Comprehensive Management of MASLD: Navigating the Clinical Care Pathway

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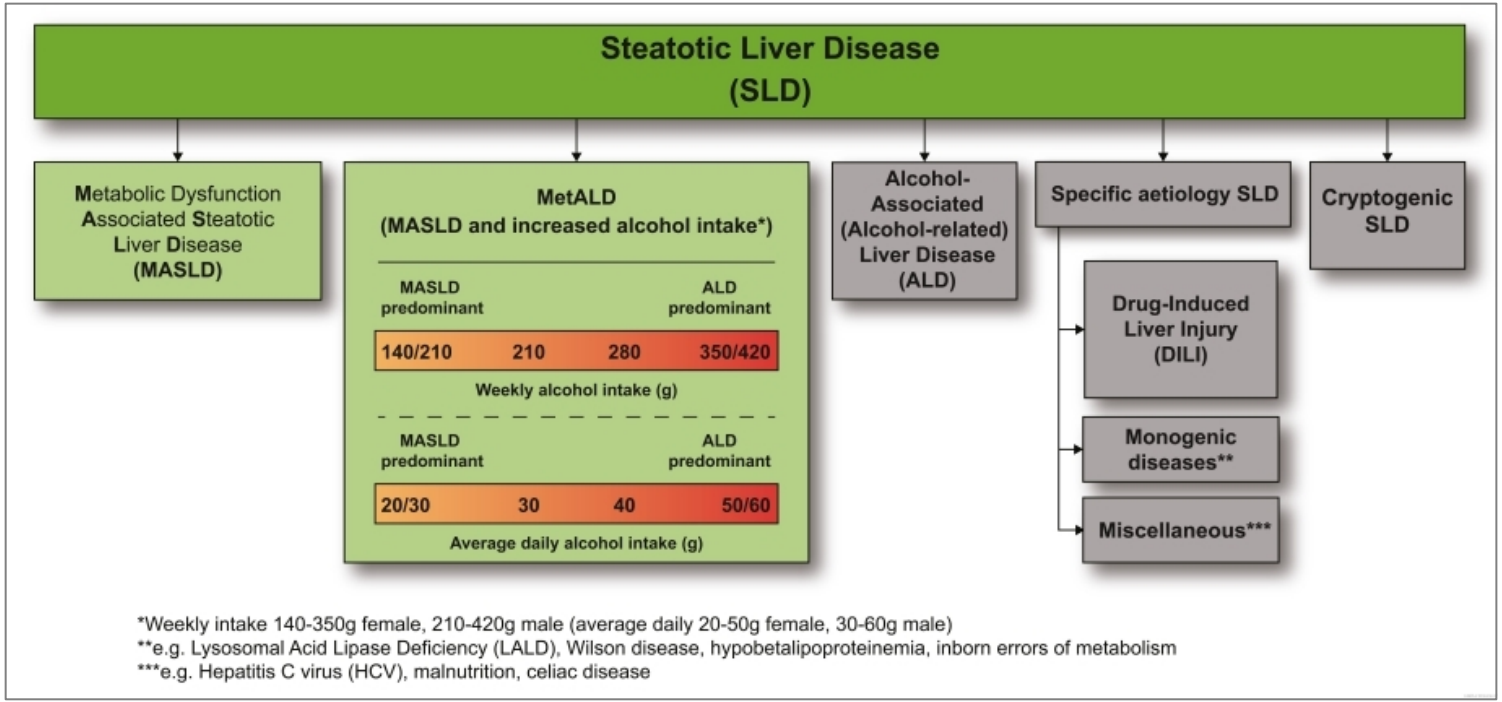
Epidemiology: Burden of MASLD

- **Globally, metabolic-dysfunction associated steatotic liver disease (MASLD) 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

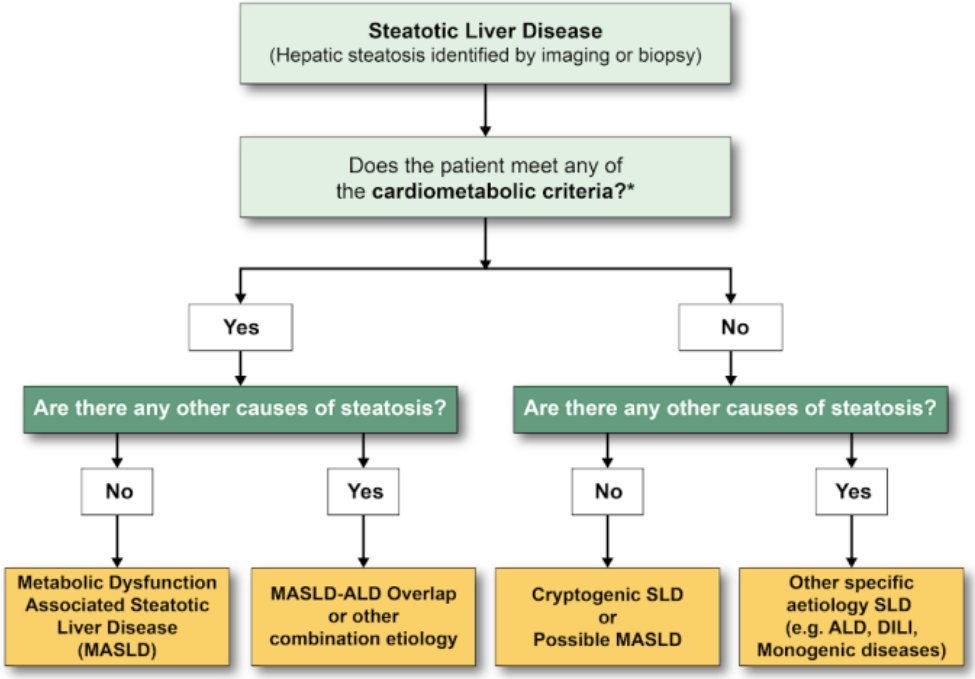
- MASLD is diagnosed
  - Either on biopsy or imaging evidence of hepatic steatosis (≥ 5% liver fat) in individuals with at least one metabolic risk factor who consume little or no alcohol without any other cause for liver disease or hepatic steatosis

Nomenclature



Rinella et al. Hepatology 2023

Nomenclature



One or more metabolic risk factors

1. **Overweight**
2. **HTN**
3. **Prediabetes/diabetes**
4. **Hypertrigylceridemia**
5. **Low HDL**

What about NASH?

- NASH is now called MASH: Metabolic-dysfunction associated steatohepatitis (MASH)
- At risk MASH: Presence of MASH with at least stage 2 fibrosis or higher

At Risk NASH Can Be Identified By Commonly Used NITs

AASLD Practice Guidance on the Clinical Assessment and Management of Nonalcoholic Fatty Liver Disease

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

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
Combined	MAST	≥0.242	≤0.165	0.242 (specificity 90%), 0.165 (sensitivity 90%)
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
	cTI	≥875 ms	<825 ms	Requires further validation

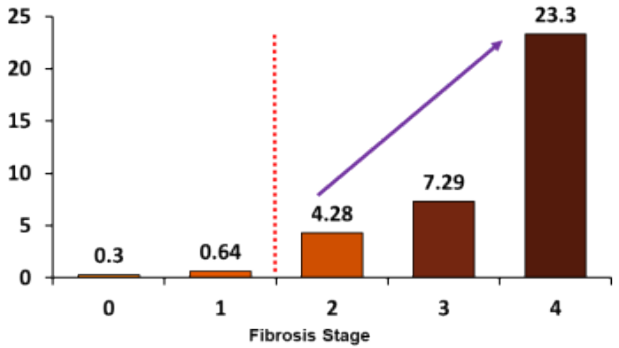
Rinella M et al. *Hepatology.* 2023.

