epidemiology: Burden of NAFLD

- **Nonalcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease in the US**
  - Afflicts 80-100 million Americans
- **Ethnic predisposition**
  - More common in Asian Indians>Hispanics>Caucasians>African Americans
- **Risk factors include metabolic syndrome**
  - Obesity, hypertension, hypertriglyceridemia, insulin resistance and diabetes
  - PNPLA3 genotype
- **NAFLD is diagnosed**
  - Either on biopsy or imaging evidence of hepatic steatosis (≥ 5% liver fat) in individuals who consume little or no alcohol without any other cause for liver disease or hepatic steatosis

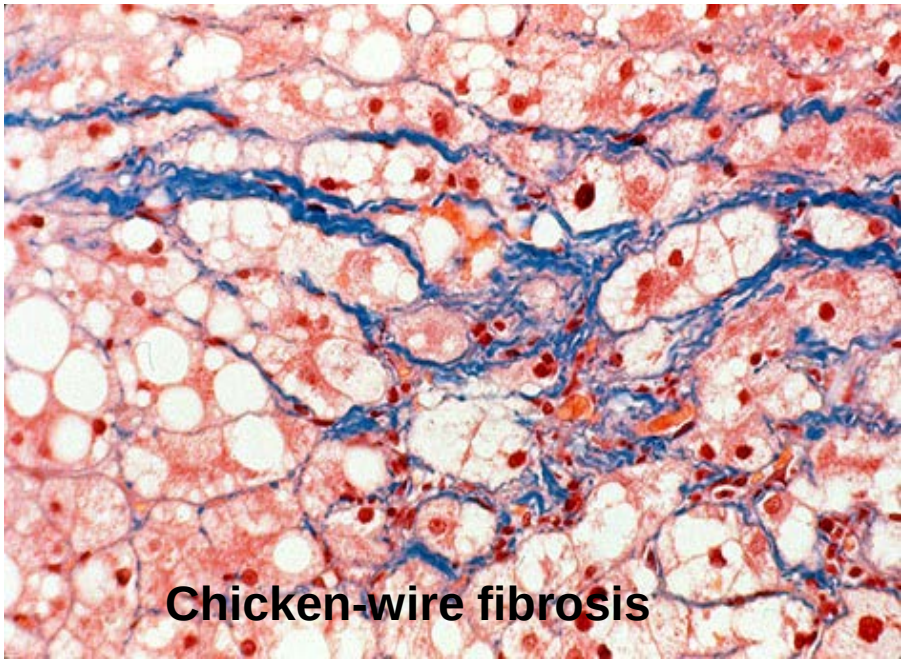
Subtypes of NAFLD

Caveats

- Presence of steatosis in ≥ 5% hepatocytes
- Minimal alcohol use
- Biopsy consistent with NAFLD
- No other etiology for liver disease
- No secondary causes of NAFLD
  - Medications
  - HIV
  - Lipodystorphy



Nonalcoholic steatohepatitis (NASH)

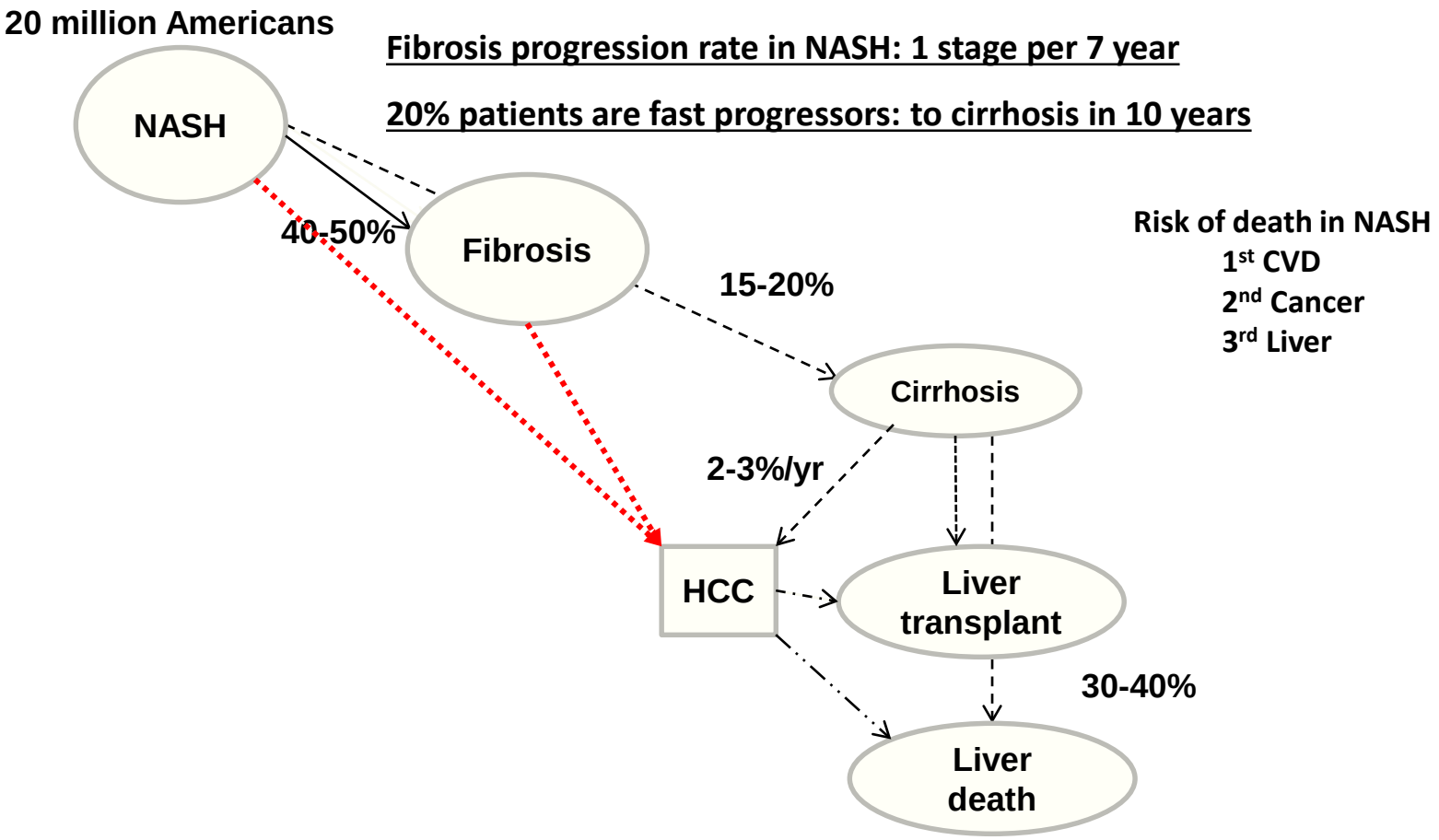


NASH

- **steatosis**
- **lobular inflammation**
- **ballooning**
- **with or without zone 3 fibrosis**

Third leading indication for liver transplant in the US

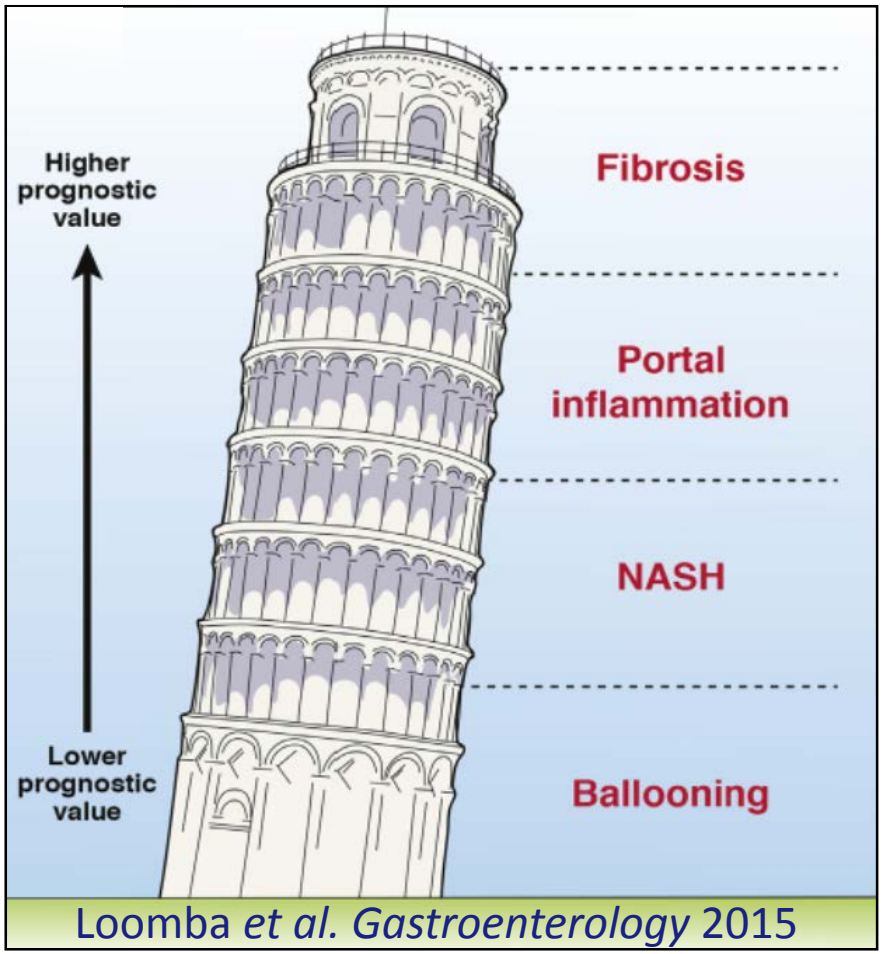
Natural history of NASH



Multiple sources: Over 40 studies

Key histologic predictors of mortality in NAFLD

Fibrosis is the single most important predictor of mortality in NASH



Advanced fibrosis

Fibrosis

NASH

Angulo et al. Gastroenterology 2015
Loomba and Chalasani. Gastroenterology 2015

There are no FDA Approved Therapies for NASH

Outline

Traditional paradigm

Quantitative, Imaging biomarker assessment and development program

- **Assessment of hepatic steatosis**
- **Assessment of hepatic fibrosis**
- **Longitudinal changes in disease severity**
  - **MRI-PDFF**
  - **MRE**

