2022 SCSG LIVER SYMPOSIUM

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THE RITZ CARLTON, LAGUNA NIGUEL

New Developments in NASH in 2022

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- **Co-founder:** Liponexus Inc.

Outline

- Epidemiology – Genetics
- New advances in non-invasive assessment
- NASH therapeutic landscape pipeline
- AASLD NAFLD practice guidelines

Epidemiology: Burden of NAFLD

- **Globally, nonalcoholic fatty liver disease (NAFLD) is present in 1 in 4 people[1]**
- **Ethnic predisposition**
  - More common in Asian Indians>Hispanics>Caucasians>African Americans
- **Risk factors include MetS**
  - Obesity, hypertension, hypertriglyceridemia, insulin resistance and diabetes
  - PNPLA3, TM6SF2, MBOAT7 genotype
  - HSD17B13

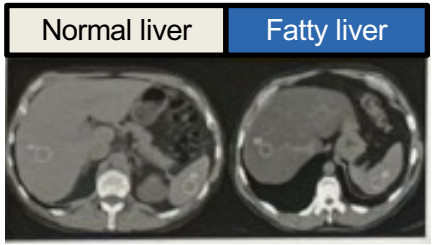
- NAFLD is diagnosed
  - Either on biopsy or imaging evidence of hepatic steatosis (≥ 5% liver fat) in individuals who consume little or no alcohol without any other cause for liver disease or hepatic steatosis

1. Younossi et al. *Hepatology.* 2015;64:73–84.

Multi Ethnic Genome-Wide Association Meta-Analysis Identifies 17 Loci Associated With NAFLD That Define New Disease Subtypes, Mechanisms, and Predict Advanced Liver Disease

Study design imaging plus ICD NAFLD – multi ancestry

GOLD Consortium	UKBB	UKBB	eMERGE	FinnGen
Quantitative:	Quantitative	Binary:	Binary:	Binary:
CT steatosis	MRI-PDFF, UNET,	ICD NAFLD	ICD NAFLD	ICD NAFLD
N=23,521	CNN 4616, PCC >0.97	1827 cases	1106 cases	651 cases
14 cohorts	N=43,293	436,262 controls	8571 controls	176,248 controls



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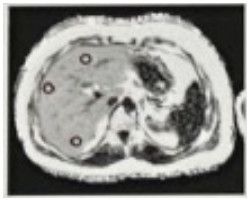


HRC + UK10K

HRC + UK10K

METAL: meta-analysis of GWAS (5 datasets)

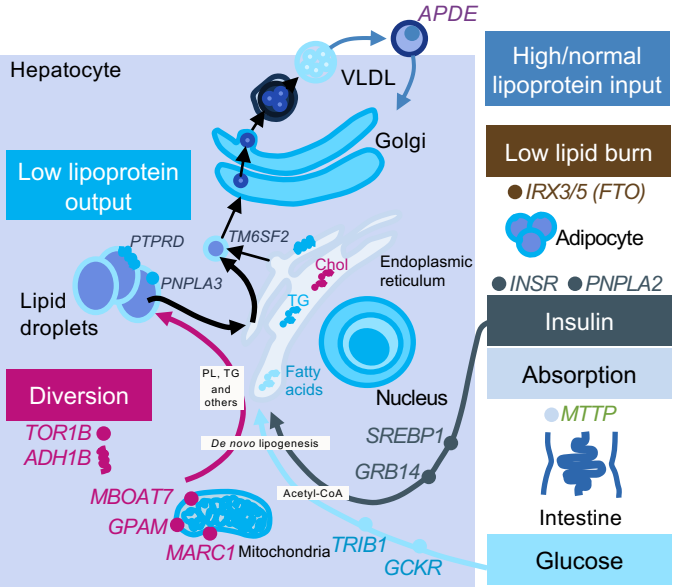
N=17 independent variants (p<5E-08)
GOLDPlus significant variants

Du X et al. AASLD 2022. Oral #14.

Multi Ethnic Genome-Wide Association Meta-Analysis Identifies 17 Loci Associated With NAFLD That Define New Disease Subtypes, Mechanisms, and Predict Advanced Liver Disease

7 distinct NAFLD subtypes identified

	Genes	Steatosis	Cirrhosis	LDL	MI	TG	HDL	DM	BMI
Low lipoprotein out	PTPRD PNPLA3 TM6SF2	↑	↑	↓	↓	↓	↓	↑	↓
High lipoprotein in	APOE	↑	↑	↓	↓	↓	↑	↑	↑
Low lipid burn	FTO	↑	–	↓	–	–	↓	●	
Insulin	INSR PNPLA2 GRB14 SREBF1	↑	–	↑	↑	↑	↓	↑	↓
Absorb	MTTP	↑	–	↑		↑	↑	↑	–
Glucose	GCKR TRIB1	↑	–	↑	↑	↑	↓	↓	↓
Divert	MBOAT7 MARC1 TOR1B ADM1B GPAM	↑	↑	↑	↑	↓	↑	↑	–
EPIDEMIOLOGY		↑	↑	↑	↑	↑	↓	↑	↑



- High quality genetic exploration of NAFLD endophenotypes
- PNPLA3 and TM6SF2 consistenly seen
- A PRS can identify 10%, 5%, and 1% of individuals with high risk (odds >2, 3, 4 respectively) of NAFLD, cirrhosis and HCC
- Subtypes of NAFLD associate with different outcomes and open up new avenues for better matching susceptible individuals to treatments

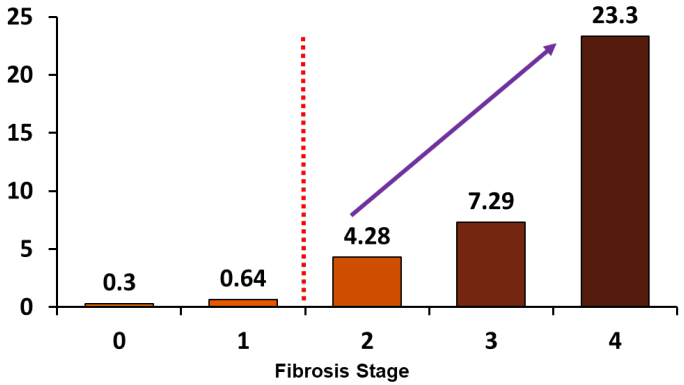
Du X et al. AASLD 2022. Oral #14.

Non-Invasive Assessment

How Best Can I Identify Who Needs to Be Treated Without a Liver Biopsy?

Diagnose "at risk" NASH = NASH with stage 2 fibrosis

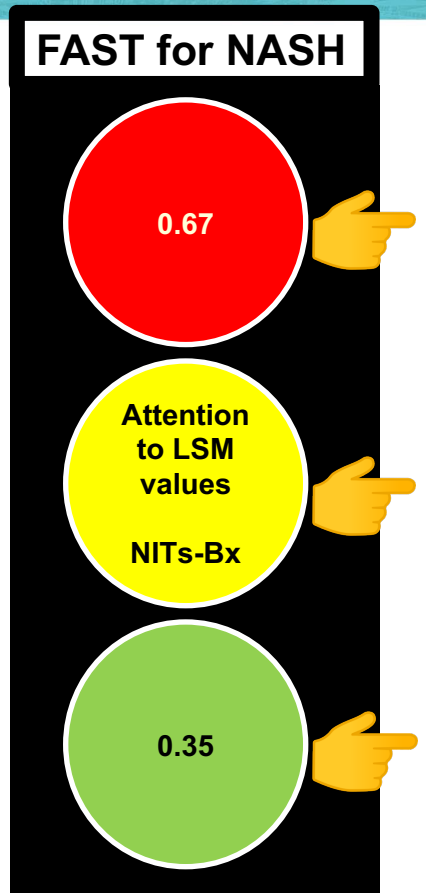
- **FAST: CAP, VCTE, AST**
- **MAST: MRI-PDFF, MRE, AST**
- **MEFIB: MRE 3.3 Kpa + FIB-4 1.6**



Anstee, Castera and Loomba. *J Hep*. 2022.

Role of FAST in Detection of High-Risk NASH

	AUROC (95% CI)	n	Prevalence of NASH + NAS ≥ 4 + F ≥ 2	Rule-out zone (FAST ≤0·35)				Grey zone (FAST 0·35–0·67), n (%)	Rule-in zone (FAST ≥0·67)			
				n (%)	Sensitivity	Specificity	NPV		n (%)	Specificity	Sensitivity	PPV
Derivation cohort	0·80 (0·76–0·85)	350	174 (50%)	113 (32%)	0·90 (157/174)	0·53 (93/176)	0·85 (93/110)	136 (39%)	101 (29%)	0·90 (159/176)	0·48 (84/174)	0·83 (84/101)
French bariatric surgery cohort	0·95 (0·91–0·99)	110	16 (15%)	69 (63%)	1·00 (16/16)	0·73 (69/94)	1·00 (69/69)	22 (20%)	19 (17%)	0·93 (87/94)	0·75 (12/16)	0·63 (12/19)
USA screening cohort	0·86 (0·80–0·93)	242	28 (12%)	194 (80%)	0·64 (18/28)	0·86 (183/214)	0·95 (183/193)	39 (16%)	9 (4%)	0·99 (212/214)	0·25 (7/28)	0·78 (7/9)
China Hong-Kong NAFLD cohort	0·85 (0·76–0·93)	83	36 (43%)	28 (34%)	0·94 (34/36)	0·55 (26/47)	0·93 (26/28)	29 (35%)	26 (31%)	0·89 (42/47)	0·58 (21/36)	0·81 (21/26)
China Wenzhou NAFLD cohort	0·84 (0·73–0·95)	104	9 (9%)	55 (53%)	0·89 (8/9)	0·56 (53/95)	0·98 (58/67)	37 (36%)	12 (11%)	0·92 (87/95)	0·44 (4/9)	0·33 (4/12)
French NAFLD cohort	0·80 (0·73–0·86)	182	78 (43%)	67 (37%)	0·88 (69/78)	0·56 (58/104)	0·87 (58/67)	69 (38%)	46 (24%)	0·89 (93/104)	0·45 (35/78)	0·76 (35/46)
Malaysian NAFLD cohort	0·85 (0·78–0·91)	176	36 (20%)	78 (44%)	0·94 (34/36)	0·54 (75/140)	0·97 (75/77)	59 (34%)	39 (22%)	0·87 (122/140)	0·58 (21/36)	0·54 (21/39)
Turkish NAFLD cohort	0·74 (0·65–0·82)	129	74 (57%)	26 (20%)	0·91 (67/74)	0·35 (19/55)	0·73 (19/26)	57 (44%)	46 (36%)	0·82 (45/55)	0·49 (36/74)	0·78 (36/46)
Pooled external patients cohort	0·85 (0·83–0·87)	1026	277 (27%)	517 (51%)	0·89 (246/277)	0·64 (483/749)	0·94 (483/514)	312 (30%)	197 (19%)	0·92 (688/749)	0·49 (136/277)	0·69 (136/197)