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

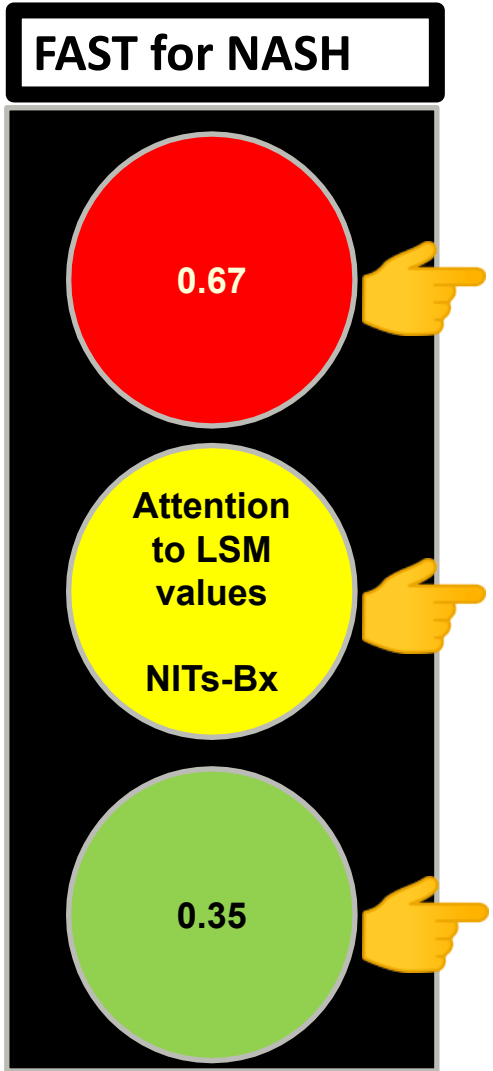
Role of FAST in detection of high-risk NASH

	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

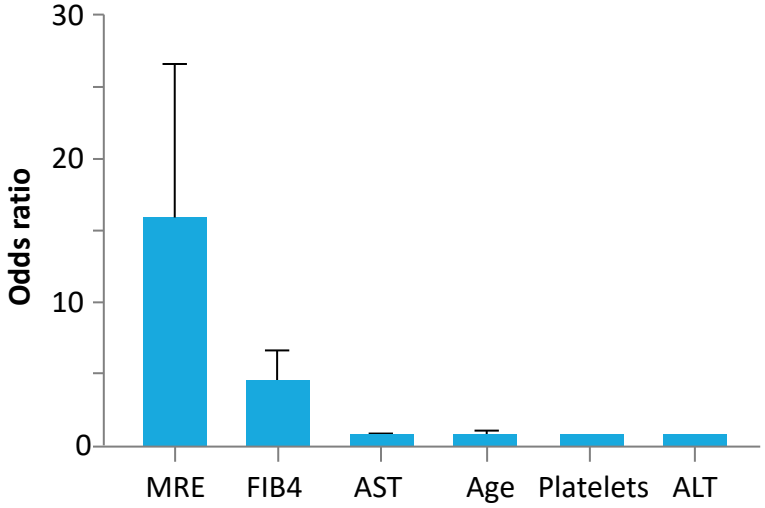
Main issue is low PPV: 0.33-0.83

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

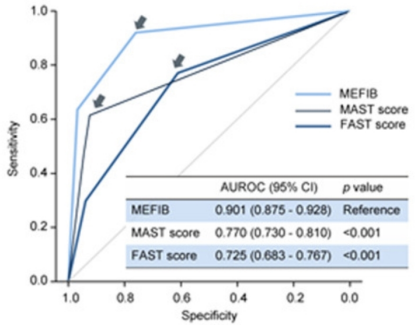
- Combination of imaging and serum markers (MRE≥3.3kPa and FIB-4≥1.6) yielded a high positive predictive value (97.1) for a clinician to rule in clinically significant disease that needs pharmacologic treatment in NAFLD

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.

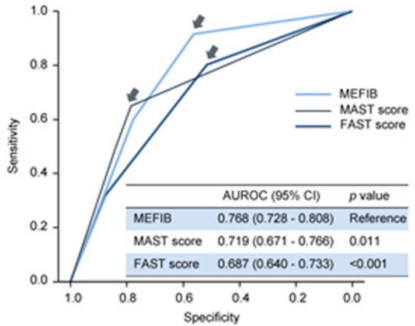
MEFIB is superior to **MAST** or **FAST** or the detection of ***significant fibrosis***



	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

Global L**o**ngitudinal Assessment of Nonalcoholic Fatty **L**iver **D**isease using **M**agnet**I**c Reso**N**ance **E**lastography

GOLDMINE Study

ACG 2023
October 20-25, Vancouver, Canada

Standardized research visit every year

- Demographics
- Anthropometrics
- Physical examination
- Fasting labs
- Medical history and medications
- Questionnaires
  - Skinner Lifetime Drinking History
  - AUDIT
- VCTE, CAP
- Endoscopy data

Patient population:
Adults with biopsy-proven NAFLD *or* NAFLD cirrhosis

Central histology at UCSD

Central MRI-PDFF and 2D & 3D MRE at Mayo

Clinical Outcomes

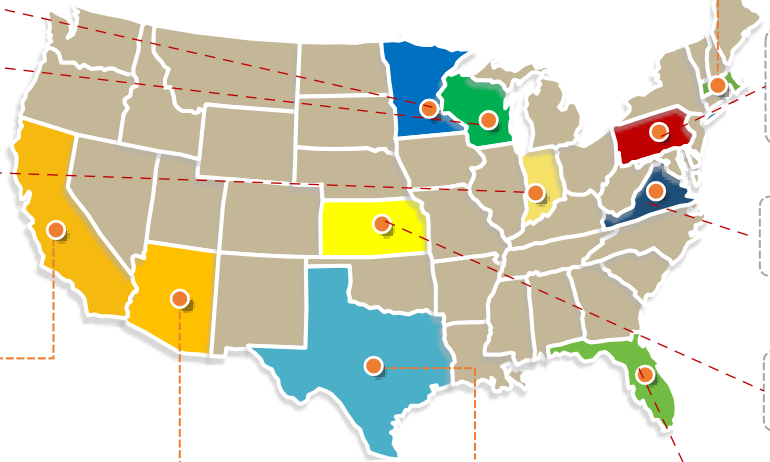
Baseline
- MR imaging
  - MRE
  - MRI-PDFF
- Biobanking

Year 2
- MR imaging
  - MRE
  - MRI-PDFF
- Biobanking

Year 4
- MR imaging
  - MRE
  - MRI-PDFF
- Biobanking

Central Review:
Pathology (baseline liver biopsy)
MR imaging (baseline, Y2, Y4)

GOLDMINE Sites



International
- Hospices Civils de Lyon
- Yokohama City University
- National University Singapore