New paradigm

Improve efficiency

Traditional paradigm for assessment of treatment response

- **2005: NASH CRN Histologic Scoring System was developed**
  - **NAFLD Activity Score is proposed: A summary score ranging from 0-8**
    - **Steatosis (0-3)**
    - **Lobular inflammation (0-3)**
    - **Ballooning (0-2)**

- **2010: PIVENS Trial (Sanyal et al. NEJM 2010)**
  - Vitamin E versus pioglitazone versus placebo
  - **96 week duration**
  - **Paired liver biopsy** before and after treatment
  - Primary endpoint: 2-point improvement in NAFLD Activity Score

Problems with traditional approach

- **Duration of trials: 96 weeks or 72 weeks**
- **Liver histologic features have low kappa**
  - Ballooning: K = 0.44
- **Subjective assessment**
- **Invasive**
- **High risk of type 2 error in early phase trials**
  - Small sample size and small treatment effect size

Solution: Quantitative, non-invasive, accurate, reproducible, precise and have significance in natural history and eventually show improvement in liver-related and overall mortality

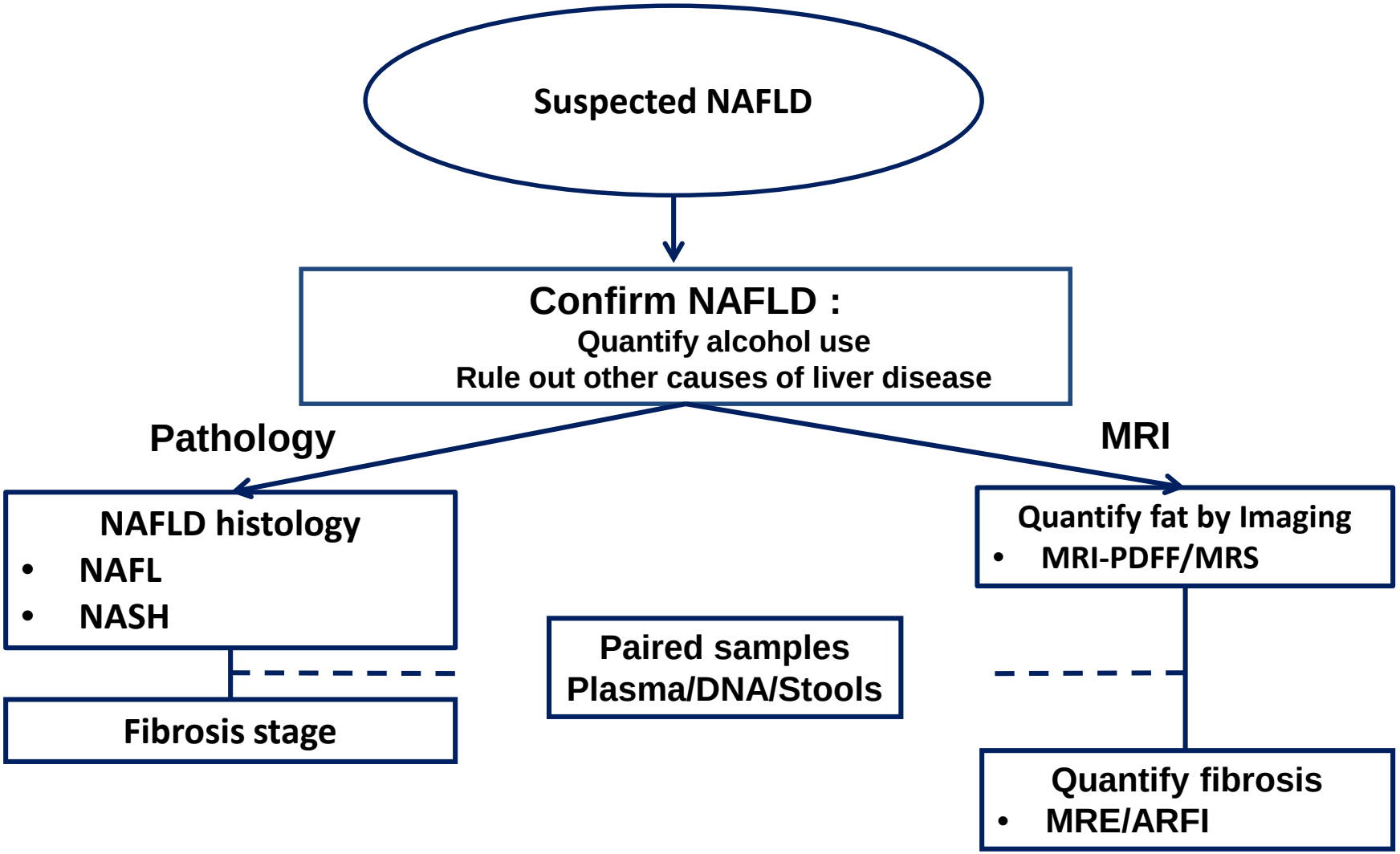
NAFLD Activity Score (NAS) = Max Score 8

Item	Score	Extent
Steatosis	0	<5%
	1	5-33%
	2	>33-66%
	3	>66%
Lobular Inflammation	0	No foci
	1	<2foci/200x
	2	2-4 foci/200x
	3	>4 foci/200x
Hepatocyte Ballooning	0	None
	1	Few balloon cells
	2	Many cells/prominent balloon
Fibrosis	0 - 4	

5. Kleiner DE. *Hepatology*. 2005

Novel MR imaging assessment of liver Fat, NASH and fibrosis

Cohort 1: UCSD NAFLD Cohort



N = 300 (200 paired stool/plasma samples) NAFLD patients available as Feb 2018

Assessment of liver fat

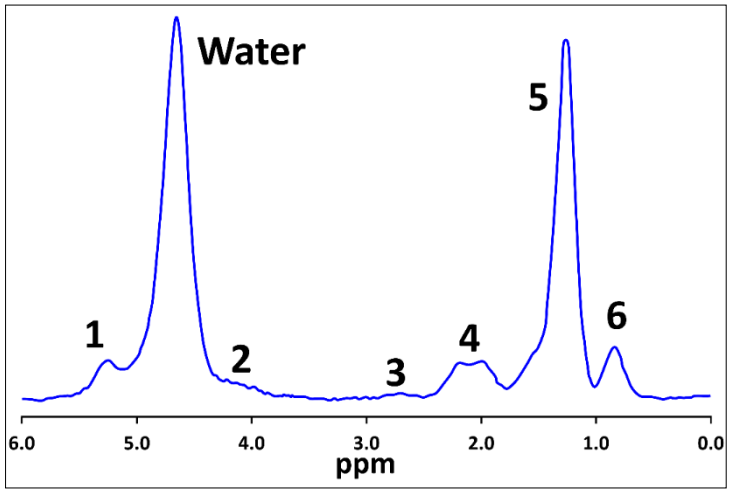
Fat (TG) has a chemical signature

This chemical signature can be detected ***directly*** by magnetic resonance spectroscopy (MRS)

Performed properly, MRS quantifies the ***proton density fat fraction (PDFF),*** a standardized measure of liver tissue [TG]

Limitations of MRS

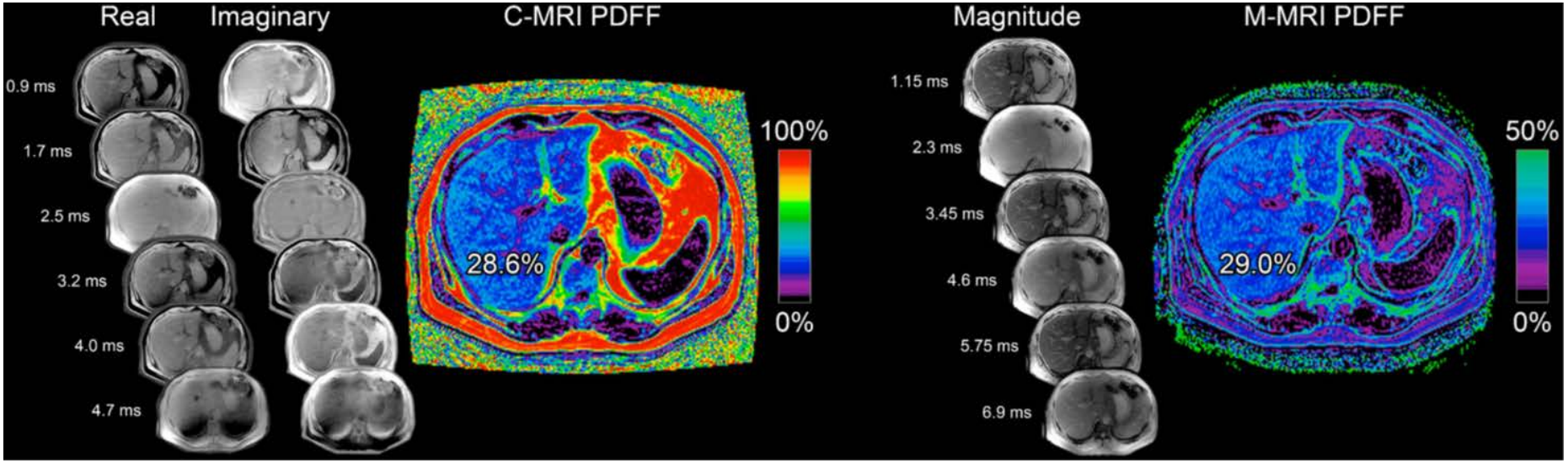
- One 8cm^3 voxel
- Not available on routine scanners
- Requires expertise



Imaging method to estimate PDFF would have advantages….

