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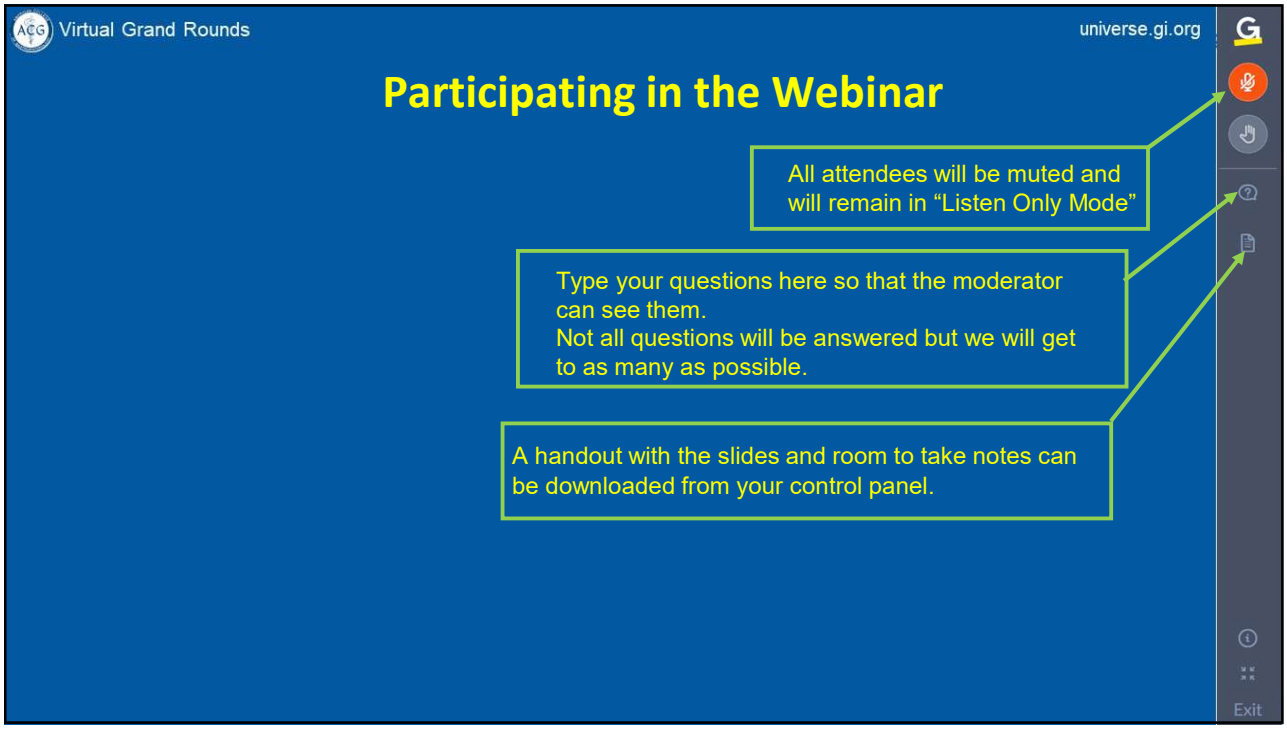
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Gilead Sciences: Research Grant (Institution)
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Mary E. Rinella, MD, FACG

Dr. Rinella has no relevant financial relationships with ineligible companies.

Joseph K. Lim, MD, FACG

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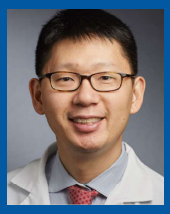

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NAFLD vs. MAFLD: What's in a Name?