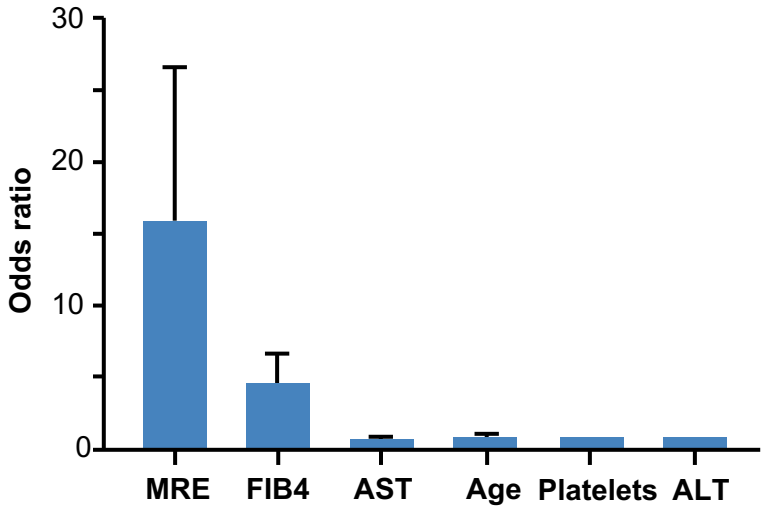


FAST: CAP+LSM+AST
Main issue is low PPV: 0.33-0.83

Newsome et al. *Lancet Gastro Hep*. 2020; Noureddin N, Alkhouri N et al. *Hepatology*. 2020.

Utility of Magnetic Resonance Elastography in Accurate Identification of Candidates for Pharmacologic Treatment of NASH Related Fibrosis: A Prospective Cohort Study

MRE has higher odds ratio in detecting **stage ≥2 fibrosis**



Combination of MRE and FIB-4 for ruling in ≥ stage 2 fibrosis

UCSD-NAFLD Cohort
(N=238)

MRE ≥ 3.3kPa
PPV: 86.9

+

FIB-4 ≥ 1.6
PPV: 61.5

MRE ≥ 3.3kPa + FIB-4 ≥ 1.6
PPV: 97.1

Japan-NAFLD Cohort
(N=222)

MRE ≥ 3.3kPa + FIB-4 ≥ 1.6
PPV: 91.0

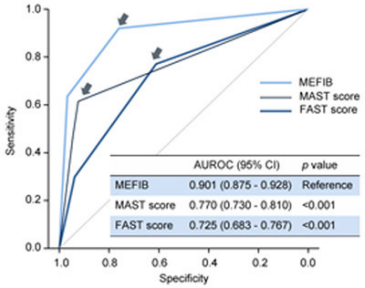
- Combination of imaging and serum markers (MRE≥3.3kPa and FIB-4≥1.6) yielded a high positive predictive value(97.1) for a clinician to rule in clinically significant disease that needs pharmacologic treatment in NAFLD

Jung J et al. EASL dILC2020. #AS097; Jung et al. *GUT*. 2020.

Head-to-Head Comparison Between MEFIB, MAST, and FAST for Detecting Significant Fibrosis in NAFLD

Study population
This prospective study included 563 biopsy proven NAFLD patients from two cohorts in the United States and Japan.

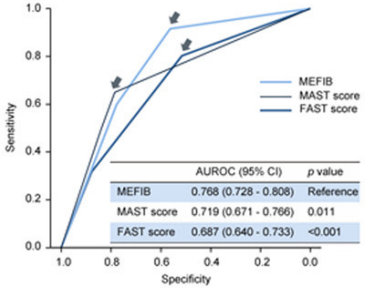
MEFIB is superior to **MAST** or **FAST** or the detection of ***significant fibrosis***



	AUROC (95% CI)	*p* value
MEFIB	0.901 (0.875 - 0.928)	Reference
MAST score	0.770 (0.730 - 0.810)	<0.001
FAST score	0.725 (0.683 - 0.767)	<0.001

Endpoints: Diagnostic models for detecting ***significant fibrosis*** and ***"at risk" NASH*** defined NAS ≥4 and fibrosis stage ≥2

MEFIB is superior to **MAST** or **FAST** for the detection of ***"at risk" NASH***



	AUROC (95% CI)	*p* value
MEFIB	0.768 (0.728 - 0.808)	Reference
MAST score	0.719 (0.671 - 0.766)	0.011
FAST score	0.687 (0.640 - 0.733)	<0.001

Procedures performed

2D MRE
MRI-PDFF
VCTE
CAP
FIB-4
Liver histology

Models assessed

MEFIB (includes MRE and FIB-4)
Rule-in: ≥3.3 kPa and FIB-4 ≥1.6
Rule-out: MRE <3.3 kPa and FIB-4 <1.6
vs.
MAST (includes MRI-PDFF, MRE and AST)
Rule-in: >0.242
Rule-out: <0.165
vs.
FAST (includes CAP, LSM by VCTE and AST)
Rule-in: ≥0.67
Rule-out: ≤0.35

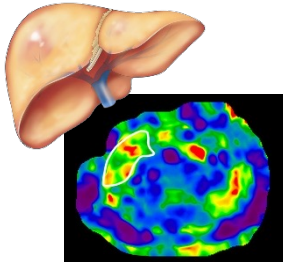
MEFIB has a high PPV (95%) and a high NPV (90%) to detect significant fibrosis and may be used as a two-step strategy

Kim…Loomba. *J Hepatology*. 2022.

Liver Stiffness on Magnetic Resonance Elastography and the MEFIB Index and Liver-Related Outcomes in Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis of Individual Participants

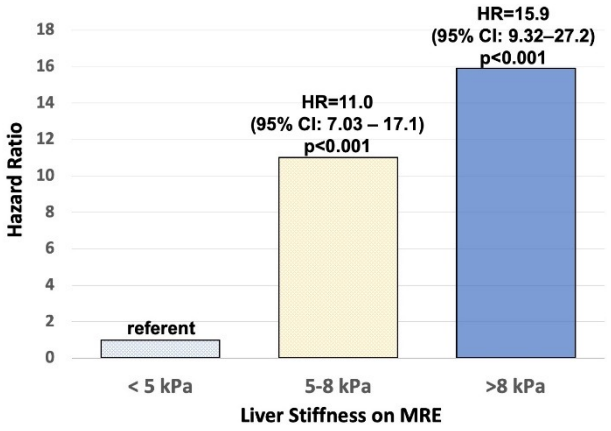
Six international cohorts with nonalcoholic fatty liver disease

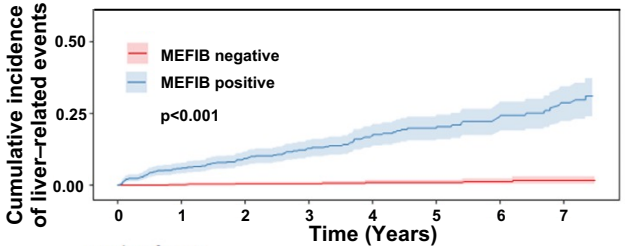
Underwent magnetic resonance elastography



Liver stiffness assessed by MRE is associated with development of ascites, hepatic encephalopathy and varices needing treatment

The MEFIB combination of MRE and FIB-4 (defined as positive when MRE ≥ 3.3kPa and FIB-4 ≥ 1.6) has excellent negative predictive value for hepatic decompensation.

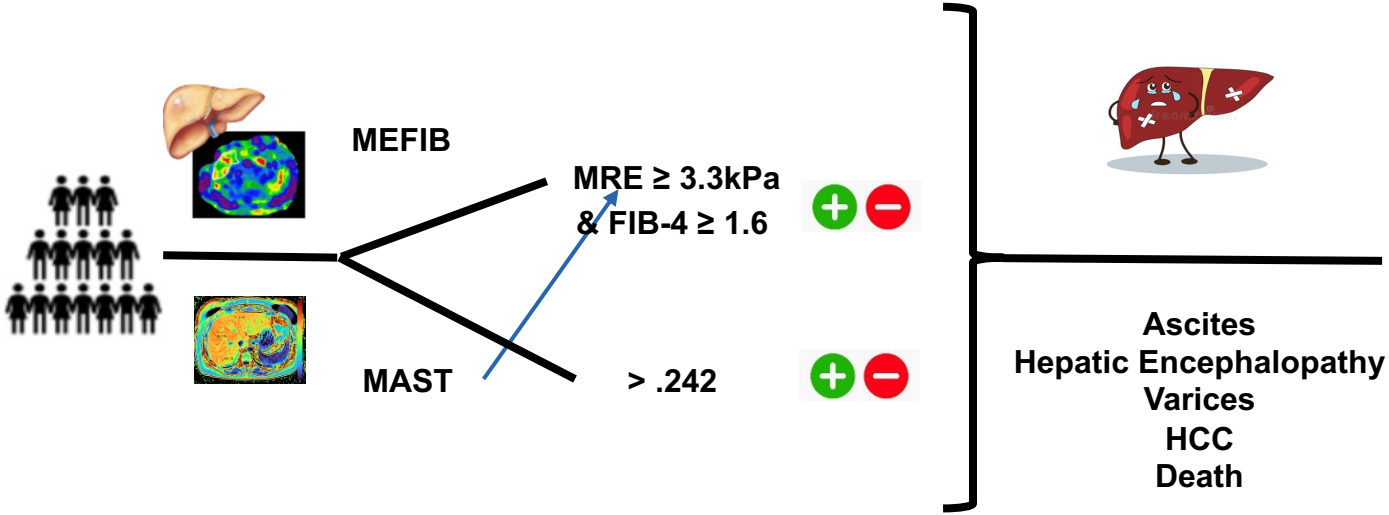




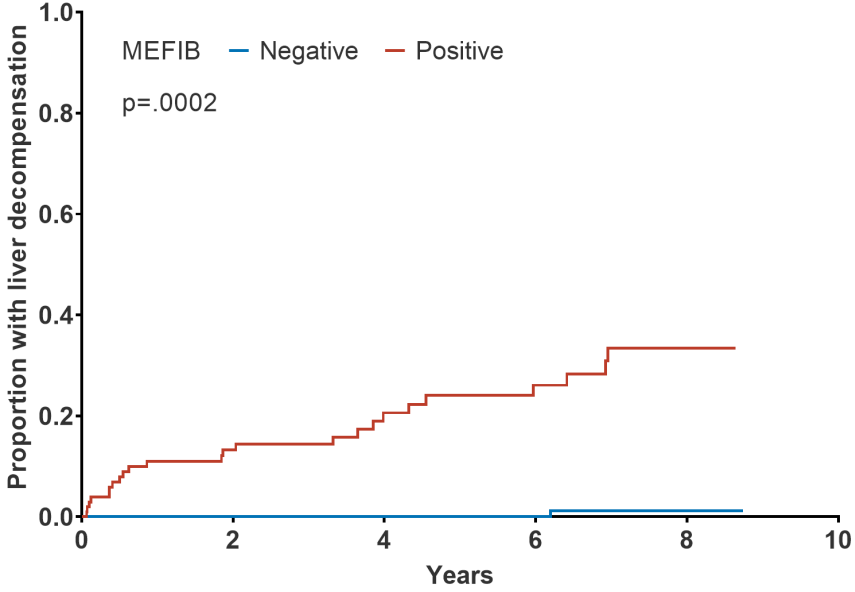
Ajmera……Loomba. *Gastroenterology*. 2022.