Thomsen MRI 1994
Hamilton JMRI 2009
Hamilton NMR Biomed. 2011
Reeder JMRI 2011

MR Imaging Methods to Estimate PDFF



MRI-PDFF addresses confounding factors, unlike conventional in-phase and opposed-phase

MRI-PDFF ***not*** affected by

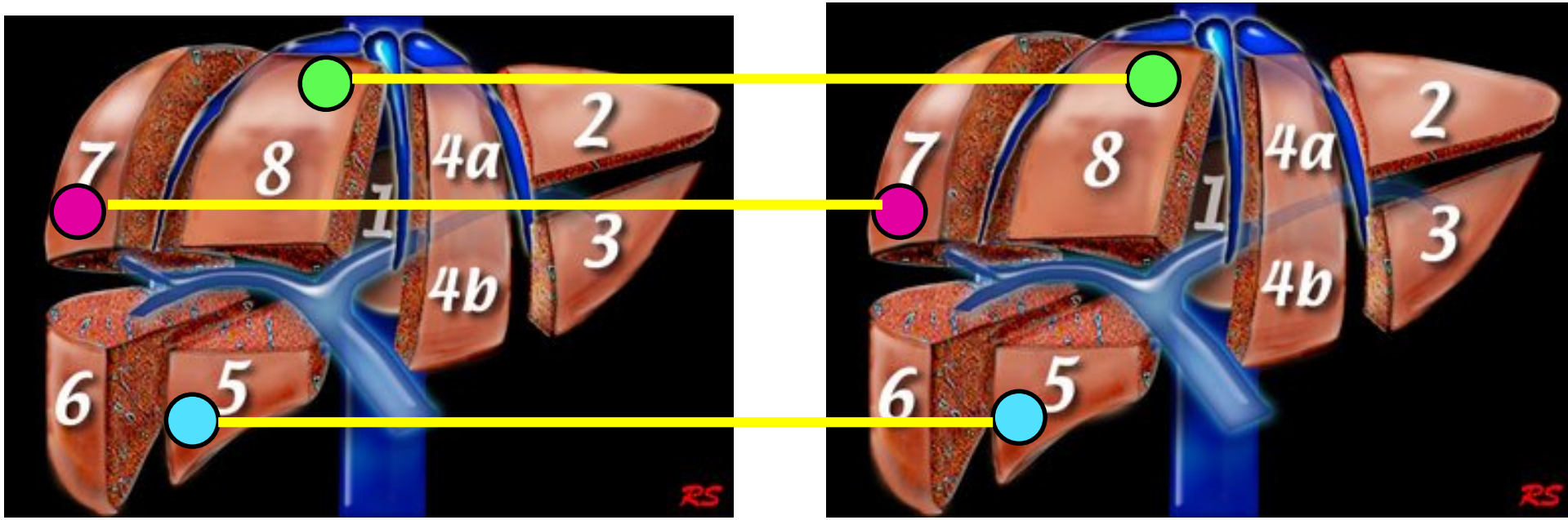
- Scanner field strength
- Patient factors: age, sex, BMI, etiology of liver disease
- Concomitant liver abnormalities: iron overload, necroinflammation

Yu MRM 2008
Bydder MRI 2008
Bydder MRI 2010
Hansen MRI 2012
Kang Invest Radiol 2012
Kuhn Radiology 2012
Tang Radiology 2013
Dulai, Sirlin, Loomba J Hep 2016

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

BASELINE

POST-TREATMENT



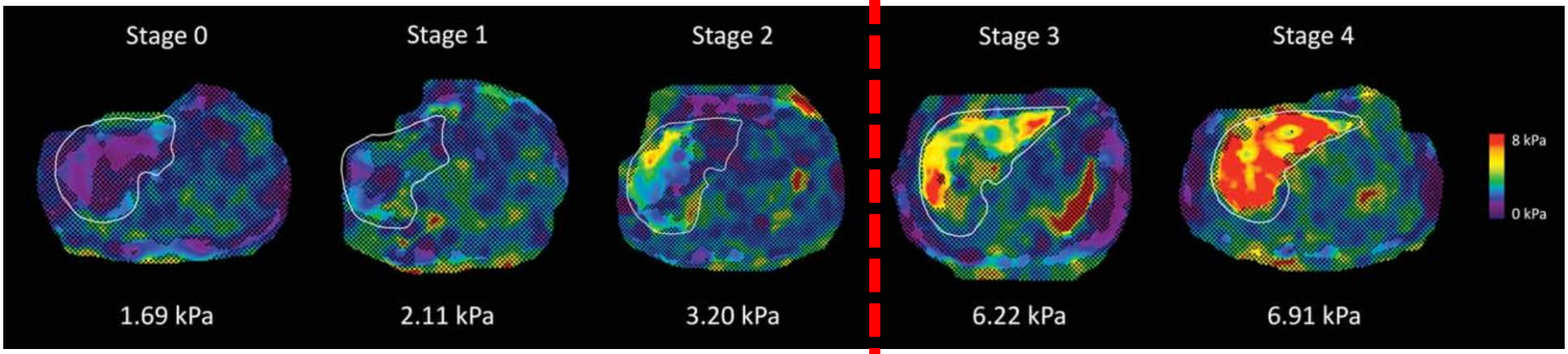
- PDFF recorded in regions of interests (ROI)s ~300-400mm^2
- The same ROIs in each of the 9 liver segments measured at baseline and post-treatment.
- Each segment fat fraction = 1 ROIs
- Total liver fat fraction = average 9 ROIs

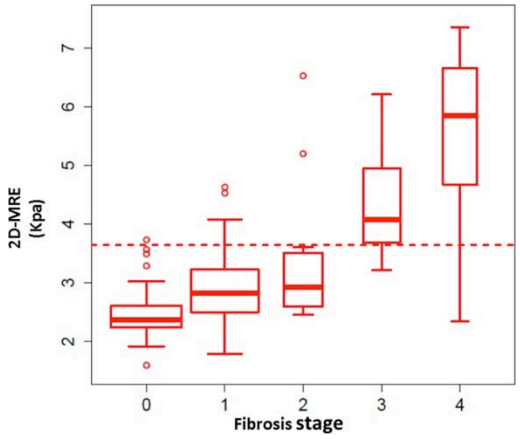
Loomba et al. Hepatology 2015

MR-based fibrosis assessment in NASH: Innovations in fibrosis assessment

Loomba et al. Hepatology 2014

MR Elastography Diagnoses Advanced Fibrosis





"Stiffness" cutoff: 3.63 kPa
Sensitivity 0.86
Specificity 0.91

AUC for diagnosis of advanced fibrosis
0.924


David Brenner


Dick Ehman


Anthony Gamst

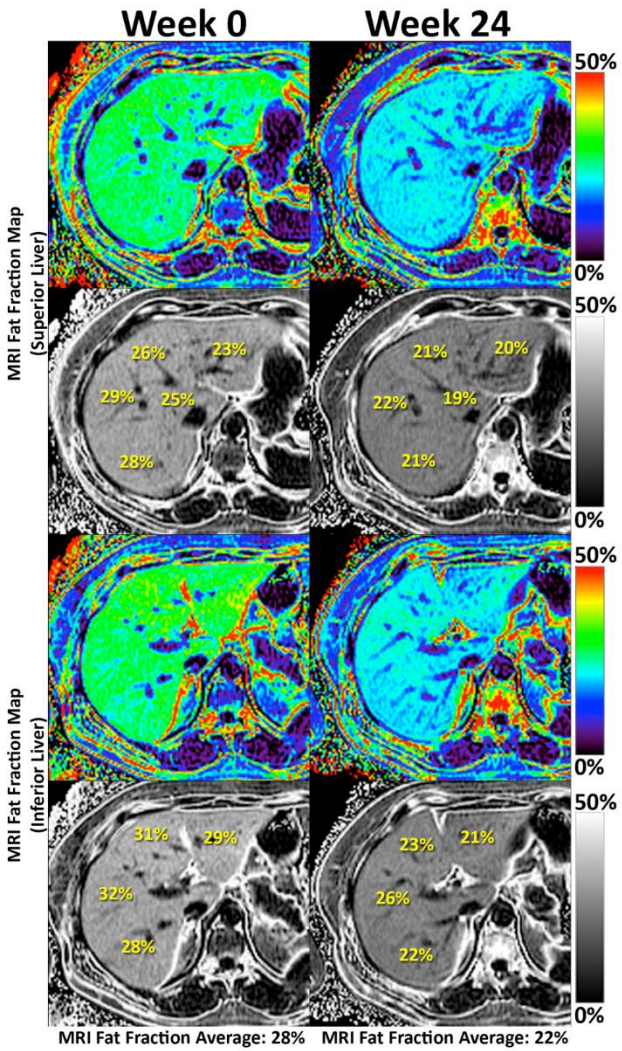

Jonathan Hooker

Loomba et al 2014

Innovations in clinical trial design

How will future clinical trials assess NASH?

Fat- and Stiffness-mapping before and after treatment



Why do we need to co-localize?