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ACG Virtual Grand Rounds – June 15, 2023

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Objectives

- Discuss the differences between nonalcoholic fatty liver disease (NAFLD) and metabolic dysfunction-associated liver disease (MAFLD) nomenclature
- Understand the differences in clinical outcomes associated with NAFLD vs. MAFLD

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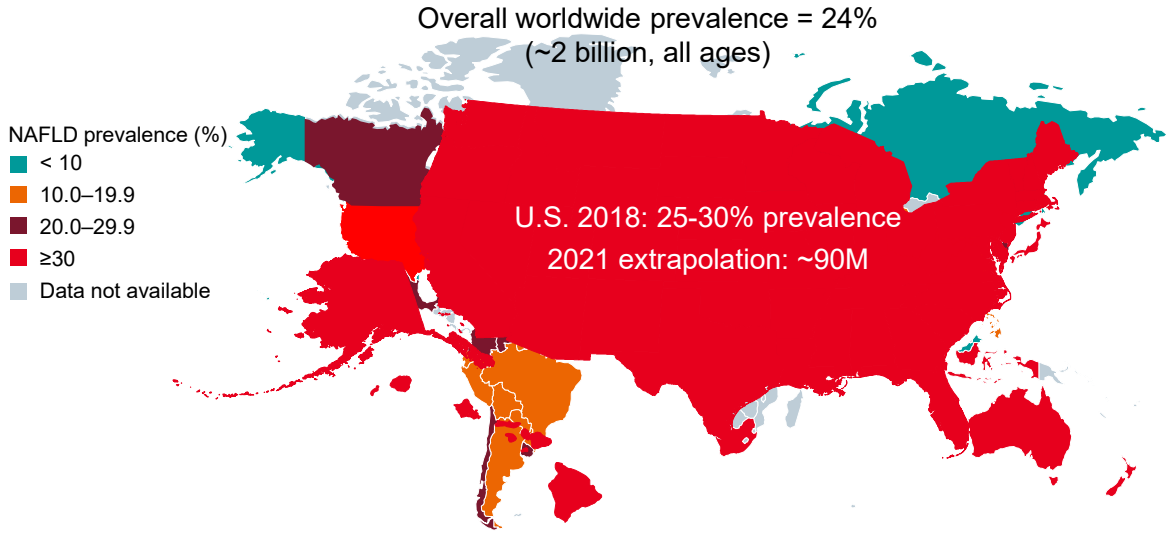
NAFLD Clinical Burden Globally and in the United States



Younossi Z et al. *Nat Rev Gastro Hepat*. 2018;15:11–20; Estes C et al. *Hepatology*. 2018;67:123-33.

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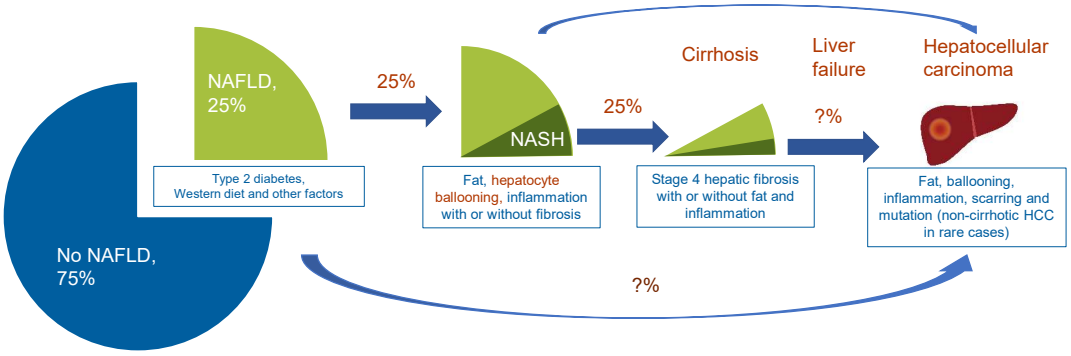
Natural History of NAFLD

- Increasing worldwide
- 25% of the global adult population
- Metabolic co-morbidities associated with increased NAFLD risk
- ***Diagnosis requires exclusion of potential concurrent liver diseases***



Progression: NAFLD: 1 stage fibrosis over 14 years; NASH: 1 stage fibrosis over 7 years

Diehl AM, Day C. *N Engl J Med*. 2017;377:2063-72; Singh S et al. *Clin Gastroenterol Hepatol*. 2015;13:643-54.