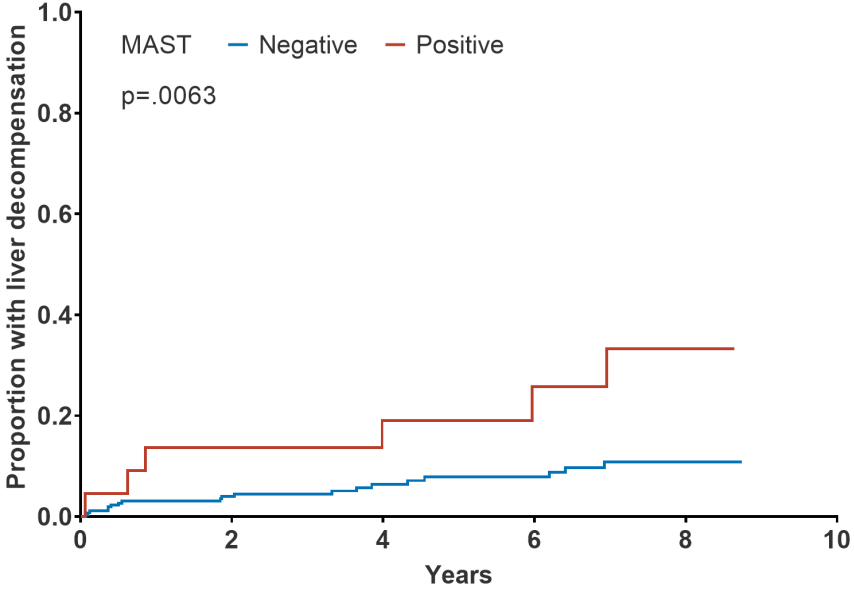
Objective

To assess the longitudinal association between MEFIB-Index compared with MAST-Score and hepatic decompensation



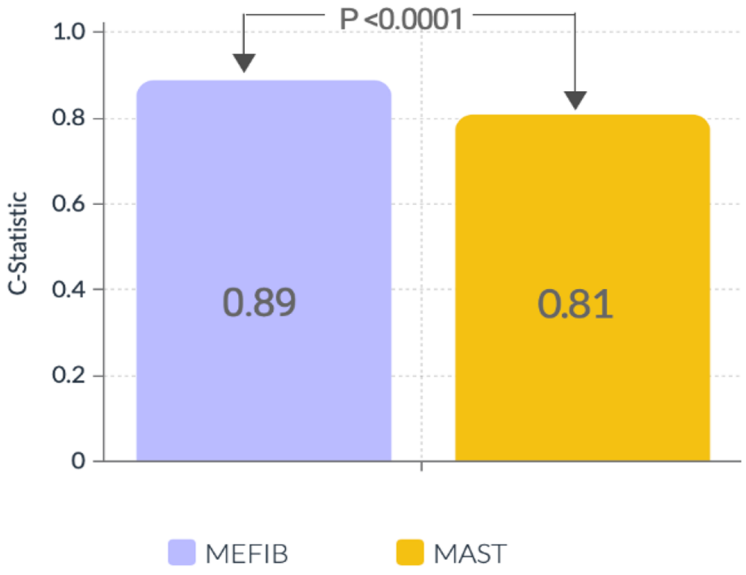
Cumulative Incidence Plots for the Primary Outcome for MEFIB-Index and MAST-Score





MEFIB-Index and MAST-Score for Predicting Hepatic Decompensation

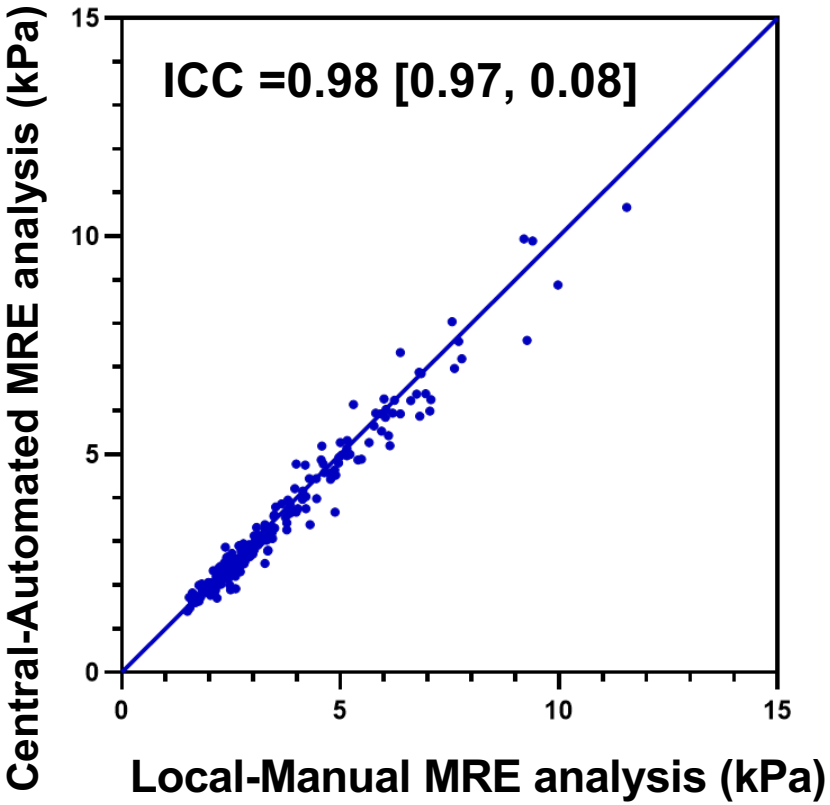
- The 1- and 3-year risk of the primary outcome were 11% vs 0% and 14% vs 0% for positive MEFIB-Index vs negative MEFIB-Index (p<0.0001 for both).
- The 1- and 3-year risk of the primary outcome were 14% vs 3% (p=0.01). and 14% and 4% (p=0.04) for positive MAST-Score vs negative MAST-Score.
- The predictive power of the MEFIB-Index (c=.89, se=0.02) was higher the MAST-Score (c-statistic: 81, se=0.03)



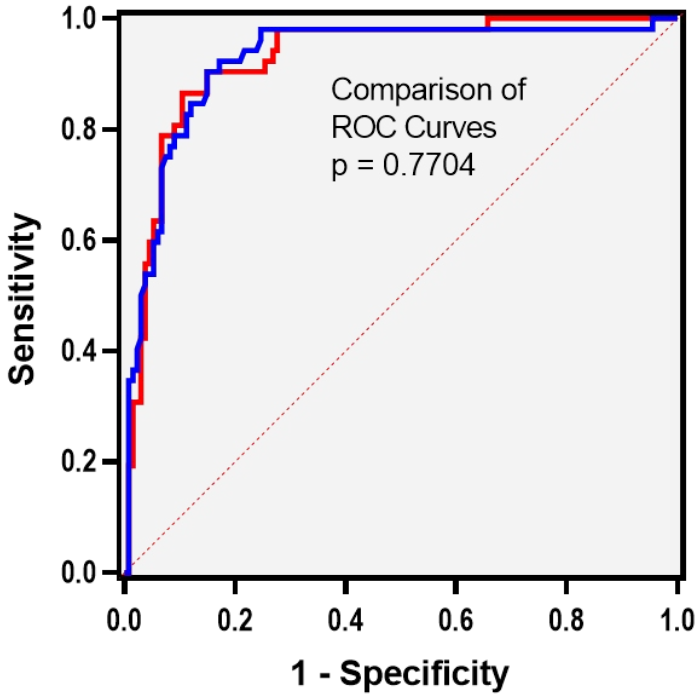
Reproducibility of Automated Versus Manual Read of Magnetic Resonance Elastography in NAFLD: A GOLDMINE Study

Suzanne Sharpton, Kay Pepin, Ricki Bettencourt, Jeremiah Heilman, Souvik Sarkar, Winston Dunn, Atsushi Nakajima, Kento Imajo, Egbert Madamba, Lisa Richards, Harris Siddiqi, Veeral Ajmera, Michael Middleton, Claude Sirlin, Cynthia Behling, Kathryn Fowler, Richard Ehman, and Rohit Loomba

MRE-Estimated Liver Stiffness Derived From Central-Automated and Local-Manual Methods Were Strongly Correlated



Central-Automated and Local-Manual Methods Both Had High Diagnostic Accuracy for Advanced Fibrosis

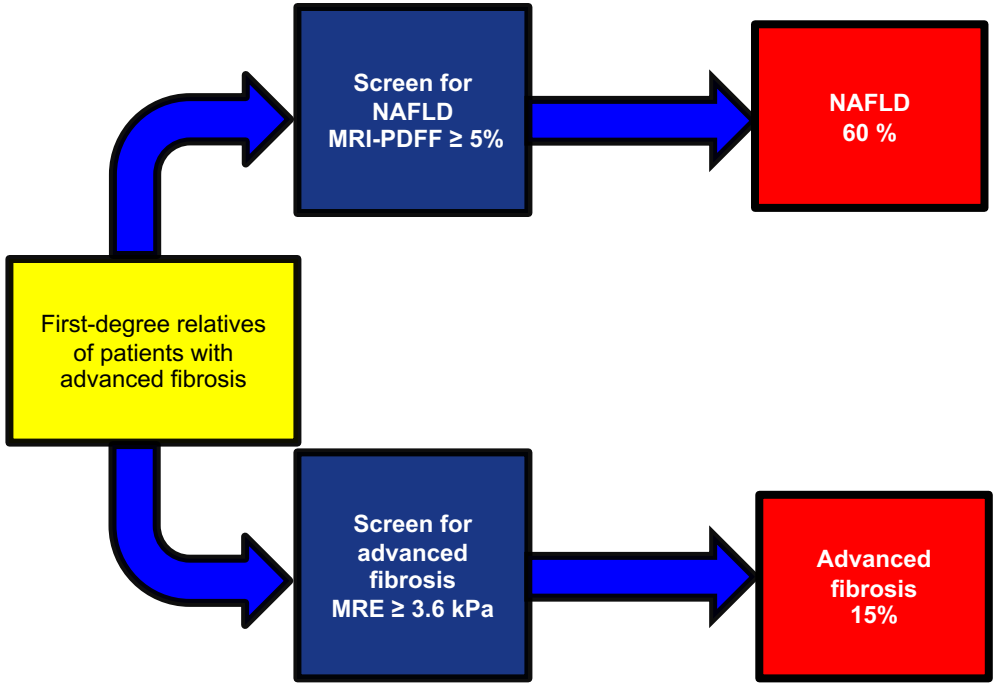


Manual MRE
0.93 (0.89-0.97)