Heterogeneity in distribution

More comprehensive assessment

↓

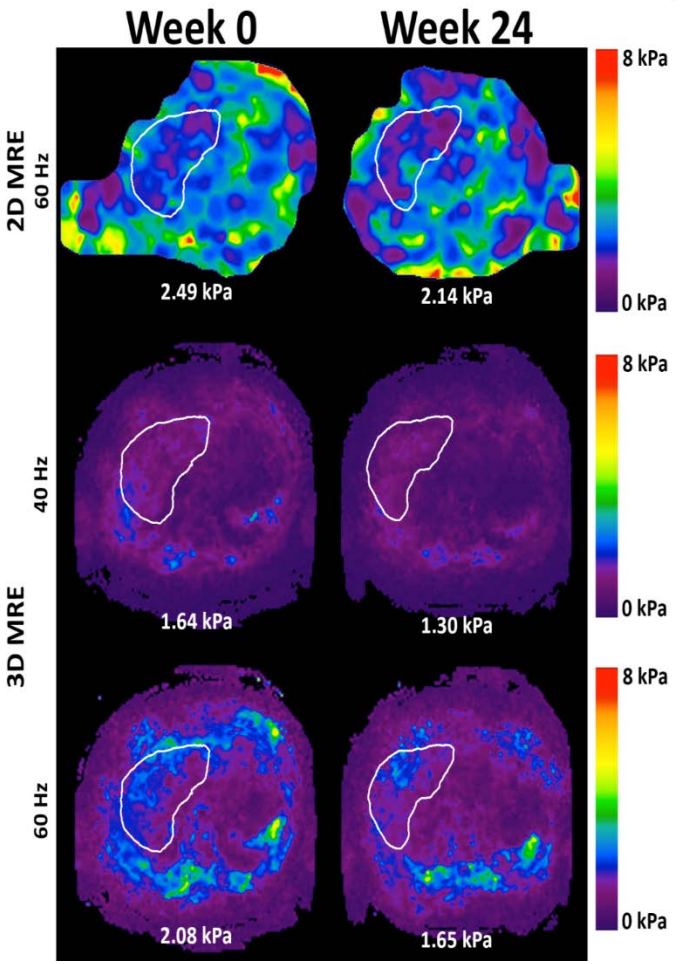
Higher precision and accuracy

↓

Enhanced responsiveness

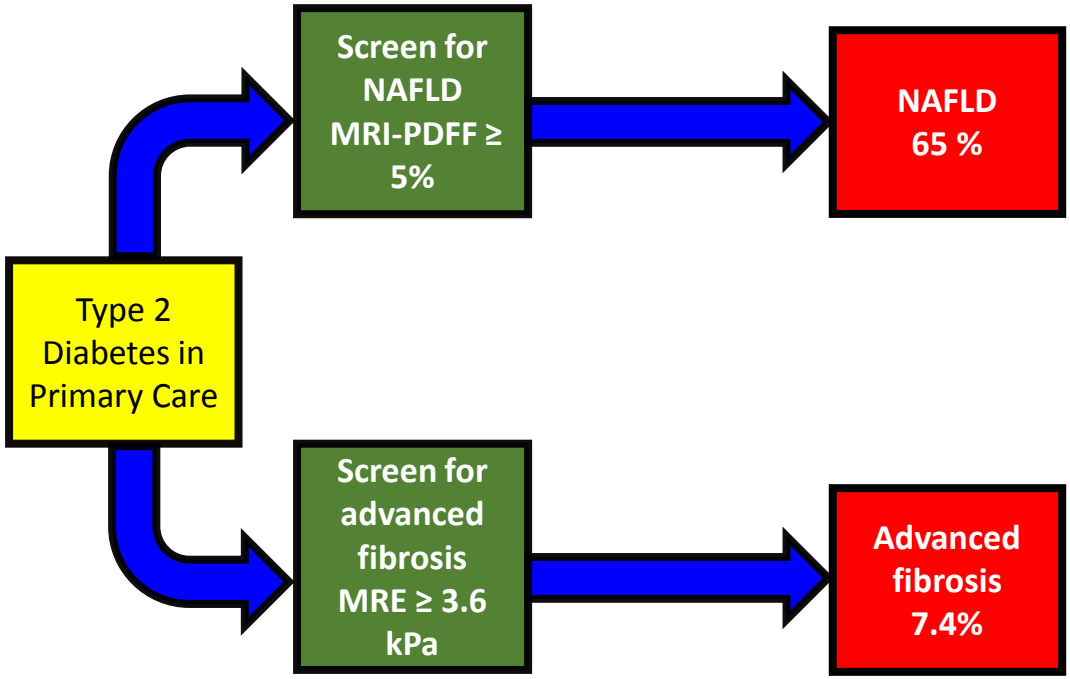
↓

Efficiency in clinical trial



Modified from Loomba et al. Hepatology 2015

Prevalence of NAFLD and advanced fibrosis among patients with Type 2 diabetes in primary care

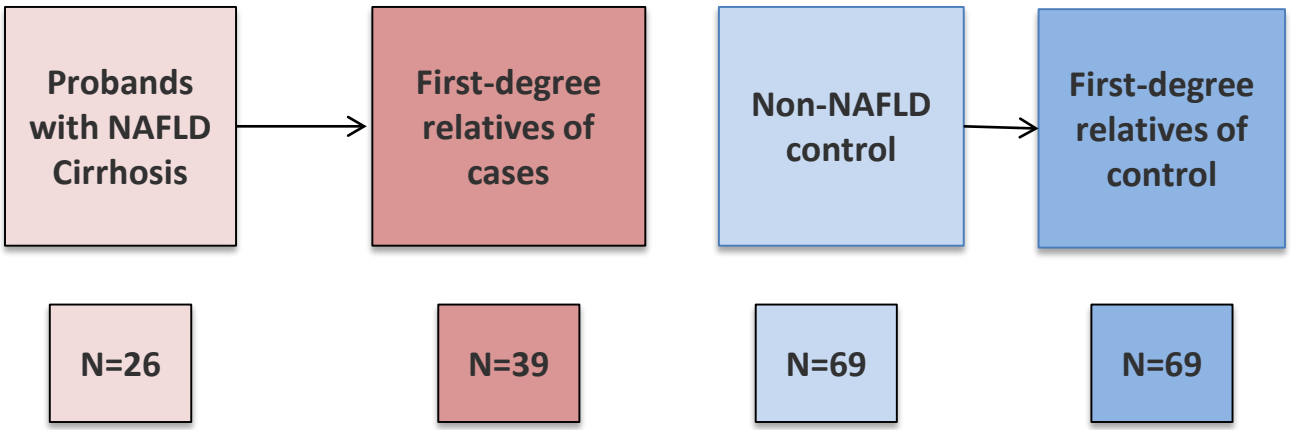


Doycheva et al. APT 2016

The Journal of Clinical Investigation CLINICAL MEDICINE

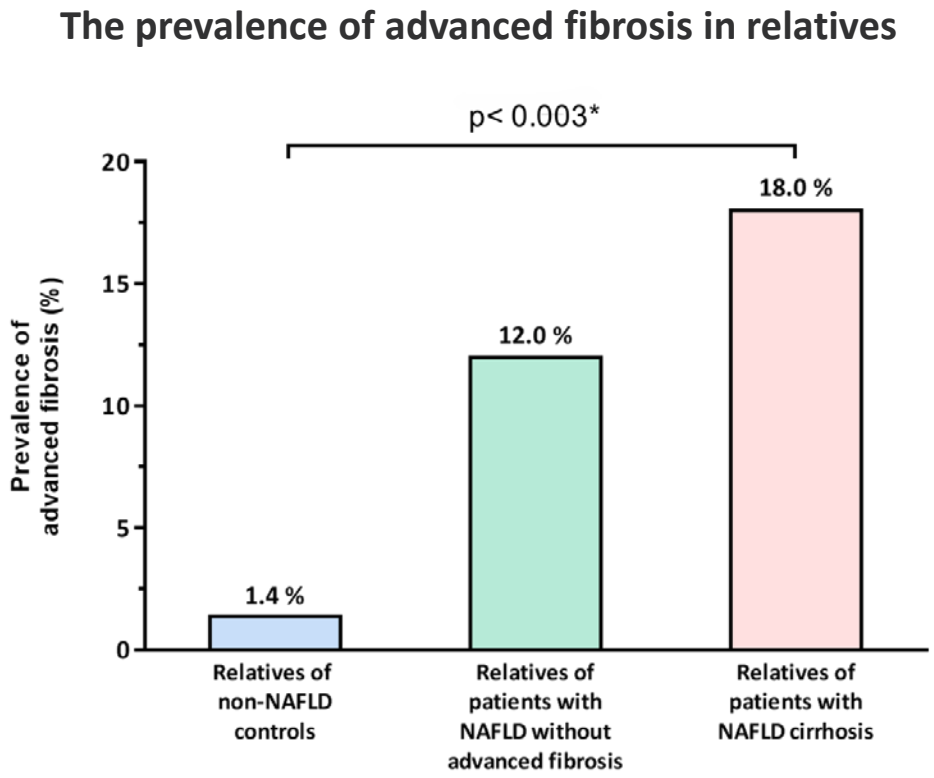
Nonalcoholic fatty liver disease with cirrhosis increases familial risk for advanced fibrosis

Cyrielle Caussy,[1,2] Meera Soni,[1] Jeffrey Cui,[1] Ricki Bettencourt,[1,3] Nicholas Schork,[4] Chi-Hua Chen,[5] Mahdi Al Ikhwan,[1] Shirin Bassirian,[1] Sandra Cepin,[1] Monica P. Gonzalez,[1] Michel Mendler,[6] Yuko Kono,[6] Irine Vodkin,[6] Kristin Mekeel,[7] Jeffrey Haldorson,[7] Alan Hemming,[7] Barbara Andrews,[6] Joanie Salotti,[1,6] Lisa Richards,[1,6] David A. Brenner,[6] Claude B. Sirlin,[8] Rohit Loomba,[1,3,6] and the Familial NAFLD Cirrhosis Research Consortium[9]



Caussy, Loomba. JCI, 2017

Advanced fibrosis on MRE is highly prevalent in first-degree relatives of NAFLD cirrhotics



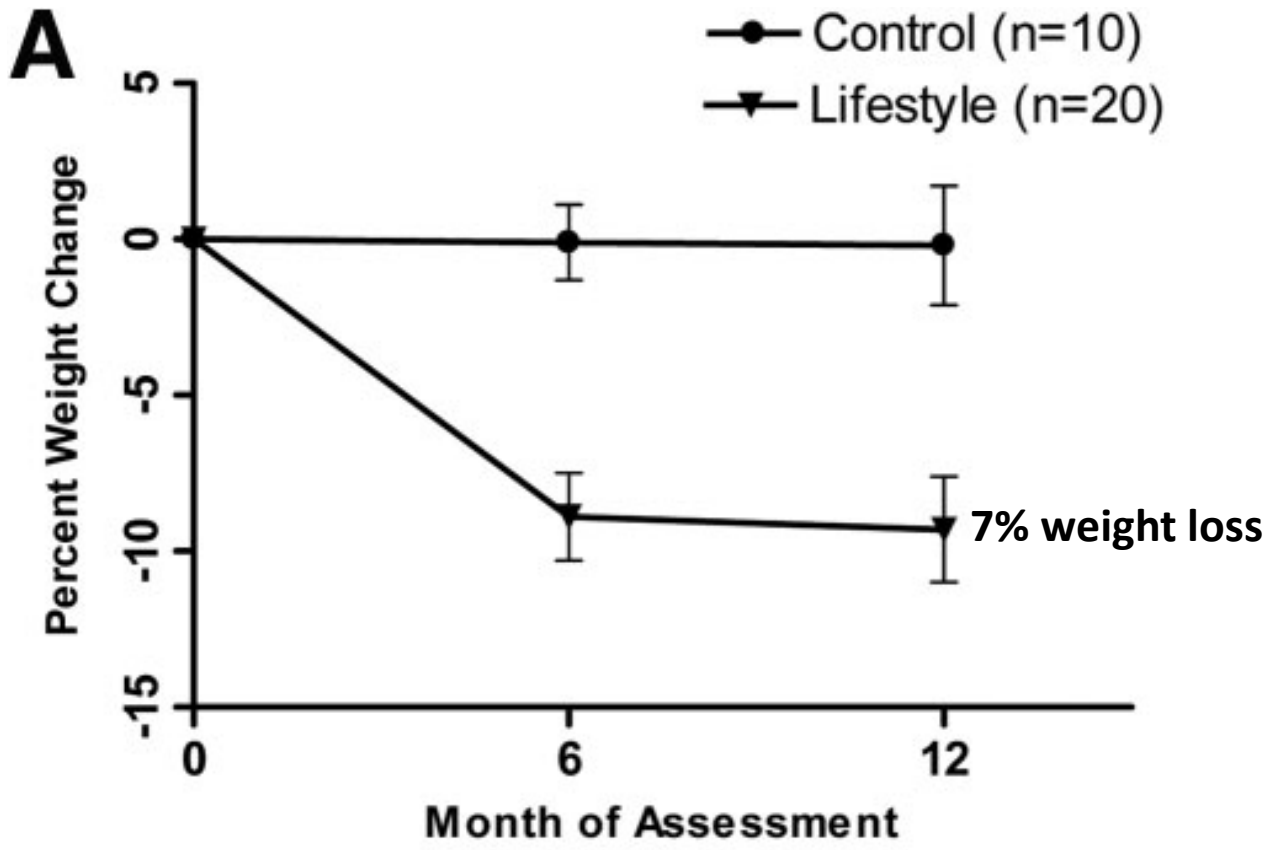
The risk of advanced fibrosis is significantly increased in first-degree relatives with NASH cirrhosis

12 times higher odds of advanced fibrosis among first-degree relatives of probands with NASH cirrhosis

Caussy, Loomba. JCI, 2017

Management of NASH

Intensive lifestyle modification causes weight loss in NASH



Promrat et al. Hepatology 2010

Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis

Eduardo Vilar-Gomez,[1,2] Yadina Martinez-Perez,[1] Luis Calzadilla-Bertot,[1] Ana Torres-Gonzalez,[1] Bienvenido Gra-Oramas,[3] Licet Gonzalez-Fabian,[3] Scott L. Friedman,[4] Moises Diago,[5] and Manuel Romero-Gomez[2]

Q1. How much weight loss is needed for improvement in NASH?