Minnesota
- Mayo Clinic

Wisconsin
- University of Wisconsin

Indiana
- Indiana University

California
- UC San Diego
- UC Davis
- UCSF
- Cedars Sinai

Arizona
- Arizona Liver Health

Texas
- Pinnacle Clinical Research
- Baylor
- Michael DeBakey VA (Baylor)

Massachusetts
- Massachusetts General Hospital
- Boston University

Pennsylvania
- UPMC
- Jefferson University

Virginia
- Hunter Holmes McGuire VA (VCU)

Kansas
- Kansas University

Florida
- University of Florida Health at Jacksonville

GOLDMINE CONSORTIUM DESIGN

- **Longitudinal international multi-center imaging study**

Patients with biopsy-proven NAFLD
- Follow-up 10 years

600 – 1000 participants

- 150 – 200 NAFLD-cirrhosis
- 450 – 800 NAFLD without cirrhosis

Event rate : 600 participants: 60 events
1000 participants: 92 events

Patients with biopsy-proven NAFLD or NASH-cirrhosis

Standardized research visit every year

Questionnaires
- AUDIT, Skinner Lifetime drinking History
- Physical activity, Food

Physical examination
Medical history and medication

Fasting labs
CBC, complete metabolic panel (including liver enzymes), iron, total iron-binding capacity, ferritin, uric acid, hbA1c, C-peptide, insulin, lipid profile, hepatitis panel (including HBsAg and anti-HCV),HIV, prothrombin time, C-reactive protein

Imaging
MRE
MRI-PDFF
CAP/VCTE

NAFLD related outcomes

Y0 Y1 Y2 Y3 Y4 Y5 Y6 Y7 Y8 Y9 Y10

Baseline
MRI-PDFF MRE
Biobanking Stool collection
Fibroscan CAP/VCTE

Year 2
MRI-PDFF MRE
Biobanking Stool collection
Fibroscan CAP/VCTE

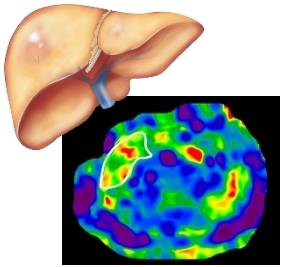
Year 4
MRI-PDFF MRE
Biobanking Stool collection
Fibroscan CAP/VCTE

Primary Outcomes
- **Progression to Cirrhosis**: biopsy-confirmed cirrhosis, or other imaging evidence of cirrhosis.
- **Hepatic Decompensation**: defined as liver-related events requiring hospitalization (*e.g.* HCC, liver transplantation, ascites, hepatorenal syndrome, variceal bleeding, etc.)
- **Death due to Liver Disease**

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

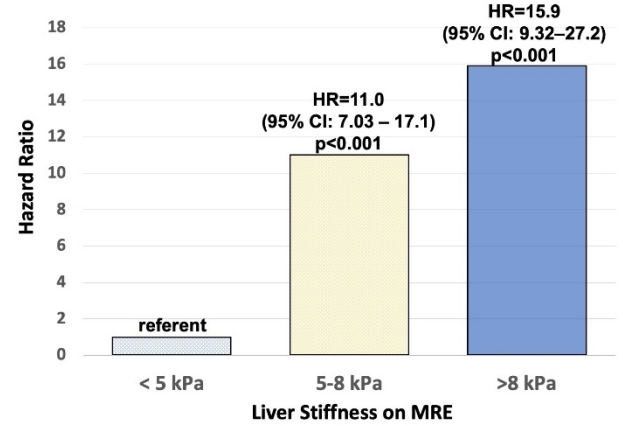
Six international cohorts with nonalcoholic fatty liver disease

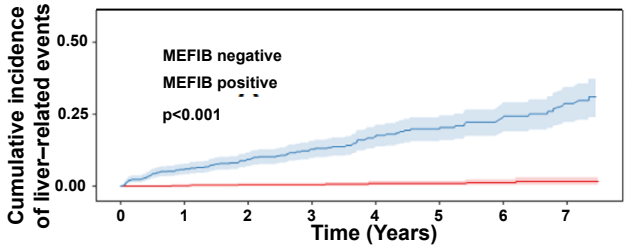
Underwent magnetic resonance elastography



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.

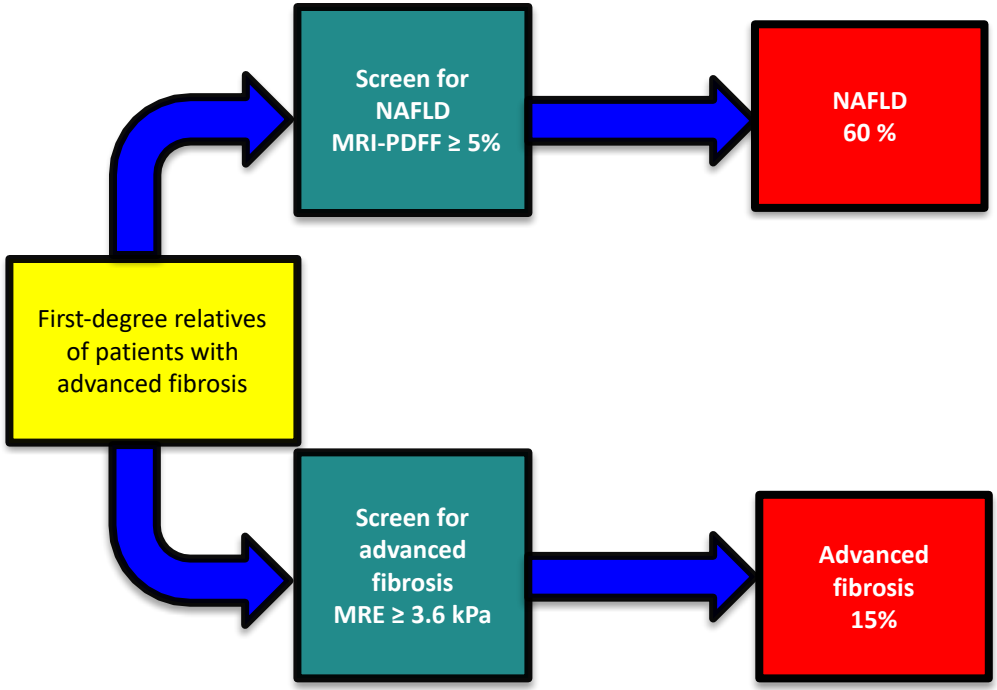




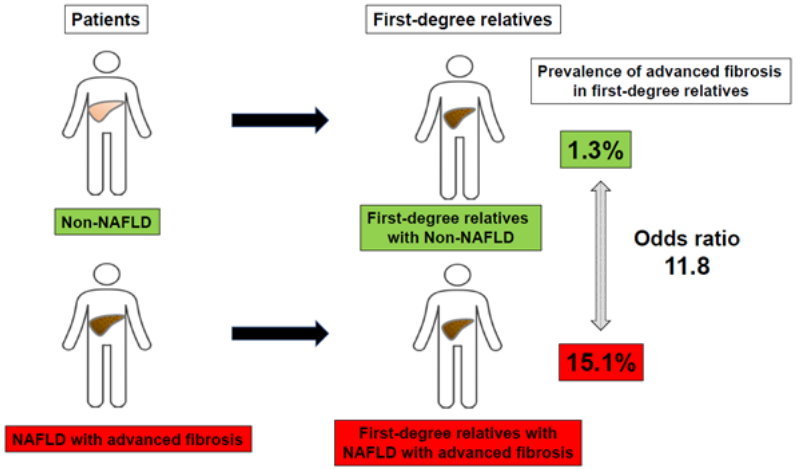
Ajmera……Loomba. Gastroenterology 2022

Who to screen new data?