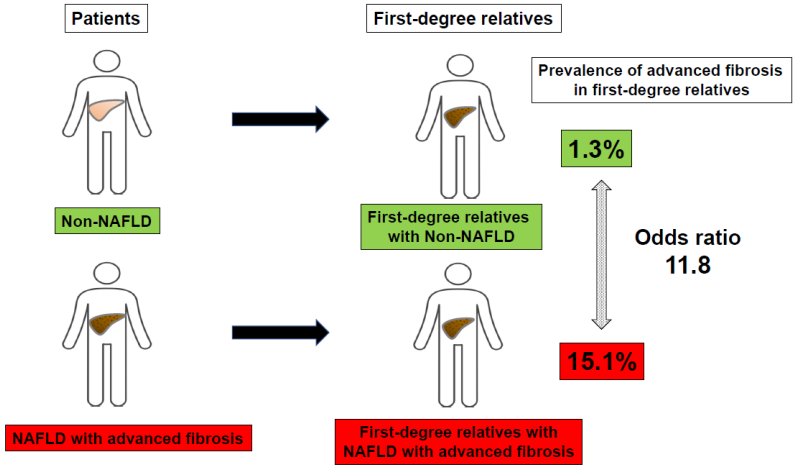
Automated MRE
0.93 (0.88-0.97)

Who to Screen New Data?

First-Degree Relatives of Patients With Advanced Fibrosis Have Increased Risk of Advanced Fibrosis Due to NAFLD

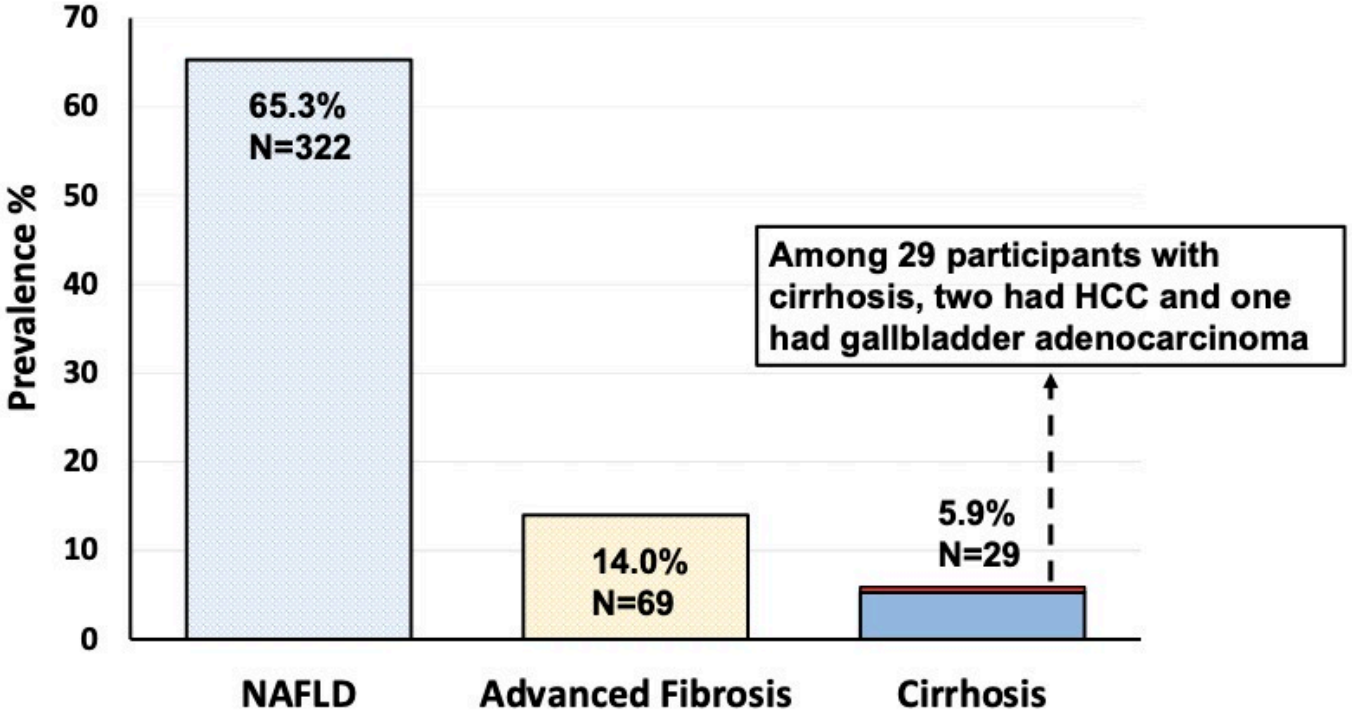


Family history of advanced fibrosis in NAFLD increases the risk by 12 times independent of age, sex, and diabetes



Tamaki……Yki-Jarvinen and Loomba. *JCI*. 2022.

Prevalence of NAFLD, Advanced Fibrosis and Cirrhosis Among Patients With T2DM



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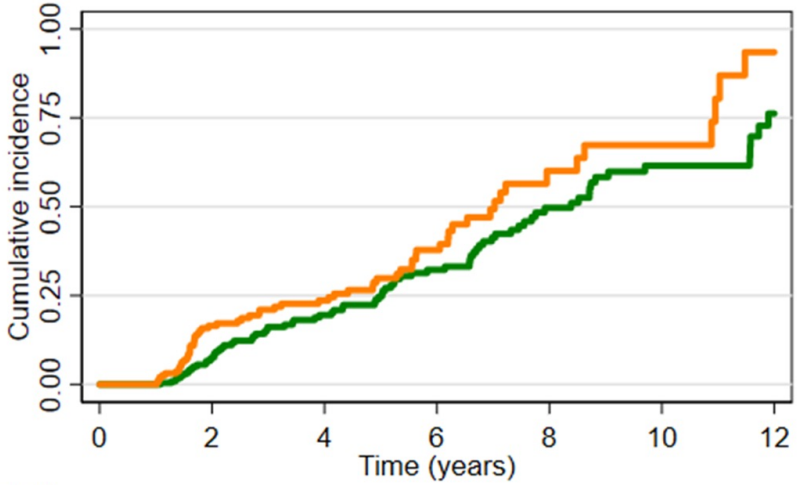
Higher Cumulative Incidence of Fibrosis Progression by ≥1 stage in T2DM vs Non-T2DM



Number at risk

T2DM	196	124	85	38	11	6	1
No T2DM	231	172	115	74	38	23	7

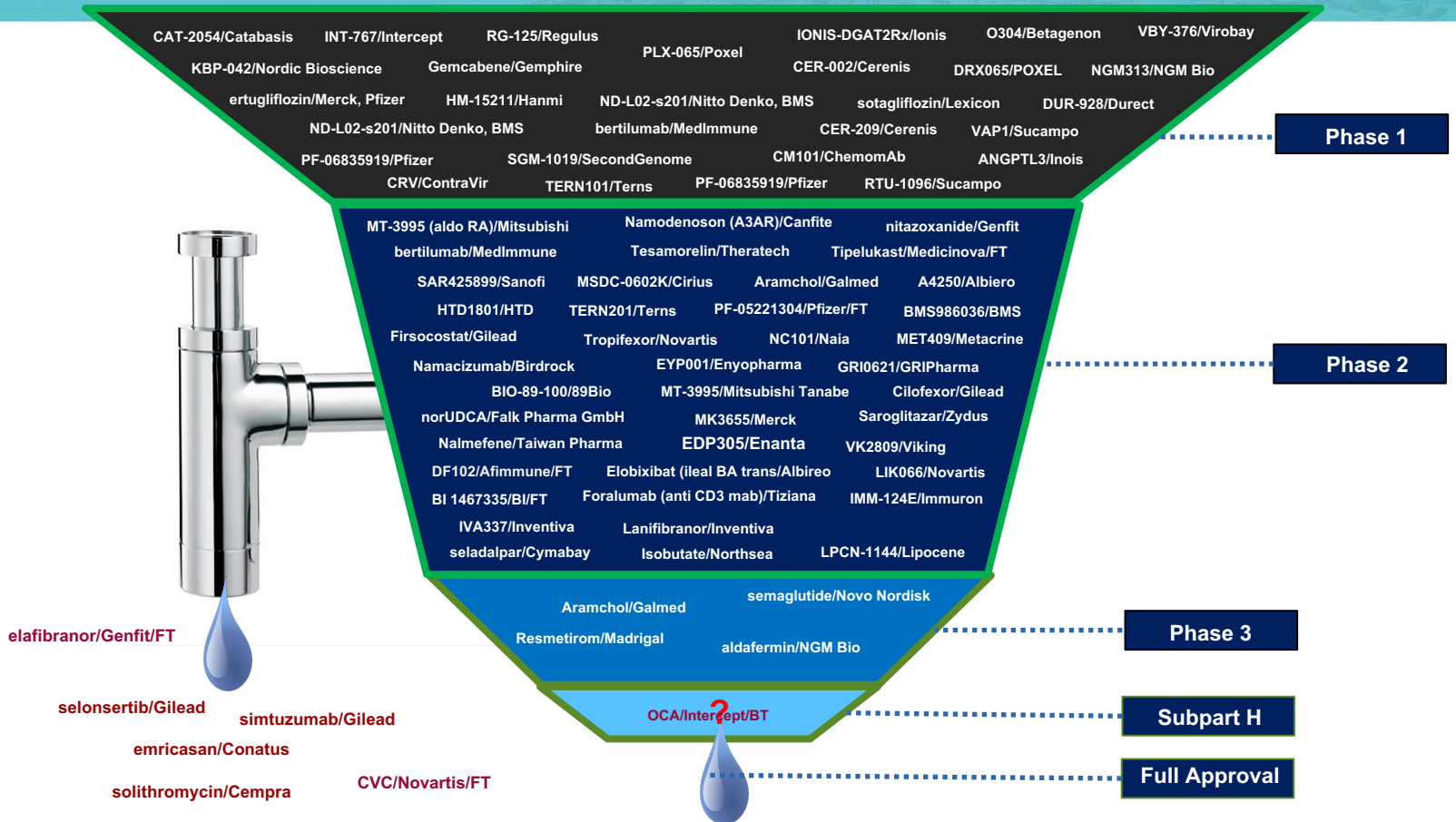
T2DM — No T2DM

Cumulative incidence (95% CI):
4 years: T2DM: 0.24 (0.18, 0.31); No T2DM: 0.20 (0.14, 0.26)
8 years: T2DM: 0.60 (0.47, 0.73); No T2DM: 0.50 (0.41, 0.59)
12 years: T2DM: 0.93 (0.76, 0.99); No T2DM: 0.76 (0.64, 0.87)
Adjusted hazard ratio (95% CI): 1.69 (1.17, 2.43), p=0.005