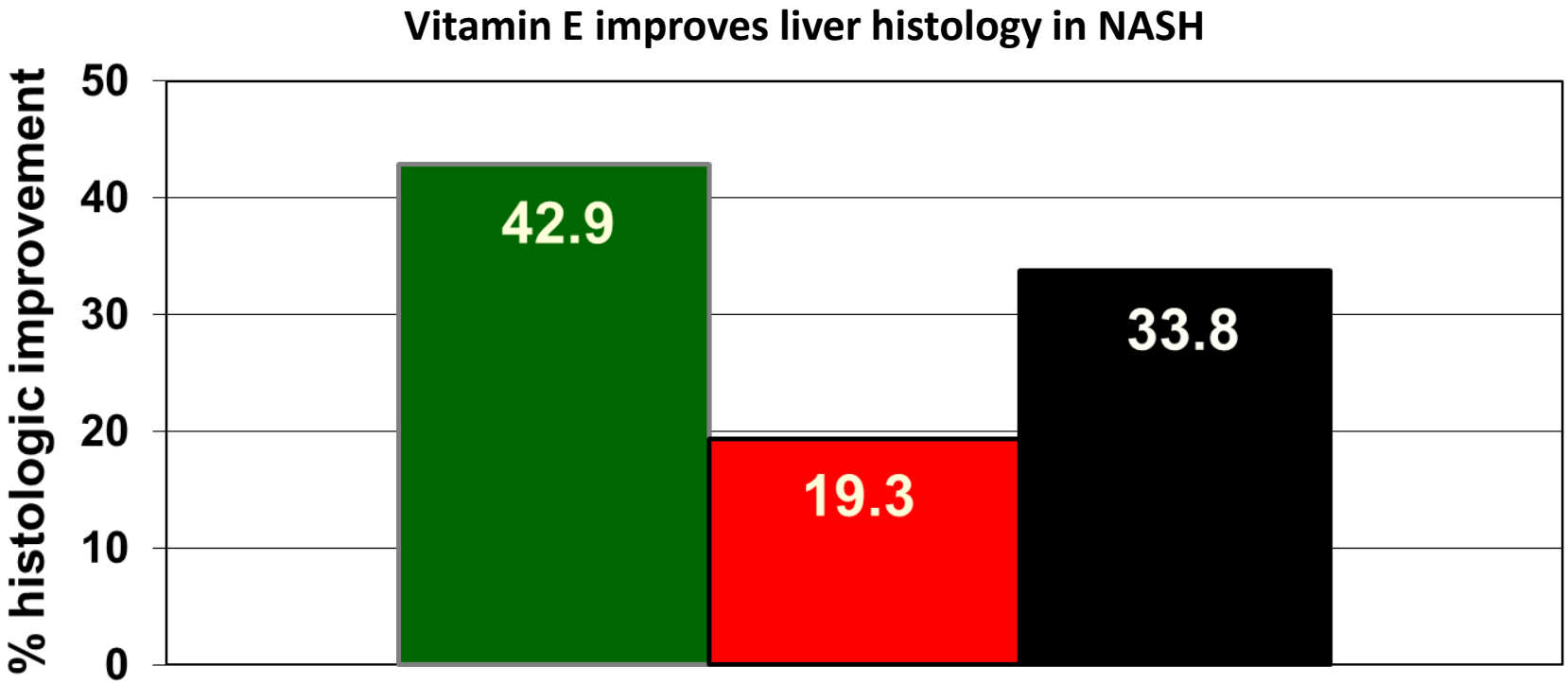
- **5% weight loss will start showing improvements in liver fat and liver stiffness**
- **5-7% weight loss will start showing improvements in NAFLD Activity Score**
- **10% weight loss will lead to resolution of NASH in 90% and 45% will have improvement in fibrosis stage**

A Randomized, Placebo-Controlled Trial of Pioglitazone and Vitamin E for Nonalcoholic Steatohepatitis (PIVENS)

The Nonalcoholic Steatohepatitis Clinical Research Network

Sanyal et al. NASH-CRN.NEJM 2010

Primary outcome: PIVENS



Vitamin E vs Placebo p-value <0.001
Pioglitazone vs. Placebo p-value <0.04

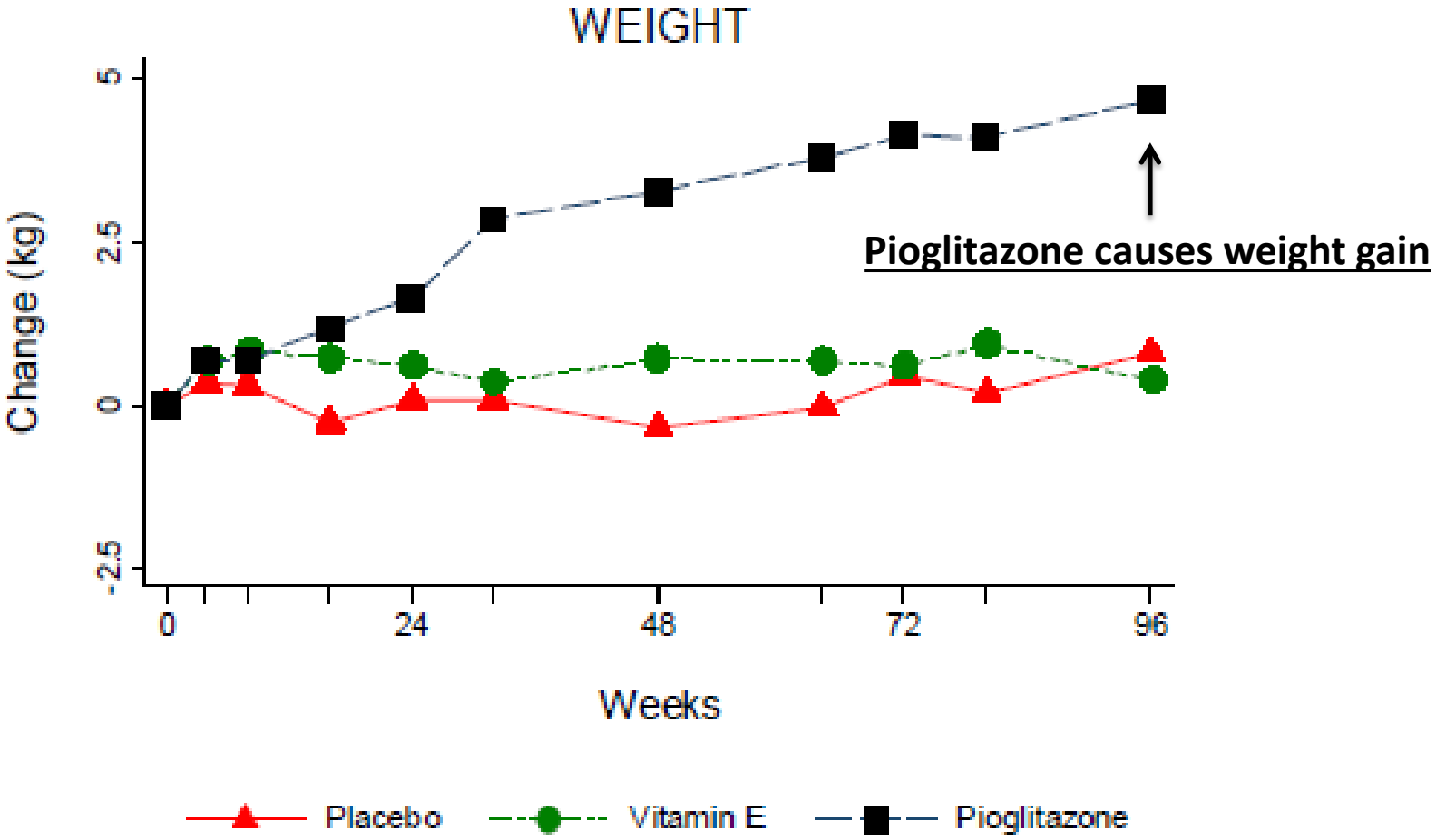
Sanyal et al. NASH-CRN.
NEJM 2010

Summary on Vitamin E

The glass is half full

- **Does Vitamin E improve NASH? = Yes**
- **Does Vitamin E reverse NASH? = Yes**
- **Does Vitamin E improve fibrosis? = No (based upon RCTs)**
- **Does Vitamin E improve long-term outcomes? = No data**

PIVENS: Weight



Sanyal et al. NASH-CRN. NEJM 2010

When and how to use pioglitazone

- **Biopsy-proven NASH with diabetes or prediabetes**
- **Monitor-**
    - **Body weight**
        - **Lifestyle interventions**
            - **Exercise and diet**
    - **ALT and AST response**
    - **DEXA Scan**

Emerging Therapies in NASH

NASH therapeutic targets by mechanisms and sites of activity and type of outcomes