First-degree relatives of patients with advanced fibrosis have increased risk of advanced fibrosis due to NAFLD

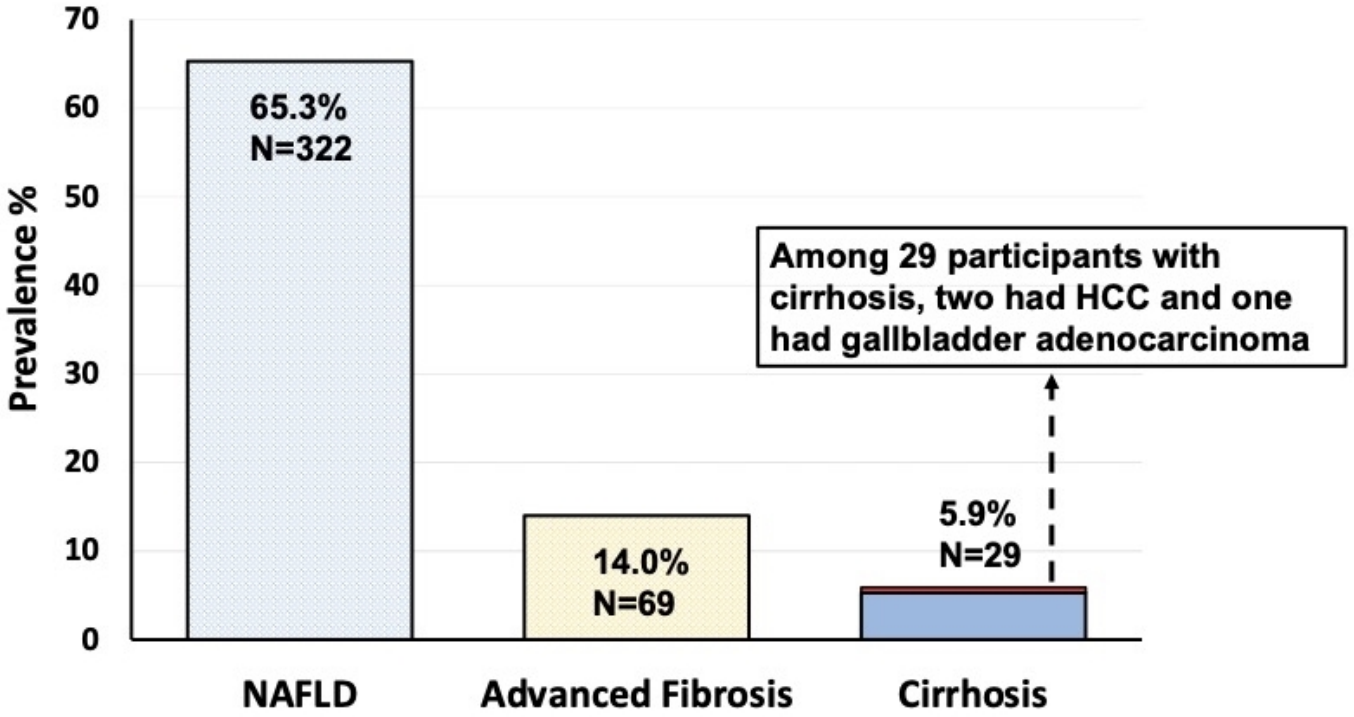


Family history of advanced fibrosis in NAFLD increases the risk by 12 times independent of age, sex, and



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

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



Treatment landscape

Lifestyle Recommendations for Treating NAFLD/NASH

Caloric intake reduction
≥30% or
~750-1,000 kcal/day
improved insulin resistance and hepatic steatosis

*Limit consumption of fructose-enriched beverages

Weight loss
of 3% to 5% can improve steatosis, but 6% to 10% is needed to improve NASH/fibrosis

Exercise
alone may reduce steatosis, but effect on other histologic features unknown

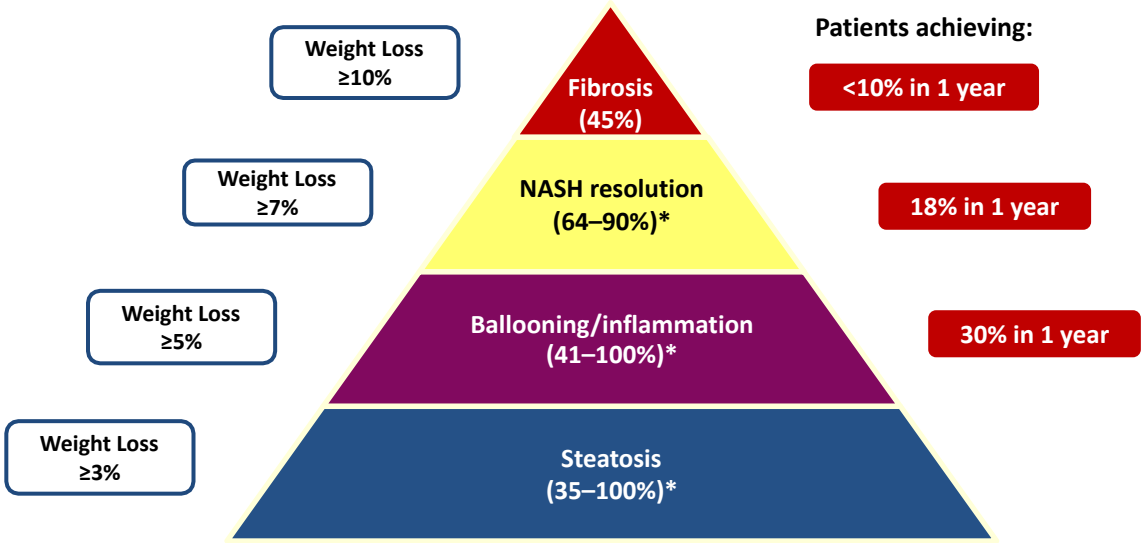
No heavy alcohol consumption
Insufficient data to guide recommendations regarding nonheavy alcohol consumption

**Drink ≥2 cups of caffeinated coffee daily

Statin use in patients with dyslipidemia
Aspirin use in diabetics
Mediterranean diet
Avoid sugar and sugar containing beverages
Bariatric surgery in those with morbid obesity and co-morbidities

Chalasani N et al. *Hepatology*. 2018;67(1):328-357; Diehl AM, Day C. *N Engl J Med*. 2017;377:2063-72.

Weight loss pyramid and NASH related outcomes



*Depending on degree of weight loss.
Information adapted from Vilar-Gomez E et al. Gastroenterology. 2015;149:367–378; Promrat K et al. Hepatology. 2010;51:121–129; Harrison SA et al. Hepatology. 2009;49:80–86; Wong VWS et al. J Hepatol. 2013;59:536–542.