*Adjusted for age, gender, ethnicity/race, BMI and baseline fibrosis stage

Treatment Landscape

Global Pipeline for NASH



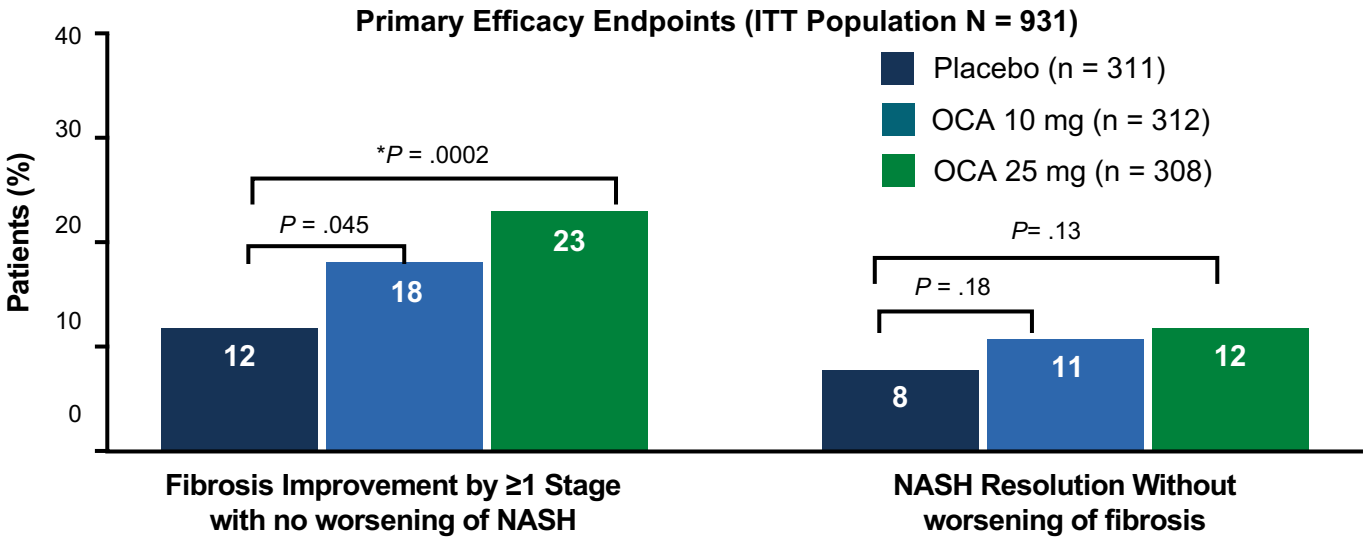
NASH Agents in Clinical Development

	Agent	Target(mechanism)	Trial, patients and primary endpoint(s)
Failed	Elafibranor	Lipotoxicity/ oxidative stress (PPARα/δ agonist)	**GOLDEN-505 (n=276, fibrosis stage 0–3)** • Reversal of NASH without worsening of fibrosis
Failed	Cenicriviroc	Inflammation/ immune activation (CCR2/5 antagonist)	**CENTAUR (n=289, fibrosis stage 1–3)** • Improvement in NAS by ≥2-points and ≥1-point decrease in lobular inflammation or hepatocellular ballooning without worsening of fibrosis at Year 1
Failed	Selonsertib	Apoptosis/necrosis (ASK1 inhibitor)	**STELLAR-4 (n=883, compensated cirrhosis)** • Fibrosis improvement ≥1 stage without NASH worsening • Event-free survival **STELLAR-3 (n=808, fibrosis stage 3)** • Fibrosis improvement ≥1 stage without NASH worsening • Event-free survival
	Aramchol	Lipotoxicity (SCD1 inhibitor)	**ARMOR (n=2000, fibrosis stage 2-3)** • Reversal of NASH without worsening of fibrosis
	Resmetirom (MGL-3196)	Lipotoxicity (TRß agonist)	**MAESTRO-NASH (n=2000, fibrosis stage 2–3)** • NASH resolution with at least a 2-point improvement in NAS without worsening of fibrosis
	Obeticholic acid	Lipotoxicity/oxidative stress (FXR agonist)	**REGENERATE (n=2370, fibrosis stage 1–3)** • Fibrosis improvement ≥1 stage without NASH worsening **FLINT (n=283, fibrosis stage 0–3)** • Decrease in NAS of ≥2 without worsening of fibrosis from baseline
	Semaglutide	Lipotoxicity/Steatosis (GLP1-RA)	**ESSENCE** • Resolution of steatohepatitis and no worsening of liver fibrosis • Improvement in liver fibrosis and no worsening of steatohepatitis • Time to first liver-related clinical event

ASK, apoptosis signal-regulating kinase; CCR, CC chemokine receptor; PPAR, peroxisome proliferator-activated receptor; FXR, farnesoid X receptor; TR, thyroid hormone.
ClinicalTrials.gov NCT01694849; ClinicalTrials.gov NCT02217475; ClinicalTrials.gov NCT03053050; ClinicalTrials.gov NCT03053063; ClinicalTrials.gov NCT02413372; ClinicalTrials.gov NCT02912260; ClinicalTrials.gov NCT02548351; ClinicalTrials.gov NCT01265498; ClinicalTrials.gov NCT04822181.

REGENERATE: Primary Outcome – Histologic Endpoints

- Phase III trial of 1968 participants with NASH, NAS ≥4 and F2/F3, or F1 with ≥1 comorbidity1 with
- Interventions: 1:1:1 OCA 10 mg QD vs 25 mg QD vs placebo
- Primary outcomes: Improvement in fibrosis with no worsening in NASH and NASH resolution with no worsening of fibrosis



OCA is not approved for the treatment of NASH.

*Statistically significant in accordance with the statistical analysis plan as agreed with FDA. All other *P* values were nominal.

Younossi. *Lancet*. 2019;394:2184.

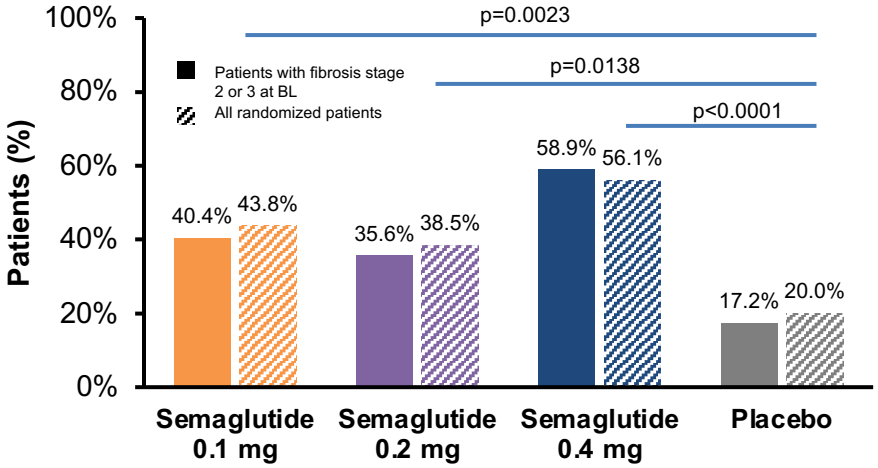
Main Issues With FXRs

- **Efficacy**
- **Side-effects**
  - LDL increase: CVD risk
  - Pruritus: Cholestasis
  - Hepatobiliary issues: DILI monitoring protocol
- **Remedy**
  - REMS
  - Plan for safe clinical use and excluding patients with cirrhosis

Efficacy and Safety of S/C Semaglutide Once Daily Versus PBO in Patients With NASH

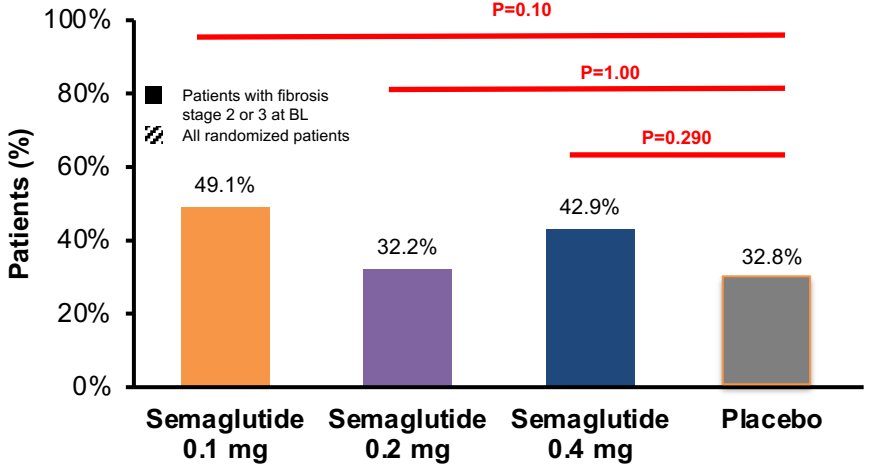
Resolution of steatohepatitis and no worsening in liver fibrosis

Patients with fibrosis Stage 2 or 3 at BL and all randomized patients



Improvement in liver fibrosis and no worsening in steatohepatitis

Patients with fibrosis Stage 2 or 3 at BL and all randomized patients



N=320

Newsome PN et al. *NEJM*. 2020/AASLD 2020.