PPAR agonist	DPP-4-i	OCA	PPAR agonist	OCA	ASK-1
Aramchol	PPAR agonist	FXR agonist	CVC	Anti-JNK-1	Simtuzumab
ASK-1 inhibitors	SGLT2-i	ASBT-I	Anti-JNK	ASK-1 inhibitors	Anti-gal 3
DGAT inhibitors	FGF-19	FGF-19	ASK-1 inhibitors	PPAR agonist	Anti-CTGF
ACC inhibitors	FGF-21	others	DHA	Nox inhibitors	ACE-R-blockers
Anti-CB1	ISIS-ANGPTL3		Anti-CB1	Others	Pentraxin-2
MetAP2 inhibitors	others		others		Anti-IL-17
Thyroid B agonist					Anti-TGF-beta

Fatty acid synthesis	Insulin sensitivity	Bile acid synthesis	Anti-inflammatory	Anti-fibrotic Early stage	Anti-fibrotic Late stage

Steatosis, ballooning, and inflammation	Stage 1-3 fibrosis	Stage 3-4 fibrosis

Resolution of NASH	Reduce the rate of progression of fibrosis or Improvement in fibrosis	Reversal of advanced fibrosis or Improvement in fibrosis

THE LANCET

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

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**

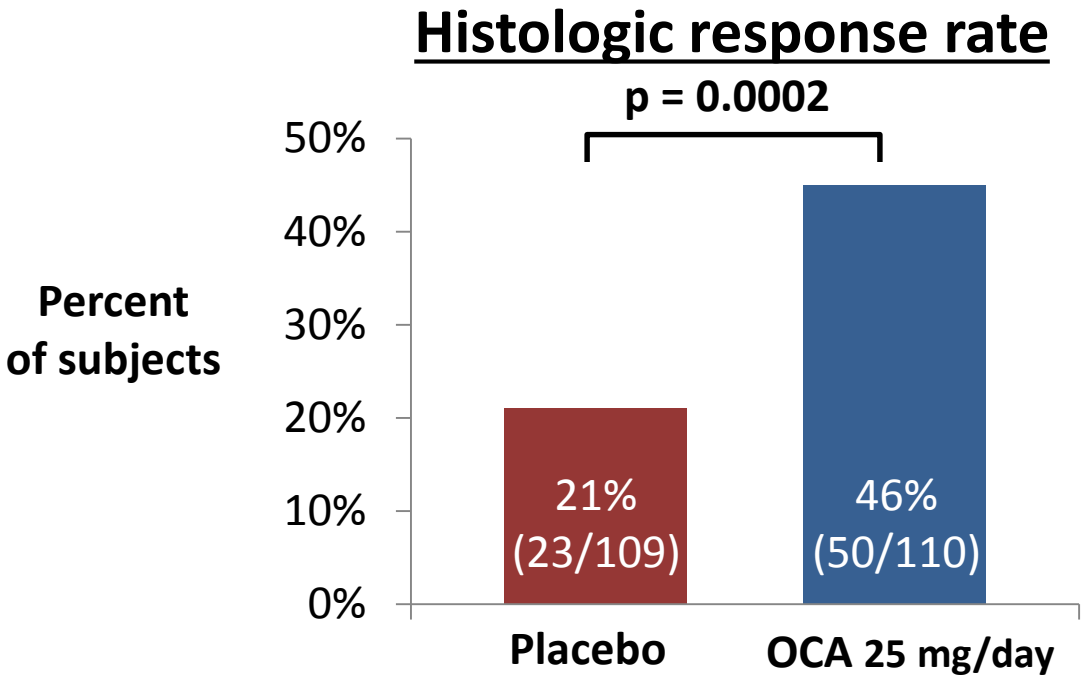
NIH National Institute of Diabetes and Digestive and Kidney Diseases

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.

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 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**

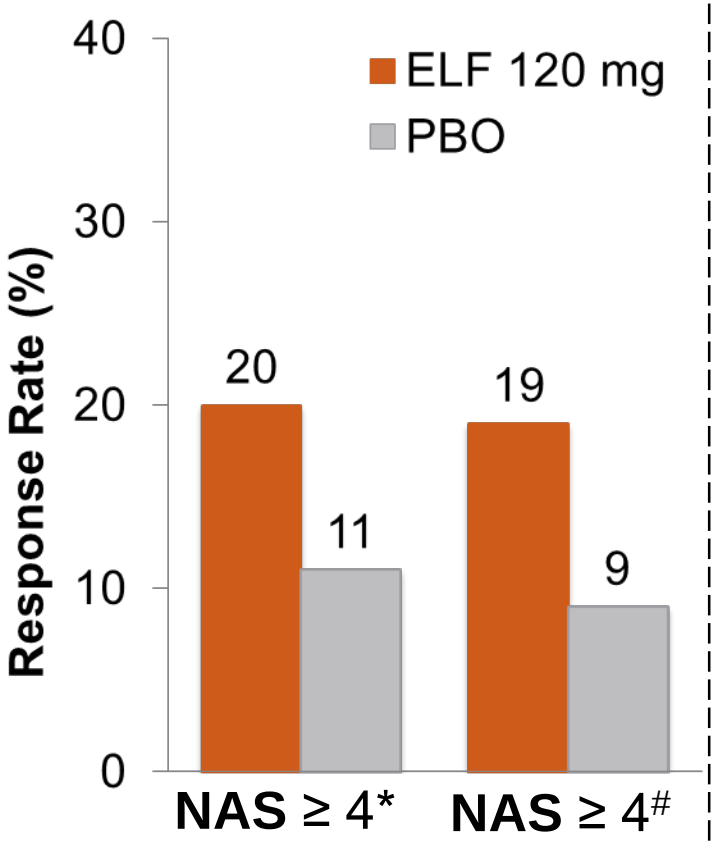
Elafibranor, an Agonist of the Peroxisome Proliferator–Activated Receptor–α and –δ, Induces Resolution of Nonalcoholic Steatohepatitis Without Fibrosis Worsening

Vlad Ratziu,[1,2] Stephen A. Harrison,[3] Sven Francque,[4] Pierre Bedossa,[5] Philippe Lehert,[6,7] Lawrence Serfaty,[8] Manuel Romero-Gomez,[9] Jérôme Boursier,[10] Manal Abdelmalek,[11] Steve Caldwell,[12] Joost Drenth,[13] Quentin M. Anstee,[14] Dean Hum,[15] Remy Hanf,[15] Alice Roudot,[15] Sophie Megnien,[15] Bart Staels,[16] and Arun Sanyal,[17] on behalf of the GOLDEN-505 Investigator Study Group

Randomized	1) GFT505 80 mg 2) GFT505 120 mg 3) Placebo
Population	270 patients with biopsy proven NASH
Endpoints	Resolution of NASH

GOLDEN—Primary Results

- **Primary endpoint was not met in initial assessment**
  - After controlling for baseline heterogeneity of severity and center effect, the primary endpoint was met



Abbreviation: ELF, elafibranor; NAS, NAFLD Activity Score; PBO, placebo.
* Per protocol, # modified criteria
Ratziu V, et al. *Gastroenterology 2016*

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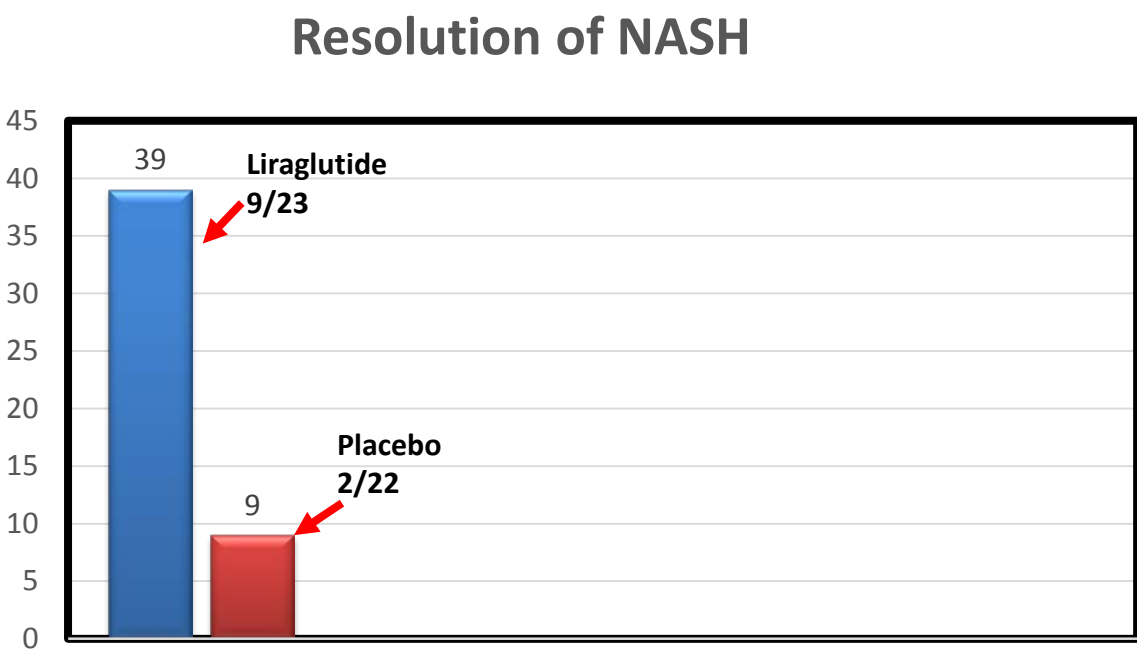
Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study

Matthew James Armstrong, Piers Gaunt, Guruprasad P Aithal, Darren Barton, Diana Hull, Richard Parker, Jonathan M Hazlehurst, Kathy Guo, LEAN trial team, George Abouda, Mark A Aldersley, Deborah Stocken, Stephen C Gough, Jeremy W Tomlinson, Rachel M Brown, Stefan G Hübscher, Philip N Newsome*



Pilot study shows that GLP-1 agonist leading to improvement in insulin resistance and weight loss led to improvement in liver histology in NASH