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NAFLD vs. MAFLD

- Presence of metabolic co-morbidities is a key risk factor:
  - Overweight/obesity, visceral adiposity
  - Insulin resistance and diabetes
  - Hypertension
  - Dyslipidemia
  - Metabolic syndrome
- Studies evaluating NAFLD have generally relied on exclusion of potential competing contributors of chronic liver disease and hepatic steatosis
- However, NAFLD can co-exist with other chronic liver diseases, and it may be challenging to tease out specifically which is the “primary” culprit
- MAFLD nomenclature proposed to more comprehensively capture cardio-metabolic risk factors without requiring exclusion of potential competing etiologies

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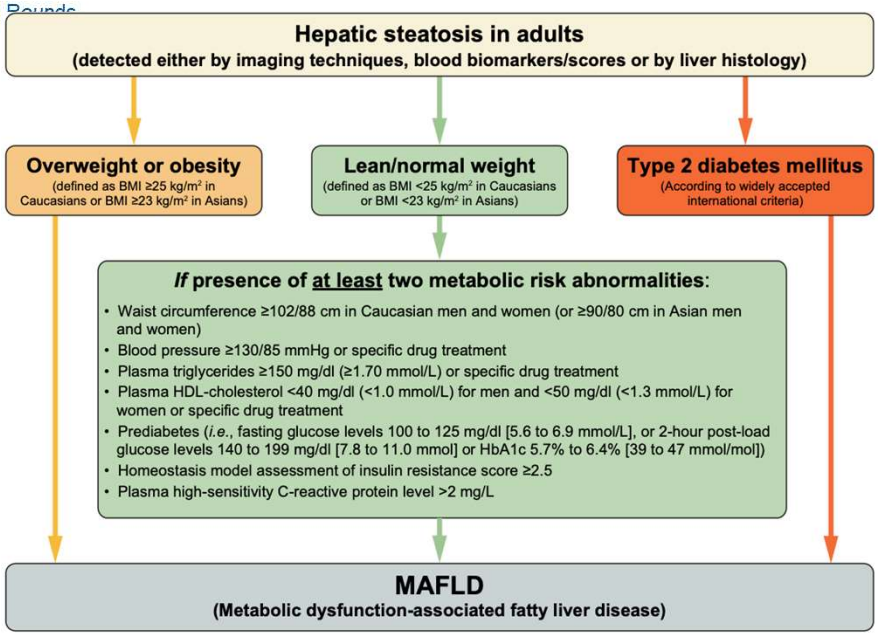

Eslam et al. *J Hepatol.* 2020

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What Are the Implications?

- How does MAFLD nomenclature alter the epidemiology of fatty liver disease?
- Are there distinct clinical differences in disease presentation or long-term clinical outcomes between NAFLD vs. MAFLD?

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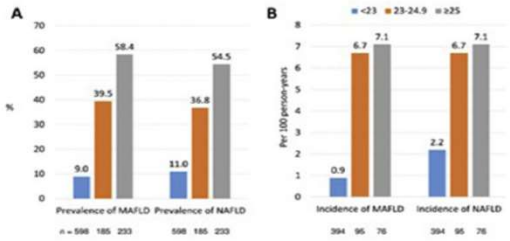
Recently, a group of hepatologists proposed to rename nonalcoholic fatty liver disease (NAFLD) as metabolic (dysfunction)-associated fatty liver disease (MAFLD).

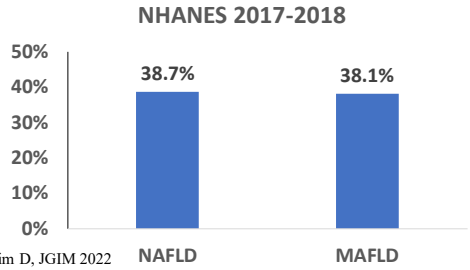
Apart from a change in name, the definition of MAFLD requires the presence of metabolic risk factors but allows the inclusion of patients with concomitant liver diseases.