Safety and tolerability of pharmacologic therapies

Vitamin E

- Increased all cause mortality risk at >400 IU/day
- Increased hemorrhagic stroke risk
  - Also shows reduced ischemic stroke risk
- Increased prostate carcinoma risk (P = 0.06)

Pioglitazone

- Increased risk of edema and weight gain
- Increased risk of osteoporosis
- Increased bladder cancer risk (HR: 1.63) in some, but not all studies

Use of these agents should be personalized for selected patients with histologically confirmed NASH after careful consideration of risk/benefit ratio

Key considerations: CVD risk reduction

- Statin use
- Lifestyle interventions
- Bariatric surgery when indicated

HR, hazard ratio; IU, international unit. Miller ER et al. Ann Intern Med. 2005;142(1):37–46; Schurks M et al. BMJ. 2010;341:c5702; Klein EA et al. JAMA. 2011;306:1549–1556; Basu A et al. Diabetes Care. 2006;29:510–514; Schwartz AV et al. J Clin Endocrinol Metab. 2006;91:3349–3354; Tuccori M et al. BMJ. 2016;352:i1541; Lewis JD et al. JAMA. 2015;314:265–277.
Pioglitazone and vitamin E are not approved for treatment of NASH

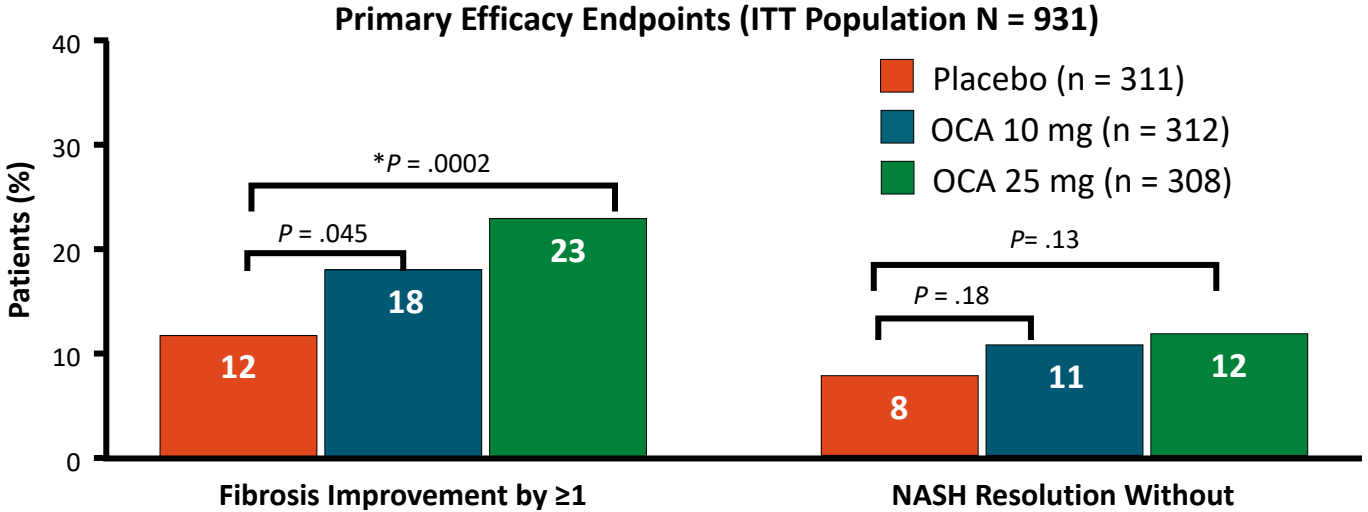
NASH agents in clinical development

	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 comorbidity
- **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.

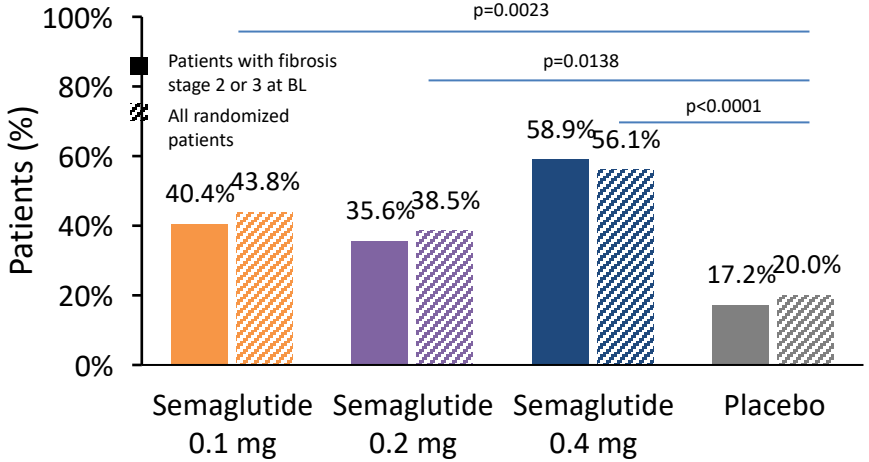
Main issues with FXRs

- **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

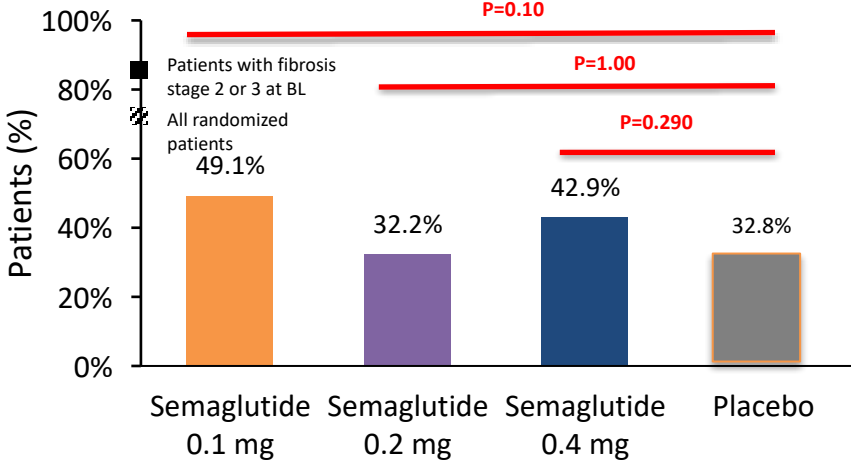
Resolution of steatohepatitis and no worsening in liver fibrosis