Main Issues With GLP-1

- **Efficacy**
- **Side-effects**
  - GI side-effects
- **Remedy**
  - Combination therapy
  - Early disease in obese and overweight NASH patients

A 52-Week Phase 3 Clinical Trial of Resmetirom in 180 Patients With Well-Compensated NASH Cirrhosis

Stephen A. Harrison,[1] Naim Alkhouri,[2] Rebecca A. Taub,[3] Guy W. Neff,[4] Kris V. Kowdley,[5] Mazen Noureddin[6]

[1]University of Oxford, United Kingdom & Pinnacle Clinical Research, San Antonio, TX; [2]Arizona Liver Health, Tucson, AZ; [3]Madrigal Pharmaceuticals, Conshohocken, PA; [4]Covenant Metabolic Specialists, Sarasota, FL; [5]Liver Institute Northwest, Seattle, WA; [6]Houston Research Institute, Houston, TX.

Presented at The Liver Meeting; 04-08 November 2022; Washington, DC.

Phase 3 MAESTRO Clinical Development Program

Clinical Trial	Status	Primary Outcome
Phase 2 **MGL-3196-05** NCT02912260	Completed[1]	Relative change in hepatic fat (by MRI-PDFF) at Week 12
Phase 3 **MAESTRO-NASH**[2] NCT03900429	Subpart H (52 weeks) – Recruited Outcomes (54 months) – Ongoing	NASH resolution or fibrosis improvement on serial liver biopsy at Week 52 Study continues to outcomes. Composite endpoint includes histologic conversion to cirrhosis, hepatic decompensation events, MELD ≥15, liver transplant, & all-cause mortality
Phase 3 **MAESTRO-NAFLD-1**[3] (presumed NASH) NCT04197479	Completed (OL Arms Ongoing) Ongoing	Safety & tolerability as measured by incidence of AEs over 52 weeks in >1200 patients Phase 3 **MAESTRO-NAFLD-OLE**[4] (NCT04951219) 52-week extension to MAESTRO-NAFLD-1: Safety & tolerability as measured by incidence of AEs over 52 weeks
Phase 3 **MAESTRO-NASH Outcomes**[5] NCT05500222	Initiated	Event-driven clinical outcome to decompensated cirrhosis in patients with well-compensated NASH cirrhosis

MAESTRO Phase 3 trials provide a comprehensive data set to support accelerated approval of resmetirom for treatment of NASH with significant liver fibrosis

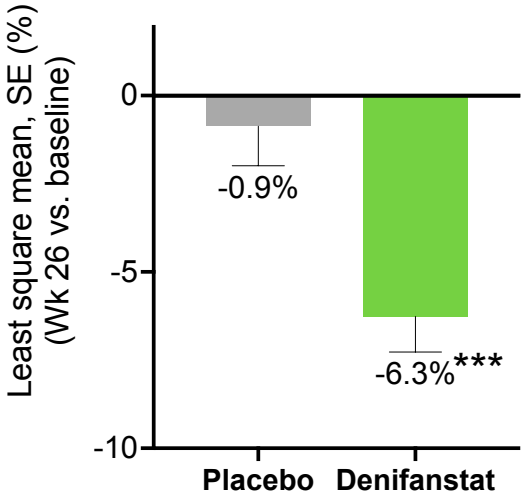
AE, adverse event; MELD, model for end-stage liver disease; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OL, open-label; OLE, open-label extension.

1. Harrison SA, et al. *Lancet*. 2019;394(10213):2012-2024; 2. ClinicalTrials.gov (NCT03900429). https://clinicaltrials.gov/ct2/show/NCT03900429. Accessed 17Oct2022;
3. ClinicalTrials.gov (NCT04197479). https://clinicaltrials.gov/ct2/show/NCT04197479. Accessed 17Oct2022; 4. ClinicalTrials.gov (NCT04951219). https://clinicaltrials.gov/ct2/show/NCT04951219. Accessed 17Oct2022;
5. ClinicalTrials.gov (NCT05500222). https://clinicaltrials.gov/ct2/show/NCT05500222. Accessed 17Oct2022.

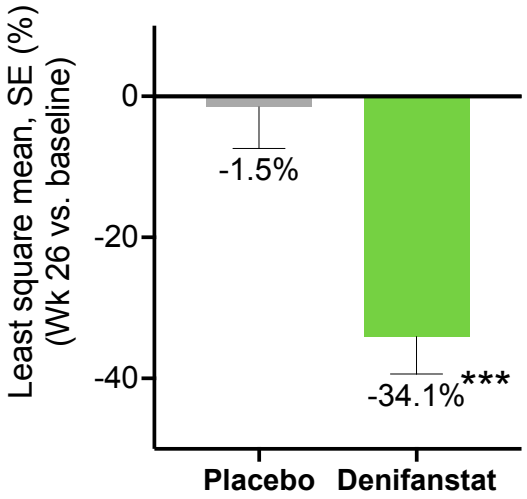
FASCINATE-2 Interim Results – Denifanstat vs. Placebo

67% MRI-PDFF Responder Rate Observed at Week 26

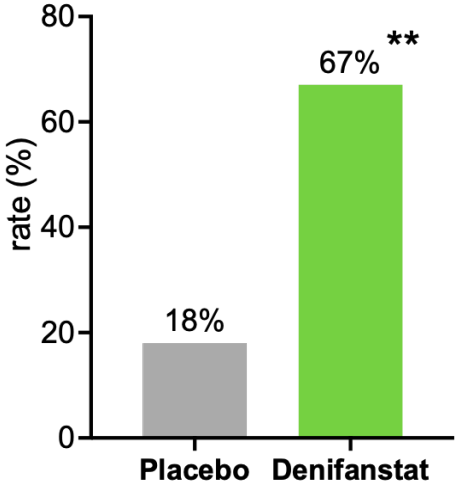
Liver fat absolute change
(MRI-PDFF)



Liver fat % change
(MRI-PDFF)



Responder analysis
(≥30% fat reduction)

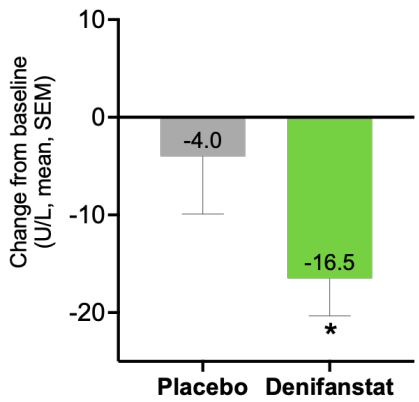


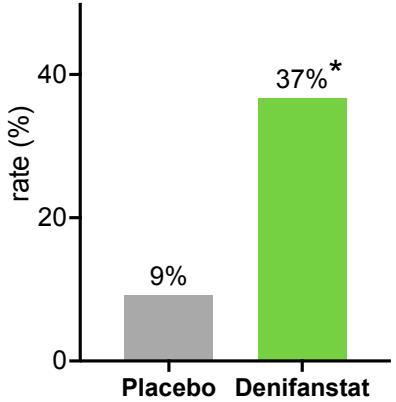
9 of 20 denifanstat responders had ≥50% liver fat reduction

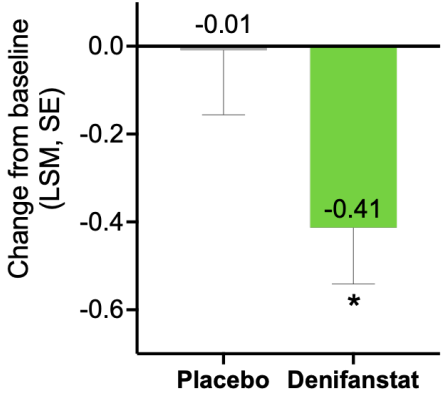
** $p < 0.01$, *** $p < 0.001$. placebo (n=22), denifanstat (n=30)
Two-sided CMH test for response analysis, and two sided ANCOVA for liver fat change.

FASCINATE-2 Interim Results – Denifanstat vs. Placebo

Significant Reduction in ALT and ELF at Week 26







- No treatment related SAEs, majority of AEs mild to moderate (Grade 1/2)
- Results confirm denifanstat activity in a biopsy-proven advanced NASH population (46% F2/54% F3)
- Inhibition of FASN impacts steatosis, inflammation and fibrosis - 3 key disease characteristics of NASH

* $p < 0.05$, placebo (n=20), denifanstat (n=29) for ALT; placebo (n=15), denifanstat (n=20) for ELF
Two sided ANCOVA. ELF results are shown for all patients with data available.

AASLD The Liver Meeting®

Efruxifermin (EFX) in Nonalcoholic Steatohepatitis With Fibrosis: Results From a Randomized, Double-Blind, Placebo-Controlled, Phase 2b Trial (HARMONY)

Stephen A. Harrison, Juan Frias, Guy Neff, Gary A. Abrams, Jeanine Lucas, William Sanchez, Sudhanshu Gogia, Muhammed A. Sheikh, Cynthia Behling, Pierre Bedossa, Lan Shao, Erica Fong, Brittany de Temple, Reshma Shringarpure, Erik J Tillman, Timothy Rolph, Andrew Cheng, and Kitty Yale

AASLD Abstract #39094
Washington, D.C.
November 2022

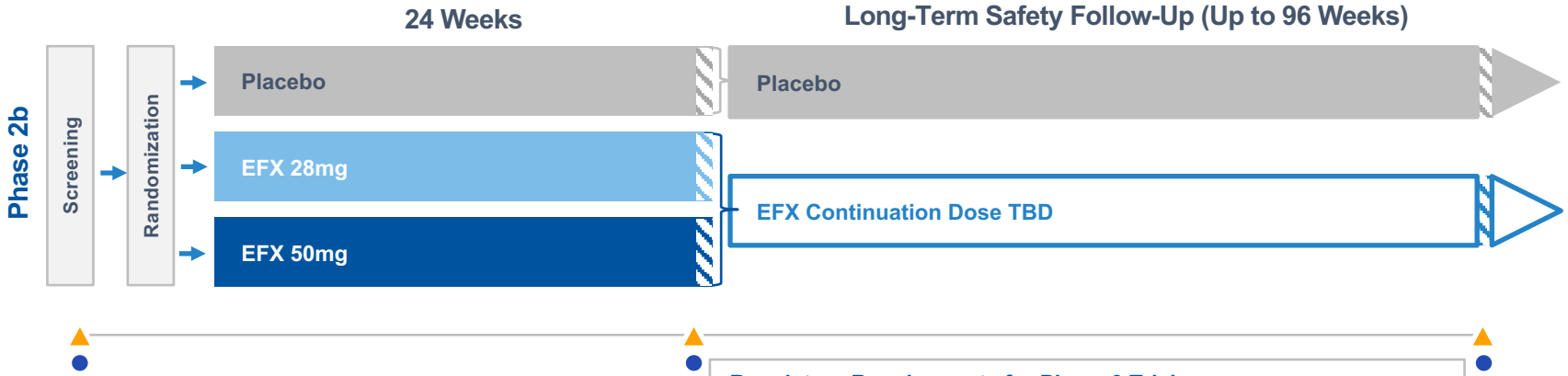
akero

HARMONY Trial Design and Objectives

Key Inclusion Criteria
- F2-F3 NASH
- NAS ≥4
- Liver Fat (MRI-PDFF) ≥8%

Phase 2b Primary Endpoint
- ≥ 1-stage fibrosis improvement without worsening of NASH

Key Secondary Efficacy Endpoints
- NASH Resolution & No Worsening of Fibrosis
- Fibrosis Markers
- Lipoproteins
- Glycemic Control
- Weight Change
- MRI-PDFF
- Liver Injury Markers



Regulatory Requirements for Phase 3 Trials
- FDA accepts one of two endpoints for Phase 3 registrational trials: (1) Fibrosis improvement ≥1 stage & no worsening of NASH or (2) NASH resolution and no worsening of fibrosis[1]
- EMA requires both endpoints to be met for marketing approval[2]

[1]FDA Draft Guidance, Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment (2018); [2] EMA, Draft Reflection paper on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH) (2018).