	MAFLD	NAFLD
Demonstration of fatty liver by imaging, histology or prediction scores	Required	Required
Exclusion of excessive alcohol consumption	Not required	Required
Exclusion of viral hepatitis and other liver diseases	Not required	Required
Exclusion of secondary causes of fatty liver (e.g. tamoxifen or methotrexate)	Not required	Required
Presence of overweight/obesity, type 2 diabetes or 2 other metabolic factors	Required	Not required

In a population study using proton-magnetic resonance spectroscopy, we showed that the prevalence of MAFLD and NAFLD was similar at 25.9% and 25.7%, respectively. However, the incidence of MAFLD (2.8 per 100 person-years) was 25% lower than that of NAFLD (3.7 per 100 person-years). The difference was more marked among individuals with low body mass index.



- NHANES 2017-2018 data from U.S.
- NAFLD defined by CAP >263 dB/m and MAFLD defined using proposed definitions
- Similar prevalence among U.S. adults population



Wong, VW, CGH 2021; Wong R, CGH 2022; Kim D, JGIM 2022

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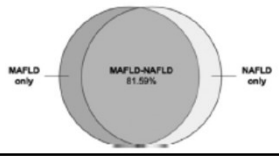
NAFLD vs. MAFLD Epidemiology

- Prospective cross sectional random sampling of households from Victoria, Australia
  - A total of 722 participants were included. Mean age was 59.3 ± 16 years, and 55.3% were women with a median body mass index of 27.8 kg/m2
  - Prevalence of MAFLD was 47.2% vs. prevalence of NAFLD was 38.7%
- Lim et al performed a meta-analyses inclusive of 22 articles involving 379,801 patients to evaluate MAFLD prevalence and patient characteristics
  - Pooled prevalence of MAFLD was 39.22% (95% CI, 30.9–48.2) with the highest prevalence in Europe and Asia
  - Among 9,006 patients with MAFLD, the pooled prevalence of patients who met the criteria of both MAFLD and NAFLD was 81.6% (95% CI, 66.5–90.8).



Kemp W, *Journal of Gastroenterology and Hepatology. 2022;* Lim G, CGH 2021

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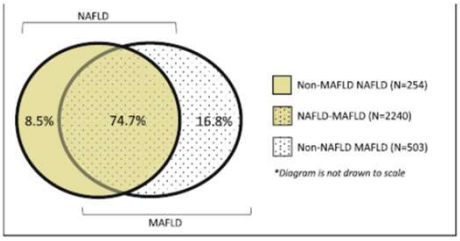
NAFLD vs. MAFLD Clinical Characteristics and Outcomes

- Nguyen et al utilized the 1988-1994 NHANES III and identified 2,997 individuals with fatty liver based on ultrasound.
- Categorized in 3 groups based on presence of NAFLD and/or MAFLD
- Compared to NAFLD only group, individuals with MAFLD or combined NAFLD/MAFLD were older and had significant greater prevalence of cardio-metabolic co-morbidities (e.g. diabetes, hypertension, dyslipidemia, stroke, cardiovascular disease)