Study Design: Cenicriviroc vs Placebo

NASH stage 1-3 fibrosis

CVC 150 mg orally daily

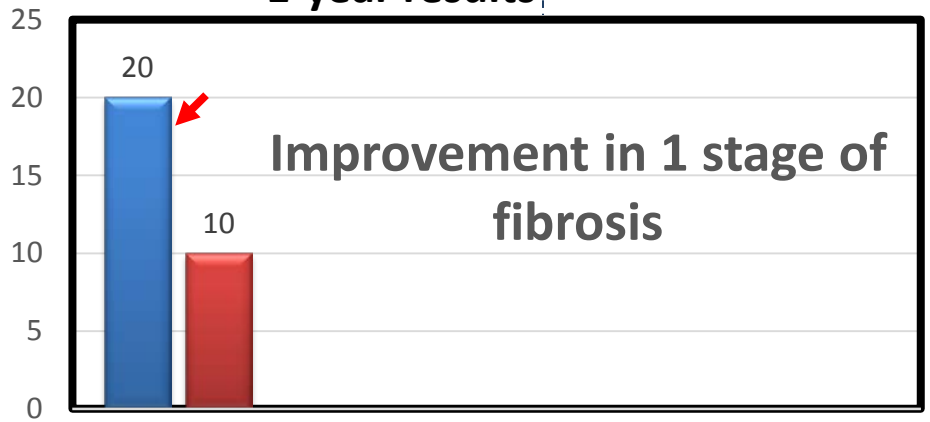
CVC 150 mg orally daily/placebo

Placebo

Year 1

Endpoint
2 pt improvement in NAS
Without any worsening fibrosis

1-year results



2 years total

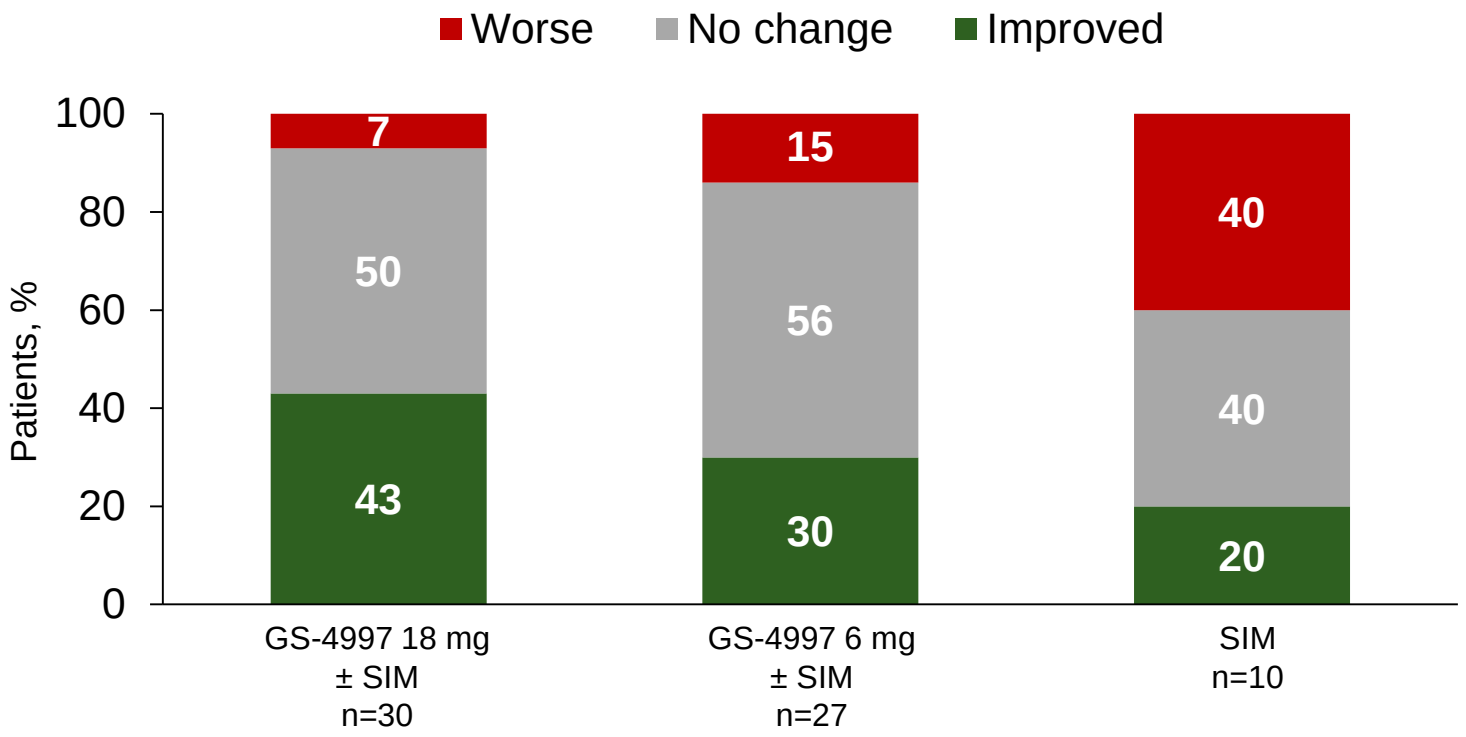
GS-4997, an Inhibitor of Apoptosis Signal-Regulating Kinase (ASK1), Alone or in Combination with Simtuzumab for the Treatment of Nonalcoholic Steatohepatitis (NASH): A Randomized, Phase 2 Trial

Rohit Loomba[1], Eric Lawitz[2], Parvez S. Mantry[3], Saumya Jayakumar[4], Stephen H. Caldwell[5], Hays Arnold[6], Anna Mae Diehl[7], C. Stephen Djedjos[8], Catherine Jia[8], Robert P. Myers[8], G. Mani Subramanian[8], John G. McHutchison[8], Zachary D. Goodman[9], Nezam H. Afdhal[10], Michael R. Charlton[11]

[1]University of California at San Diego, San Diego, CA; [2]Texas Liver Institute, San Antonio, TX;
[3]The Liver Institute at Methodist Dallas, Dallas, TX; [4]University of Calgary, Calgary, AB, Canada;
[5]University of Virginia, Charlottesville, VA; [6]Gastroenterology Consultants of San Antonio, San Antonio, TX;
[7]Duke Clinical Research Institute, Durham, NC; [8]Gilead Sciences, Inc., Foster City, CA; [9]Inova Fairfax Hospital, Falls Church, VA;
[10]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA;
[11]Intermountain Medical Center, Salt Lake City, UT

Loomba et al. Hepatology 2018

Results: Fibrosis Responses



Loomba et al. Hepatology 2018

Data for patients with liver biopsies evaluable for fibrosis at baseline and week 24 (N=67).

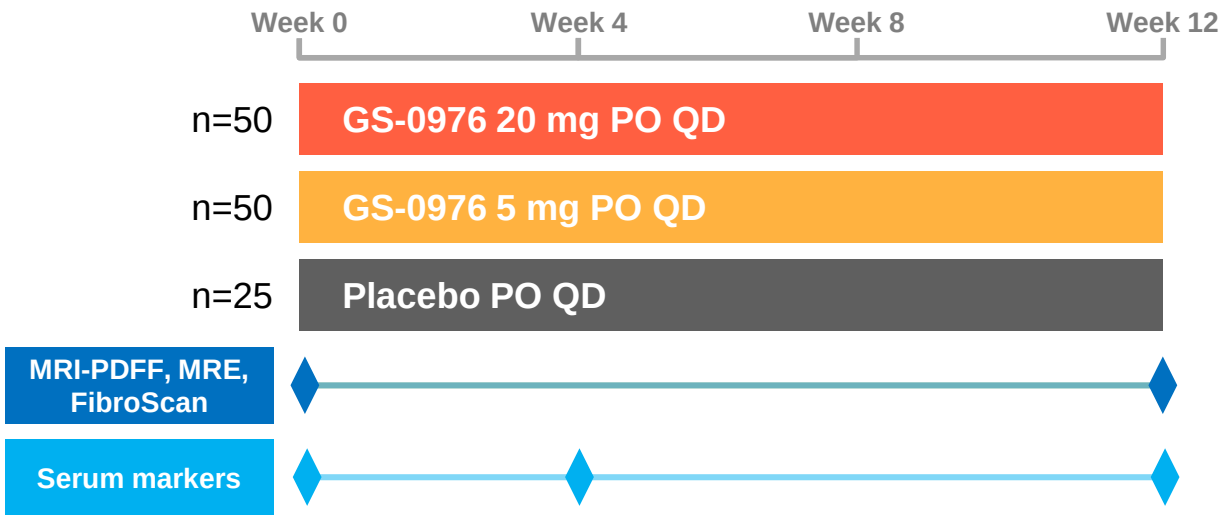
Acetyl-CoA Carboxylase Inhibitor GS-0976 Leads to Significant Improvements in MRI-PDFF in a Phase 2, Randomized, Placebo-Controlled Trial of Patients with NASH

Rohit Loomba,[1] Zeid Kayali,[2] Mazen Noureddin,[3] Peter Ruane,[4] Eric J. Lawitz,[5] Norman Gitlin,[6] Michael Bennett,[7] ElizaJing Harting,[8] Bryan J. McColgan,[8] Robert P. Myers,[8] G. Mani Subramanian,[8] John G. McHutchison,[8] Michael S. Middleton,[1] Claude Sirlin,[1] Michelle Lai,[9] Michael Charlton,[10] Stephen A. Harrison[11]

1. University of California at San Diego, La Jolla, CA; 2. Inland Empire Liver Foundation, Rialto, CA; 3. Cedars-Sinai Medical Center, Los Angeles, CA; 4. Ruane Medical and Liver Health Institute, Los Angeles, CA; 5. Texas Liver Institute, University of Texas Health San Antonio, San Antonio, TX; 6. Atlanta Gastroenterology Associates, Atlanta, GA; 7. Medical Research Associates Group, San Diego, CA; 8. Gilead Sciences, Inc., Foster City, CA; 9. Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; 10. University of Chicago, Chicago, IL; 11. Pinnacle Clinical Research, San Antonio, TX