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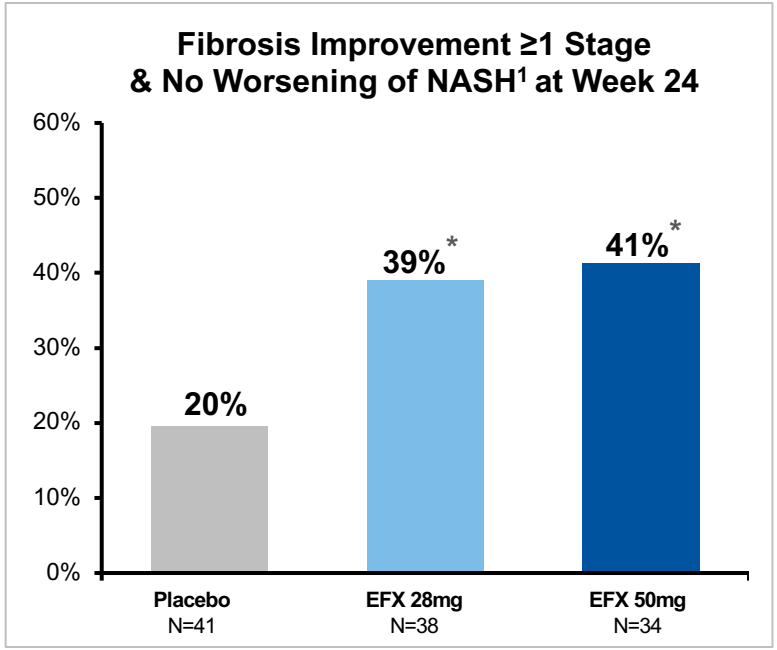
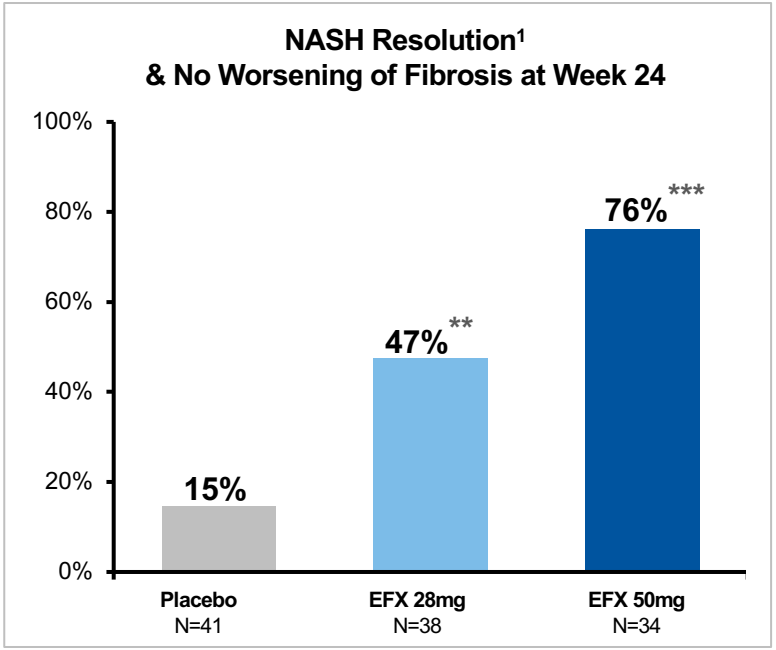
Both EFX Doses Achieved Statistical Significance on Fibrosis Improvement and NASH Resolution





[1] Improvement in liver fibrosis greater than or equal to one stage and no worsening of NASH (defined as no increase in NAS for ballooning, inflammation, or steatosis)

* p<0.05, versus placebo (Cochran–Mantel–Haenszel test [CMH])

[1] NAS score of 0 or 1 for lobular inflammation and a score of 0 for ballooning

** p<0.01, *** p<0.001, versus placebo (CMH)

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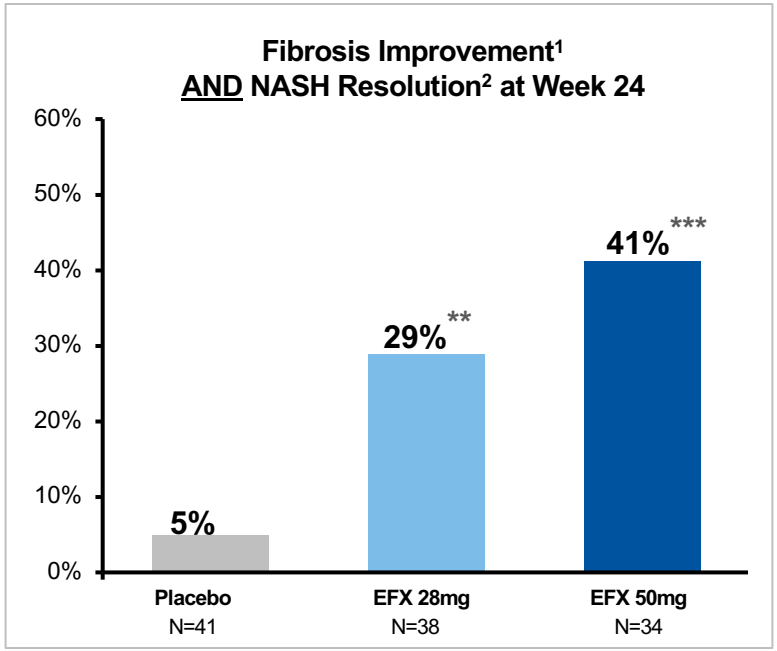
Source Data: Liver Biopsy Analysis Set.

Both EFX Doses Also Achieved Statistical Significance on Composite Endpoint (Fibrosis Improvement and NASH Resolution)



[1] Improvement in liver fibrosis greater than or equal to one stage
[2] NAS score of 0 or 1 for lobular inflammation and a score of 0 for ballooning
** p<0.01, *** p<0.001, versus placebo (CMH)

Patients Achieving Fibrosis Improvement ≥2 Stages and No Worsening of NASH at Week 24

Placebo (N=41)	EFX 28mg (N=38)	EFX 50mg (N=34)
5%	16%	15%

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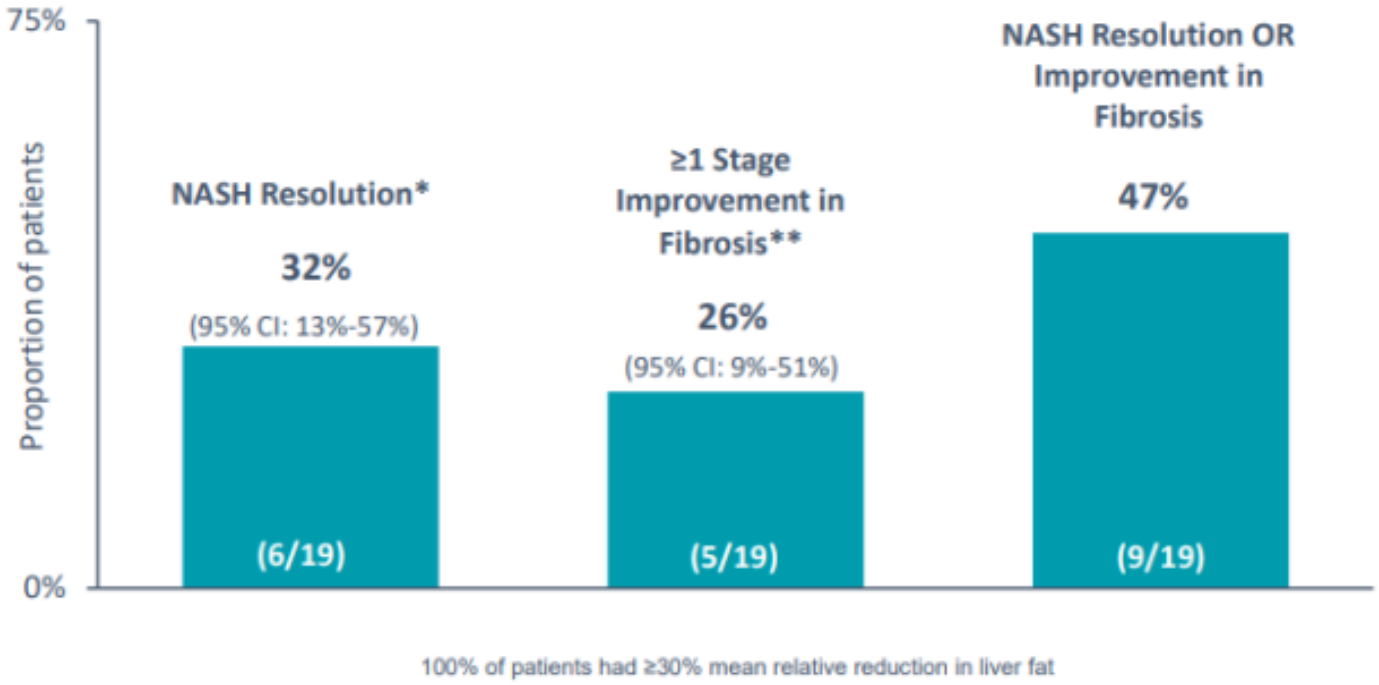
Source Data: Liver Biopsy Analysis Set.