Nguyen V, et al. CGH 2021;19:2172–2181

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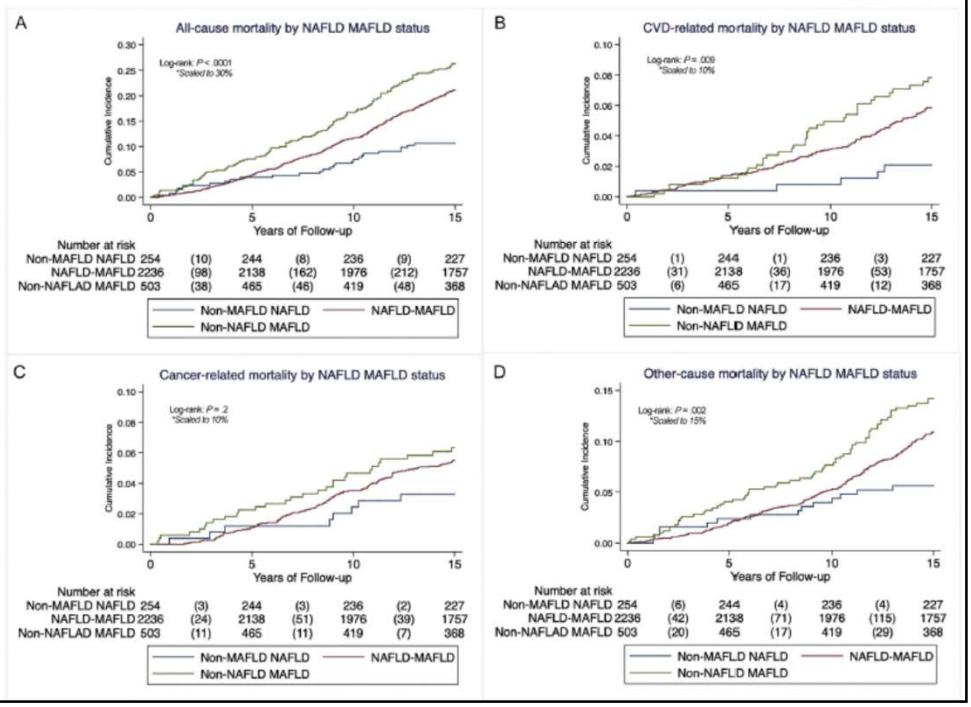
- On multivariate analyses, MAFLD only patients had significantly greater risk of overall mortality compared to NAFLD only patients (HR 2.4, 95% CI 1.2-4.6, p=0.01.
- No difference in mortality was seen in patients with NAFLD-MAFLD combined



Nguyen V, et al. CGH 2021;19:2172–2181

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NAFLD vs. MAFLD Clinical Characteristics and Outcomes

- Lim et al meta-analyses inclusive of 22 articles involving 379,801 patients:
  - Pooled prevalence of MAFLD was 39.22% (95% CI, 30.9–48.2)
  - MAFLD patients were more likely to be men and had significantly higher risk of metabolic co-morbidities

Table 3. Risk Factors of MAFLD vs NAFLD

	Total sample size						
Risk factors	MAFLD	NAFLD	Effect Size	95% CI	*P*-value	I^2	Cochran Q
Age, *y*	20,378	18,832	0.06	−0.48 to 0.59	.8400	81.60%	< .001
Gender, *male*	20,378	18,832	1.24	1.10–1.39	**< .0010**[a]	80.30%	< .001
BMI, *kg/m²*	19,234	17,783	0.46	0.12–0.80	**.0078**[a]	92.70%	< .001
Hypertension	19,925	18,756	1.17	1.07–1.29	**.0007**[a]	66.90%	< .001
Diabetes	20,377	18,829	1.09	1.00–1.19	**.0420**[a]	49.20%	.016
Hyperlipidemia	10,116	9604	1.39	0.54–3.55	.4900	98.70%	< .001
Hba1c, %	8542	8046	0.02	0.00–0.04	.0810	57.80%	.020
HDL, *mmol/L*	10,116	9604	-0.02	−0.04 to 0.00	**.0290**[a]	66.40%	.002
TG, *mmol/L*	10,988	10,363	0.09	0.04 to 0.14	**< .0010**[a]	83.30%	< .001
LDL, *mmol/L*	9003	8718	0.01	−0.04 to 0.06	.6900	54.10%	.033
AST, *U/L*	12,257	11,234	0.89	0.35 - 1.44	**.0014**[a]	79.30%	< .001
ALT, *U/L*	12,257	11,234	1.32	0.58–2.07	**.0005**[a]	74.00%	< .001
NFS	7607	7229	0.17	0.10–0.25	**< .0001**[a]	46.80%	.110
Fibrosis-4 score	7827	7372	0.04	0.03–0.06	**< .0001**[a]	0.00%	.810
eGFR, *mL/min/1.73m²*	13,819	13,798	−0.75	−1.55 to 0.05	.0660	48.10%	.100

Lim G et al. CGH 2021

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NAFLD vs. MAFLD Clinical Characteristics and Outcomes

- Younossi, et al. utilized data from NHANES III (1988-94) and NHANES (2017-2018) to compared long term outcomes between NAFLD vs. MAFLD
- Fatty liver disease was defined as moderate to severe hepatic steatosis by ultrasound (NHANES III) or controlled attenuation parameter ≥285 dB/m (NHANES 2017–2018)
- NAFLD was defined as fatty liver disease without other liver diseases and excess alcohol use.
- MAFLD was defined based on existing criteria, which includes presence of fatty liver disease and metabolic co-morbidities.