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



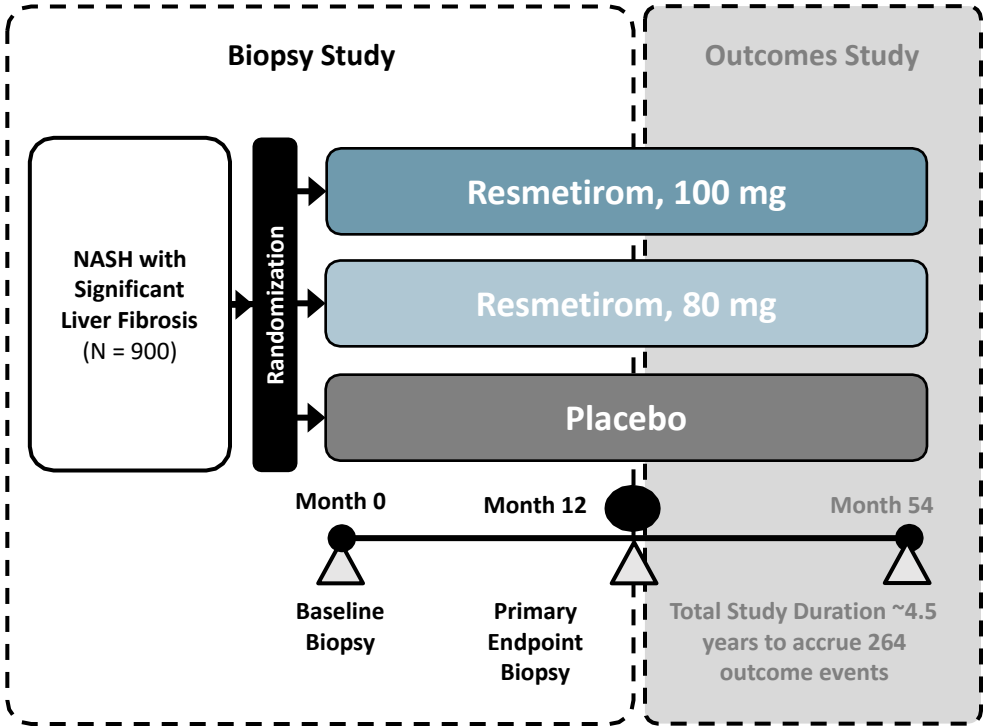
N=320

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

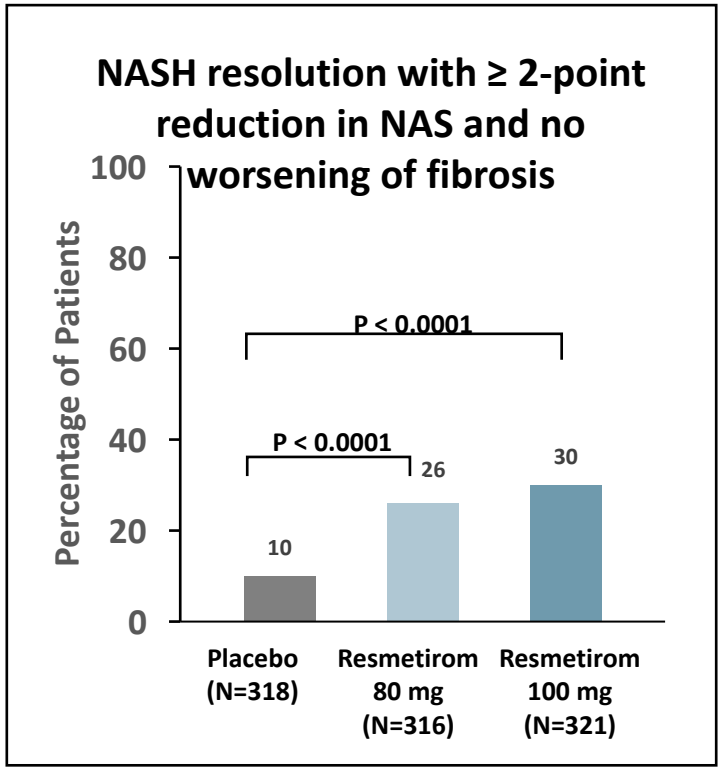
MAESTRO-NASH Phase 3 Trial

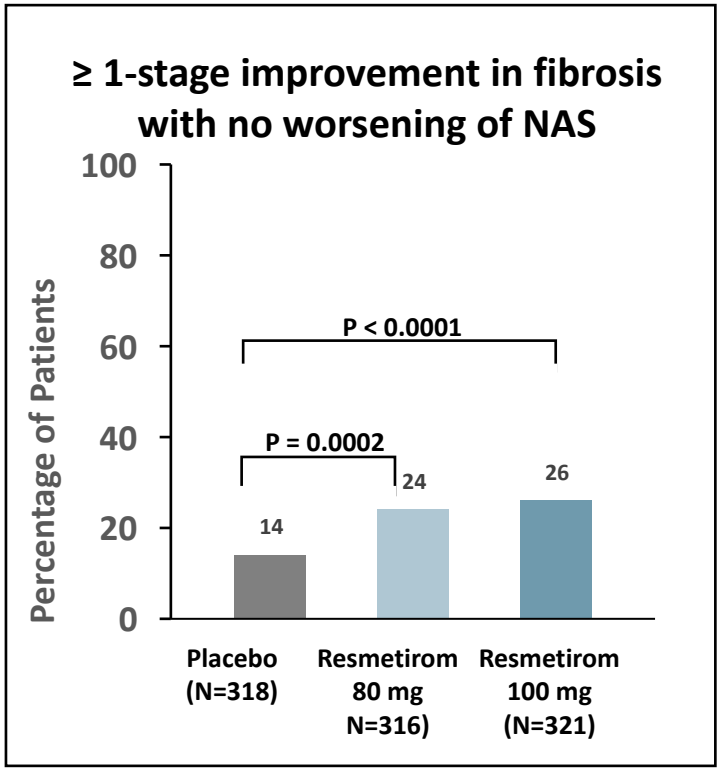


Primary endpoints:

1. NASH resolution and ≥2-point NAS reduction with no worsening of fibrosis
2. Fibrosis improvement by at least one stage with no worsening of NAS

MAESTRO-NASH: Resmetirom, 80 mg and 100 mg, achieved both primary endpoints at 52 weeks





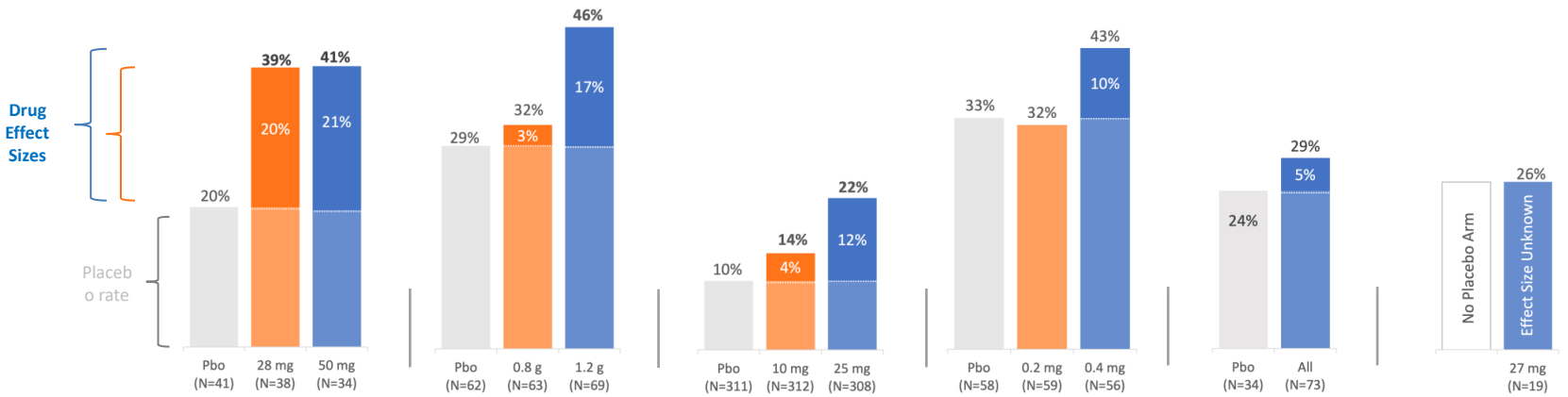
Madrigal press release and NASH TAG 2023

Fibrosis improvement landscape monotherapies

Proportion of Subjects with ≥1 Stage Improvement in Fibrosis

Efruxifermin	**Lanifibranor**	**Obeticholic Acid**	**Semaglutide**	**Resmetirom**	**Pegozafermin**
24 Wks[1] (Ph2b)	24 Wks[2] (Ph2b)	72 Wks[3] (Ph3)	72 Wks[3] (Ph2b)	36 Wks[4] (Ph2)	20 Wks[5] (Ph2a)
F2-F3 (66% F3)	F1-F3	F2-F3 (54% F3)	F2-F3 (69% F3)	F1-F3 (20% F3)	F2-F3 (65% F3)
Weekly Injection	Daily Oral	Daily Oral	Daily Injection	Daily Oral	Weekly Injection

By Reported Effect Size
(Treatment Minus Placebo)



Note: These data are derived from different clinical trials at different points in time, with differences in trial design and patient populations. As a result, cross-trial comparisons cannot be made, and no head-to-head clinical trials have been conducted.