Pegozafermin (FGF-21 Analogue) Led to Improvements in NASH Resolution and/or Fibrosis Improvement



100% of patients had ≥30% mean relative reduction in liver fat

Clinical Assessment and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance from the American Association for the Study of Liver Diseases

Mary E. Rinella, Brent A. Neuschwander-Tetri*, Mohammad Shadab Siddiqui, Manal F. Abdelmalek, Stephen Caldwell, Diana Barb, David E. Kleiner, Rohit Loomba*

AASLD Practice Guidelines Patient Debrief Session
Nov 7, 2022

Rohit Loomba, MD, MHSc FAASLD
University of California at San Diego

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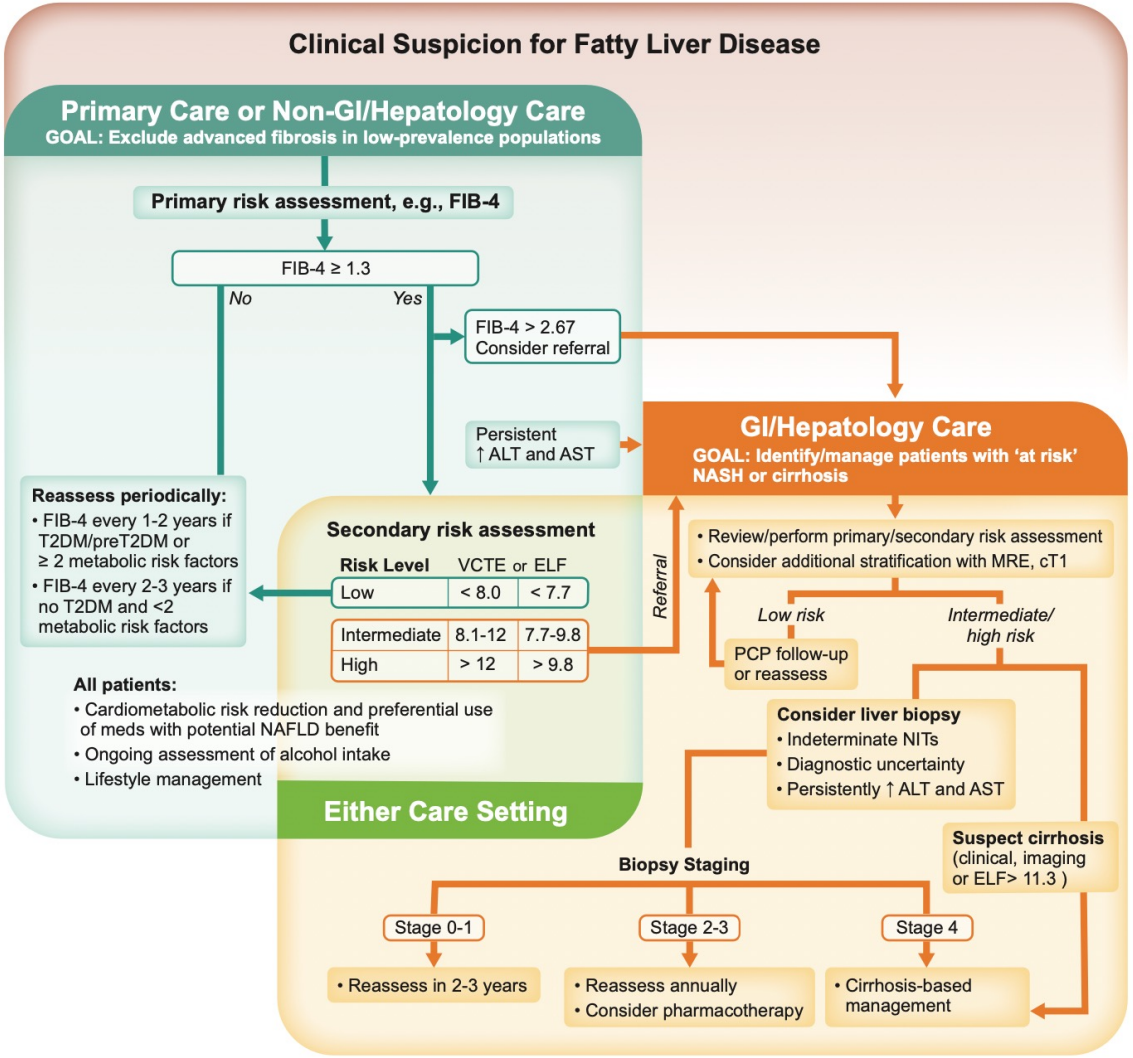
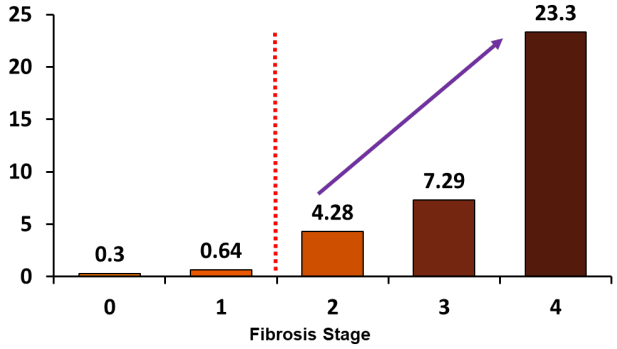

Clinical Suspicion for Fatty Liver Disease
Primary Care or Non-GI/Hepatology Care
GOAL: Exclude advanced fibrosis in low-prevalence populations
Primary risk assessment, e.g., FIB-4
FIB-4 ≥ 1.3
No
Yes
FIB-4 > 2.67
Consider referral
Persistent
↑ ALT and AST
GI/Hepatology Care
GOAL: Identify/manage patients with 'at risk' NASH or cirrhosis
Reassess periodically:
• FIB-4 every 1-2 years if T2DM/preT2DM or ≥ 2 metabolic risk factors
• FIB-4 every 2-3 years if no T2DM and <2 metabolic risk factors
Secondary risk assessment
Risk Level VCTE or ELF
Low < 8.0 < 7.7
Intermediate 8.1-12 7.7-9.8
High > 12 > 9.8
Referral
• Review/perform primary/secondary risk assessment
• Consider additional stratification with MRE, cT1
Low risk
Intermediate/ high risk
PCP follow-up or reassess
All patients:
• Cardiometabolic risk reduction and preferential use of meds with potential NAFLD benefit
• Ongoing assessment of alcohol intake
• Lifestyle management
Consider liver biopsy
• Indeterminate NITs
• Diagnostic uncertainty
• Persistently ↑ ALT and AST
Either Care Setting
Suspect cirrhosis (clinical, imaging or ELF> 11.3)
Biopsy Staging
Stage 0-1
Stage 2-3
Stage 4
• Reassess in 2-3 years
• Reassess annually
• Consider pharmacotherapy
• Cirrhosis-based management

How Best Can I Identify Who Needs to Be Treated Without a Liver Biopsy?

Diagnose "at risk" NASH = NASH with stage 2 fibrosis

- **FAST: CAP, VCTE, AST**
- **MAST: MRI-PDFF, MRE, AST**
- **MEFIB: MRE 3.3 Kpa + FIB-4 1.6**
- **cT1**



Anstee, Castera and Loomba. *J Hep*. 2022.

Noninvasive Parameters for 'At Risk' NASH

Identification of 'at risk' NASH				
Combined	FAST	≥0.67	<0.35	• ≤0.35 (sensitivity 90%) • ≥ 0.67 (specificity 90%) • In validation cohorts, the PPV of FAST ranged between 0.33 and 0.81.[1-2]
Combined	MEFIB	FIB-4 ≥ 1.6 plus MRE ≥ 3.3 kPa	FIB-4 < 1.6 plus MRE < 3.3 kPa	• Sequential approach identifies patients with at least stage 2 fibrosis with > 90% PPV.[3]
	cT1	≥ 875 msec	< 825 msec	• Requires further validation as data is derived from one study[4]

Newsome et al. *Lancet Gastro Hep*. 2020[1]; Woreta et al. *PLoSONE*. 2022[2]; Jung et al. *Gut.* 2021[3]; Andersson et al. *CGH.* 2022[4].

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Noninvasive Parameters for Advanced Fibrosis and Cirrhosis

Detection of advanced fibrosis				
Serum	FIB-4	≥ 2.67	<1.3	• No added cost[1-3] • Not accurate in age < 35 years and lower rule-out threshold among high-risk individuals who have high pre-test probability
Serum	ELF	≥ 9.8	<7.7	• Blood test sent to a reference laboratory[4] • Cost
Imaging	VCTE	≥12 kPa	< 8 kPa	• Point of care[5]
Imaging	MRE	≥3.63 kPa	<2.55 kPa	• MRE LSM ≥3.63 kPa (associated with advanced fibrosis, AUROC of 0.93)[6]

Diagnosis of cirrhosis (rule-in or rule out)				
		Rule-in	**Rule-out**	
CPR	FIB-4	≥3.48	< 1.67	• 90% specificity cut-point for ruling-in and 90% sensitivity for ruling-out cirrhosis, respectively[6, 7]
Serum	ELF	≥11.3	<7.7	• ELF ≥ 11.3 is associated with increased risk of hepatic decompensation among patients with cirrhosis[4]
Imaging	VCTE	≥ 20 kPa	< 8 kPa	• LSM by VCTE ≥ 20 kPa is associated with cirrhosis but for ruling out cirrhosis optimal cut-point is < 8 kPa[5]
Imaging	MRE	≥ 5 kPa	< 3 kPa	• LSM by MRE ≥ 5 kPa has a very good (approaches 95%) specificity for diagnosis of cirrhosis and is also associated with increased risk of incident hepatic decompensation[8, 9]

Barb et al. *Obesity.* 2021[1]; McPherson et al. *AJG.* 2017[2]; Graupera et al. *CGH.* 2022[3]; Day et al. *J Applied Lab Med.* 2019[4]; Mózes et al. *Gut.* 2022[5]; Loomba et al. *Hepatology.* 2014[6]; Brandman et al. *APT.* 2022[7]; Hsu et al. *CGH.* 2019[8]; Loomba et al. *Hepatology.* 2014[9].
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Summary of (Selected) Key Concepts to Guide Clinical Practice: *Off-Label Use of Approved Medications for Co-Morbid Conditions*

- ***Statins are safe and recommended for CVD risk reduction*** *in patients with NAFLD across the disease spectrum, including compensated cirrhosis.*
- *Limited data exist on the safety and efficacy of statins in patients with decompensated cirrhosis, though statin use could be considered in patients with high CVD risk with careful monitoring.*

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Summary of (Selected) Key Concepts to Guide Clinical Practice: *Alcohol and Other Considerations*

- *In patients with NAFLD,* ***alcohol can be a co-factor*** *for liver disease progression and intake should be assessed on a regular basis.*
- ***Patients with clinically significant hepatic fibrosis (≥F2)should abstain from alcohol use completely.***
- *Improvement in ALT or reduction in liver fat content by imaging in response to an intervention may indicate histological improvement in disease activity.*
- ***First-degree relatives of patients with NASH cirrhosis should be counseled regarding their increased individual risk and offered screening for advanced hepatic fibrosis.***

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Thank you

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