Younossi, et al. Hepatology. 2022;00:1–15.

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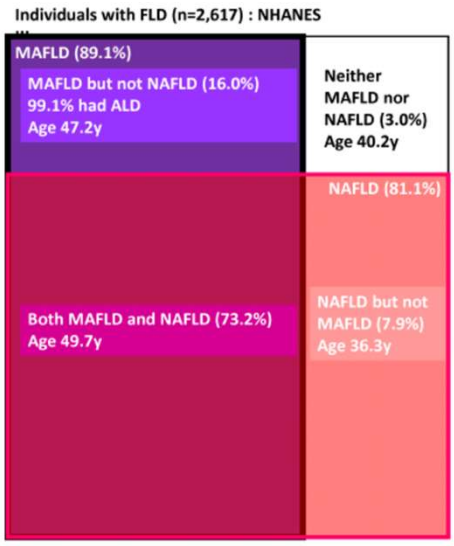
- Among 12,878 eligible individuals in NHANES III, 2617 were identified with fatty liver.
  - 89.1% (n = 2332) could be classified as MAFLD
  - 81.1% (n = 2122) could be classified as NAFLD
  - There was excellent concordance between the MAFLD+ and the NAFLD+ (Cohen's kappa coefficient of 0.83 [95% CI: 0.82–0.85])
- 15.4% of MAFLD had excessive alcohol use compared to none in NAFLD
- Similar characteristics except those unique to the definition of NAFLD vs. MAFLD



Younossi, et al. Hepatology. 2022;00:1-15.

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- During up to 27 years of follow-up (median, 22.8 years); IQR, 20.4–24.8 years), among individuals with MAFLD (MAFLD+) and subjects with NAFLD (NAFLD+), there were
  - 1049 and 881 deaths from all causes
  - 362 and 295 deaths associated with CVD,
  - 214 and 183 deaths associated with extrahepatic cancer
  - 70 and 38 deaths associated with liver
  - and 57 and 53 deaths associated with diabetes, respectively.
- No significant differences were identified in cumulative incidence rates of all-cause and cause-specific mortality between the groups

Characteristics	MAFLD+ (*n* = 2,332)	NAFLD+ (*n* = 2,122)
Low HDL[g]	59.33 (54.50–64.16)	59.70 (55.53–63.87)
Prediabetes[h]	38.66 (35.66–41.66)	35.11 (32.23–37.99)
Insulin resistance[i]	71.16 (68.09–74.23)	66.34 (62.83–69.85)
High C-reactive protein[j]	3.08 (2.06–4.10)	3.03 (2.10–3.97)
CKD, %	14.66 (12.33–16.98)	13.75 (11.51–16.00)
High cardiac risk, %	71.55 (66.30–76.80)	70.83 (64.58–77.09)
High-risk fibrosis, %[k]	1.96 (1.35–2.58)	1.45 (1.03–1.87)
History of, %		
Cancer	7.94 (6.41–9.47)	7.35 (5.88–8.81)
CVD	8.33 (6.80–9.87)	7.87 (6.27–9.46)
Family CVD	17.73 (15.20–20.26)	19.16 (16.38–21.94)
Cumulative Mortality[l], %		
All causes	44.98 (41.64–48.31)	41.53 (38.29–44.78)
Cardiac	15.52 (13.44–17.60)	13.88 (11.82–15.94)
Extrahepatic cancer	9.17 (7.54–10.81)	8.62 (6.64–10.59)
Liver	3.01 (1.99–4.03)	1.81 (0.95–2.66)
Diabetes	2.46 (1.41–3.51)	2.52 (1.28–3.76)

Younossi, et al. Hepatology. 2022;00:1–15.