Baseline and Week 24 biopsies available; 2 End-of-study biopsy available with no major protocol deviations; 3 Missing biopsies were imputed as non-responders; 4 Completed 36 weeks of treatment and had end-of-study biopsy; 5 End-of-study biopsy available.

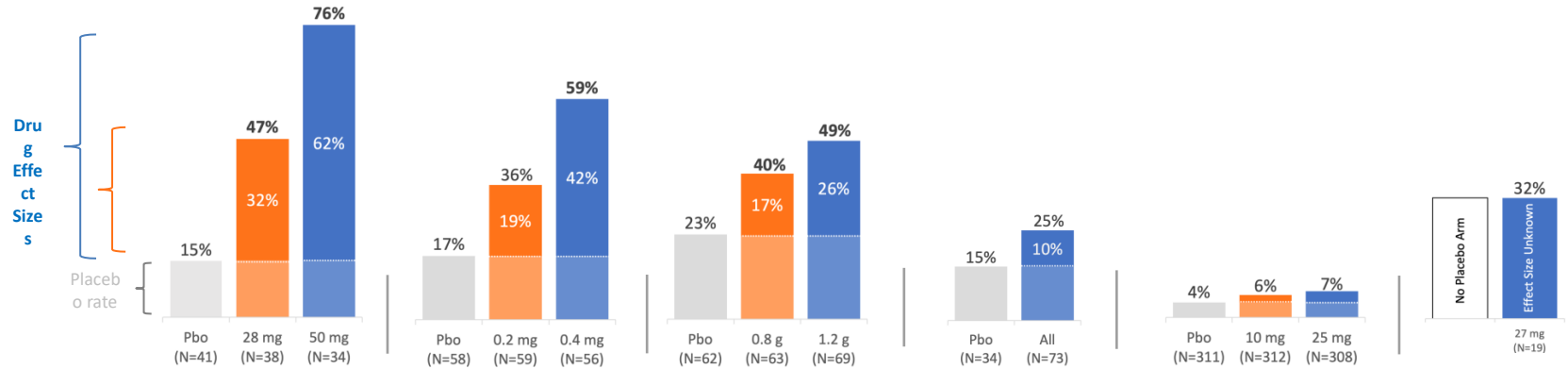
Lanifibranor - Francque et al. (2021) New Engl J Med 385, 1547–1558; Obeticholic acid - Intercept (2022) July 7 Press Release; Semaglutide - Newsome et al. (2020) New Engl J Med 384, 1113–1124; Resmetirom - Harrison, S et al. (2019) Lancet 394(10213):2012-24; Pegozafermin - 89Bio (2022) August 1 Corporate Presentation.

NASH resolution landscape monotherapies

Proportion of Subjects with Resolution of NASH without Worsening of Fibrosis

Efruxifermin	Semaglutide	Lanifibranor	Resmetirom	Obeticholic Acid	Pegozafermin
24 Wks[1] (Ph2b)	72 Wks[2] (Ph2b)	24 Wks[3](Ph2b)	36 Wks[4] (Ph2)	72 Wks[2] (Ph3)	20 Wks[6] (Ph2a)
F2-F3 (66% F3)	F2-F3 (69% F3)	F1-F3	F1-F3 (20% F3)	F2-F3 (54% F3)	F2-F3 (65% F3)
Weekly Injection	Daily Injection	Daily Oral	Daily Oral	Daily Oral	Weekly Injection

By Reported Effect Size
(Treatment Minus Placebo)



Note: These data are derived from different clinical trials at different points in time, with differences in trial design and patient populations. As a result, cross-trial comparisons cannot be made, and no head-to-head clinical trials have been conducted.

[1] Baseline and Week 24 biopsies available; [2] Missing biopsies were imputed as non-responders; [3] End-of-study biopsy available with no major protocol deviations; [4] Completed 36 weeks of treatment and had end-of-study biopsy; [5] End-of-study biopsy available.

Semaglutide - Newsome et al. (2020) New Engl J Med 384, 1113–1124; Lanifibranor - Francque et al. (2021) New Engl J Med 385, 1547–1558; Resmetirom - Harrison, S et al. (2019) Lancet 394(10213):2012-24; Obeticholic acid - Intercept (2022) July 7 Press Release; Pegozafermin - 89Bio (2022) August 1 Corporate Presentation.

Clinical Drug Development Pathway in NASH

- Phase 1
- Phase 2A
- Phase 2B
- Phase 3
- Phase 4 (and pediatric plan)

Summary

- **Non-invasive assessment is taking the center stage in risk stratification and response assessment**

- **Fibrosis improvement requires longer-term treatment and typically requires liver specific targeted therapies**

- **Several classes of drugs are showing promise in the treatment of NASH**
  - **FXR**
  - **THBR**
  - **GLP-1 analogues**
  - **FGF-21**