AASLD 2017, Washington, DC

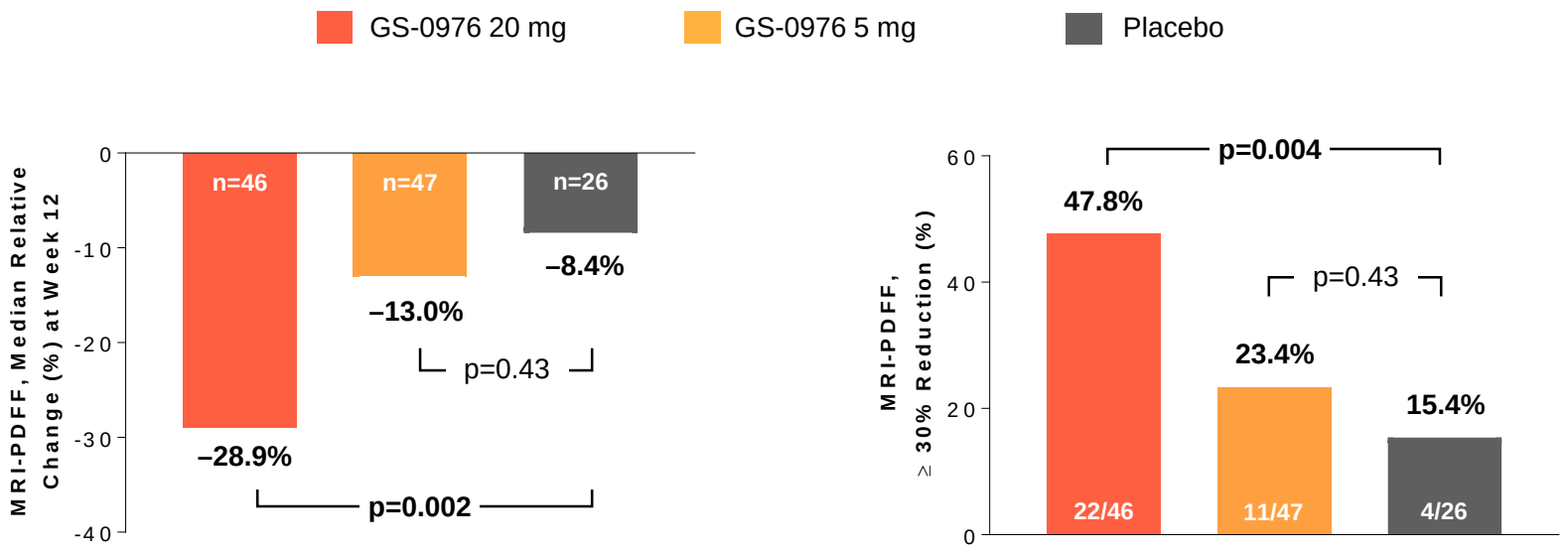
Study Design:
Randomized, Placebo-Controlled Trial at 41 U.S. Sites



- Key inclusion criteria
  - Clinical diagnosis of NAFLD
  - MRI-PDFF ≥8% and MRE ≥2.5 kPa, or biopsy consistent with NASH and F1-F3
  - Noncirrhotic (FibroTest < 0.75, historical imaging and liver biopsy)
- Stratified by presence or absence of diabetes

MRI-PDFF; MRI-proton density fat fraction; MRE, magnetic resonance elastography; NAFLD, nonalcoholic fatty liver disease.

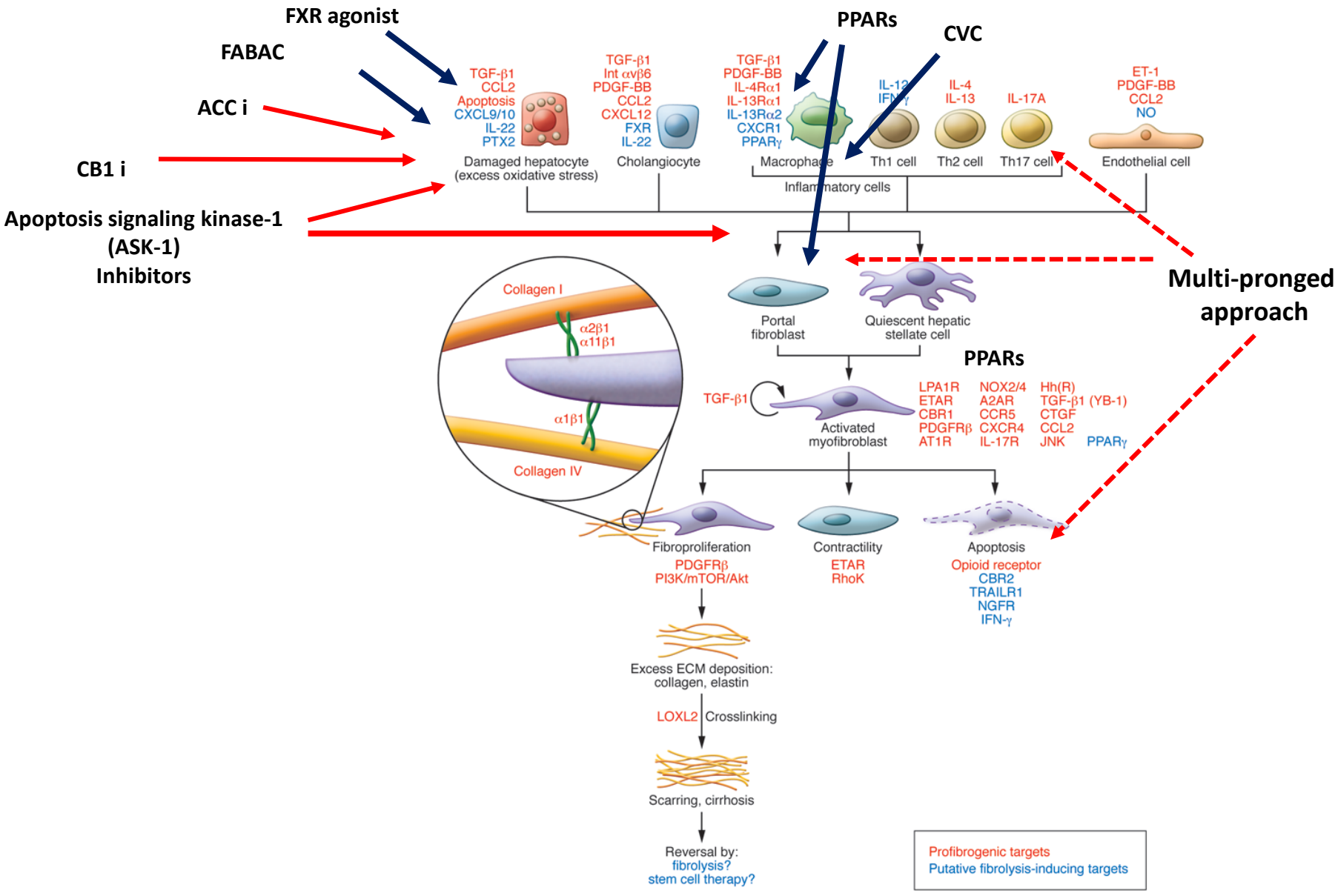
Results: Significant Reduction in MRI-PDFF



- GS-0976 20 mg resulted in a clinically significant reduction in MRI-PDFF[1,2]

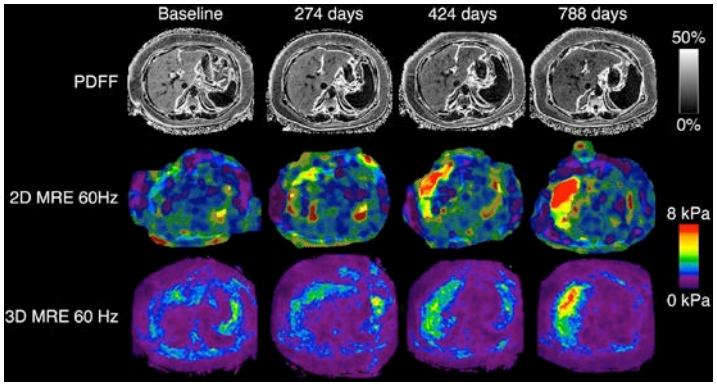
p-values for change in MRI-PDFF at Week 12 by Wilcoxon rank-sum test.
p-values for proportion of subjects with ≥30% reduction in MRI-PDFF by Mantel-Haenszel test with adjustment for diabetes status.
1. Patel J, et al. Therap Adv Gastroenterol 2016;9:692-701; 2. Loomba R, et al. AASLD 2017. Abstr 2169

Future of NASH: Rationale for combination therapy

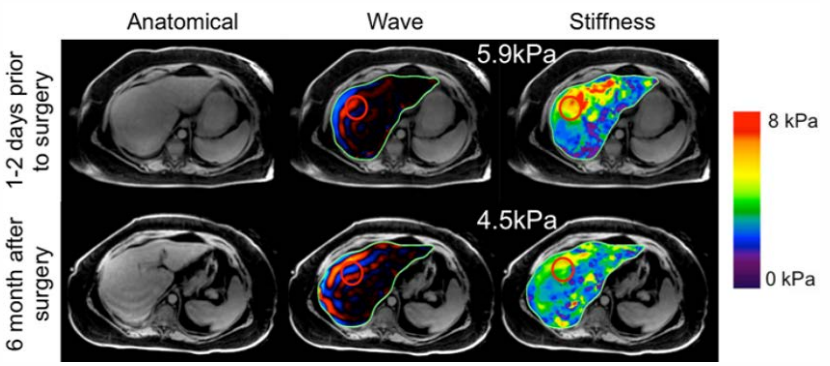


How about longitudinal quantitative changes in fibrosis assessment?

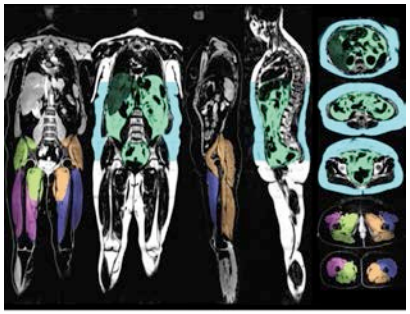
MRE and whole body composition for progression or regression monitoring



MRE showing a fibrosis progression to cirrhosis



MRE showing improvement in stiffness after bariatric surgery



AMRA collaboration: Whole body MRI assessing total visceral fat, total subcutaneous fat, and total muscle mass

Shifting the paradigm

Traditional paradigm

Quantitative, Imaging biomarker assessment and development program

- Assessment of hepatic steatosis
- Assessment of hepatic fibrosis
- Longitudinal changes in disease severity
  - MRI-PDFF
  - MRE

New paradigm

- Shorter trial
- Advanced MRI-PDFF X 30 trials
- MRE X 10 trials
- Greater precision
- Greater efficiency
- Smaller sample size
- Faster to Phase 3
- Liver histology in Phase 2b/3 trials

Improve efficiency

Conclusion

- **NASH can lead to cirrhosis and HCC**
  - **Initial assessment**
  - **Natural history**
- **MRI-PDFF is emerging to be the lead candidate for non-invasive steatosis assessment in NAFLD**
- **MRE is emerging to be the lead candidate for non-invasive fibrosis assessment in NAFLD**
- **Several exciting molecules are in clinical development for the treatment of NASH**

Thank you

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