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 Guidance

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

ACG 2023
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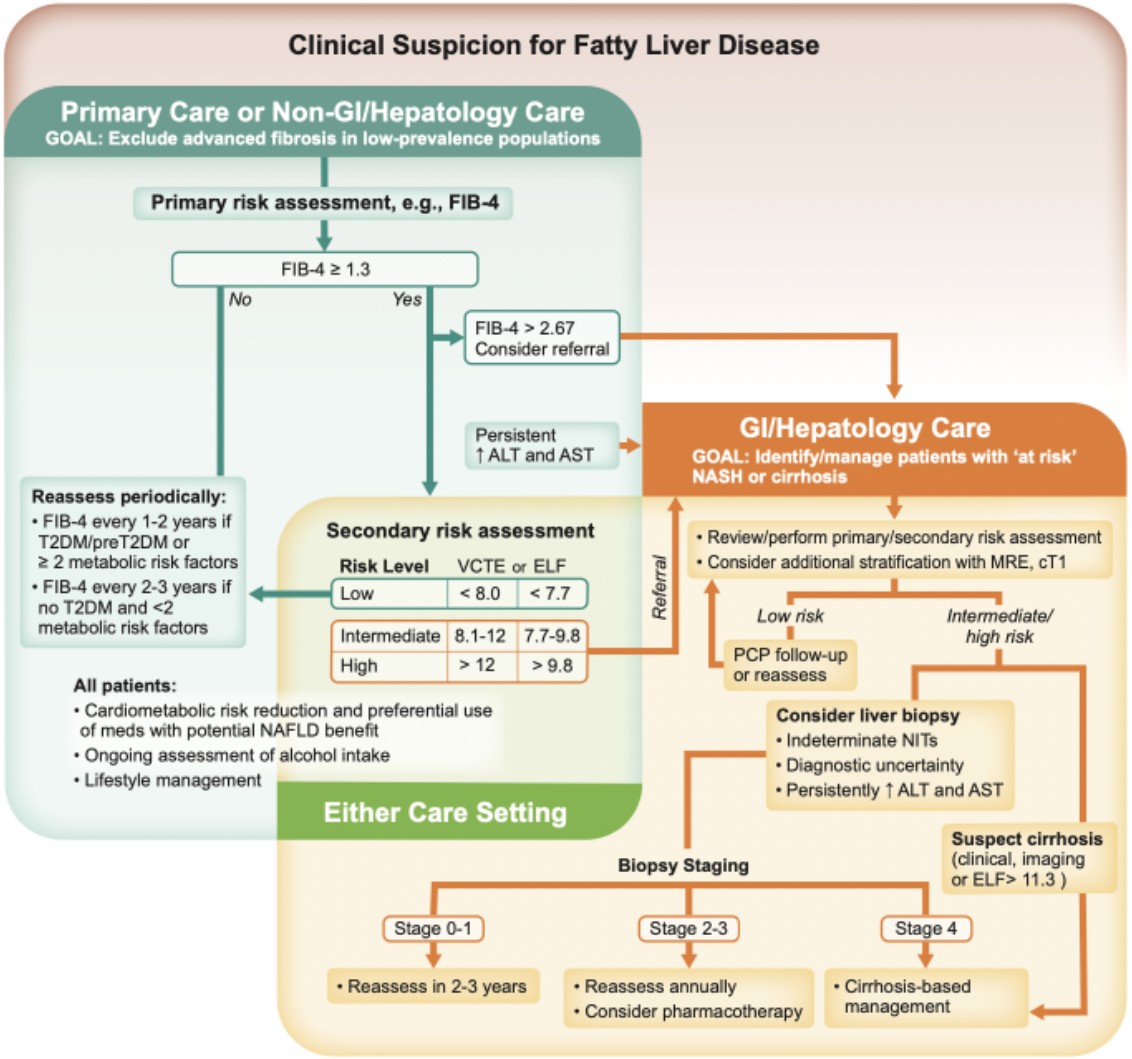
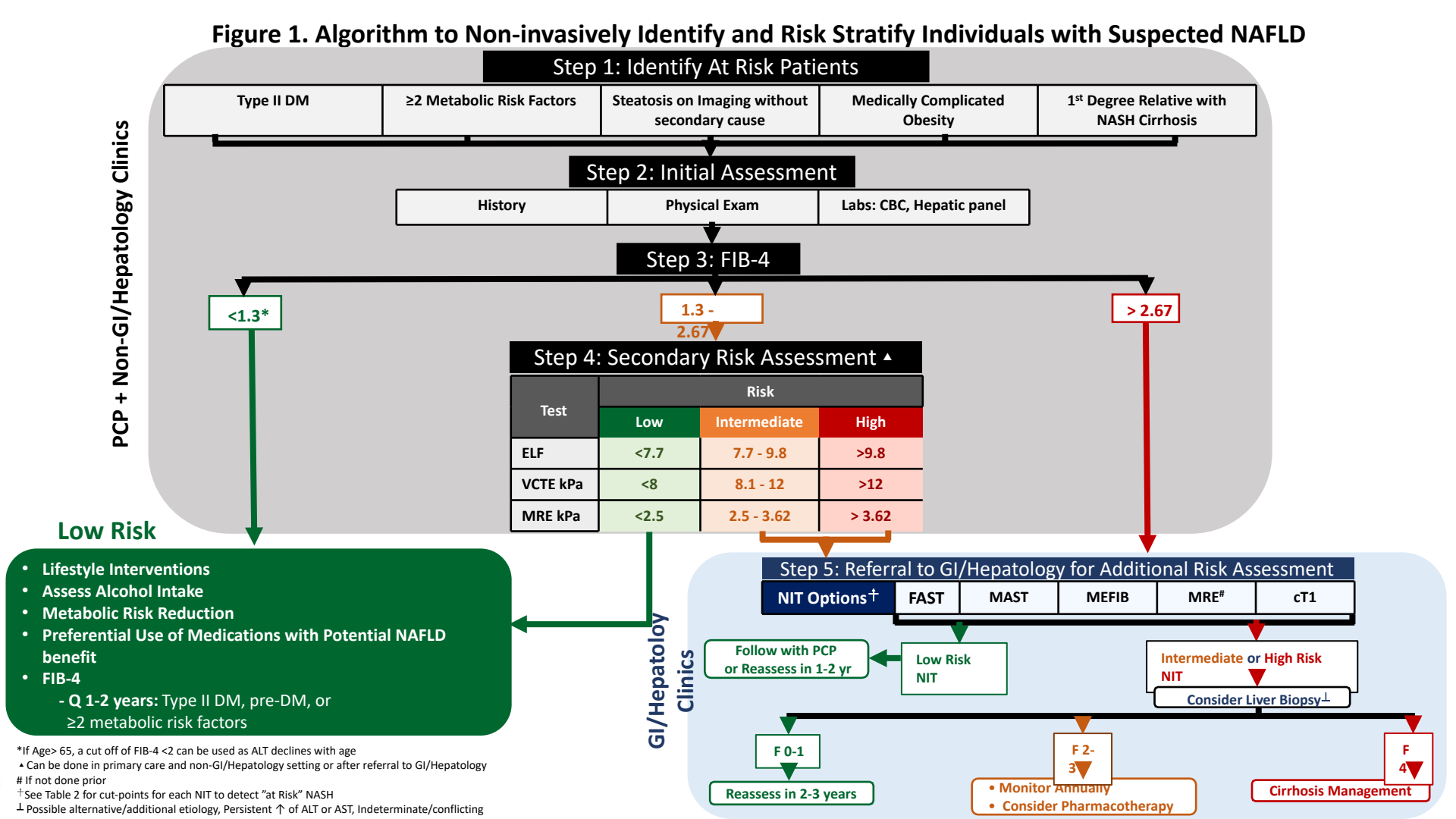

Clinical Suspicion for Fatty Liver Disease
Primary Care or Non-GI/Hepatology Care
GOAL: Exclude advanced fibrosis in low-prevalence populations
Primary risk assessment, e.g., FIB-4
FIB-4 ≥ 1.3
No
Yes
FIB-4 > 2.67
Consider referral
Persistent
↑ ALT and AST
GI/Hepatology Care
GOAL: Identify/manage patients 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
Consider liver biopsy
• Indeterminate NITs
• Diagnostic uncertainty
• Persistently ↑ ALT and AST
All patients:
• Cardiometabolic risk reduction and preferential use of meds with potential NAFLD benefit
• Ongoing assessment of alcohol intake
• Lifestyle management
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

Figure 1. Algorithm to Non-invasively Identify and Risk Stratify Individuals with Suspected NAFLD



*If Age> 65, a cut off of FIB-4 <2 can be used as ALT declines with age

▲ Can be done in primary care and non-GI/Hepatology setting or after referral to GI/Hepatology

If not done prior

† See Table 2 for cut-points for each NIT to detect "at Risk" NASH

⊥ Possible alternative/additional etiology, Persistent ↑ of ALT or AST, Indeterminate/conflicting

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.*

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.***

Thank you

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