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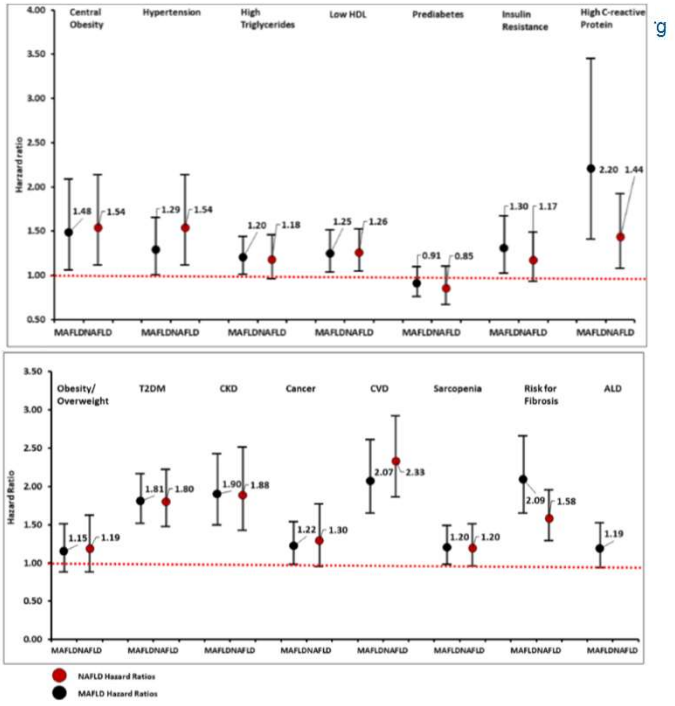
- Assessing risk factors for all cause mortality among both groups of individuals with NAFLD and individuals with MAFLD
- Central obesity, high triglycerides, high CRP, T2DM, CKD, history of CVD, and high-risk score for fibrosis were factors associated with an increased risk for all-cause mortality for both the groups
- In sensitivity analyses, MAFLD mortality outcome is influenced by ***ALD and the stage of fibrosis***, while the outcome of NAFLD mortality is driven primarily by ***insulin resistance and stage of fibrosis.***



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- Among 1594 individuals with fatty liver (NHANES 2017-2018), 98.5% could be classified as MAFLD and 93.0% could be classified as NAFLD.
- There were no differences in characteristics between MAFLD+ and NAFLD+.
- The agreement between diagnosis of MAFLD and NAFLD remained excellent with a Cohen's kappa of 0.94 (95% CI: 0.93–0.95).

TABLE 5 Odds ratios of risk factors for significant and advanced fibrosis among the MAFLD+ and among the NAFLD+: NHANES 2017–2018

	Significant fibrosis (liver stiffness >8.0 kPa)				Advanced fibrosis (liver stiffness >13.1 kPa)			
	MAFLD+		NAFLD+		MAFLD+		NAFLD+	
Risk factors	OR[a] (95% CI)	*p*	OR[a] (95% CI)	*p*	OR[a] (95% CI)	*p*	OR[a] (95% CI)	*p*
Metabolic risk abnormalities								
Central obesity	2.89 (1.15–7.27)	0.0273	3.48 (1.15–10.59)	0.0303	7.85 (1.77–34.80)	0.0100	13.90 (2.49–77.51)	0.0052
Hypertension	1.53 (1.03–2.27)	0.0376	1.73 (1.11–2.69)	0.0193	1.69 (0.80–3.58)	0.1537	2.36 (0.87–6.36)	0.0852
High triglycerides	1.22 (0.65–2.29)	0.5170	1.34 (0.70–2.58)	0.3572	0.52 (0.23–1.15)	0.0984	0.52 (0.23–1.17)	0.1044
Low HDL	1.41 (0.95–2.08)	0.0810	1.44 (1.00–2.08)	0.0492	1.82 (0.85–3.87)	0.1129	2.05 (1.01–4.16)	0.0475
Prediabetes	0.61 (0.38–0.97)	0.0401	0.63 (0.37–1.05)	0.0749	0.49 (0.26–0.92)	0.0282	0.55 (0.29–1.06)	0.0725
Insulin resistance	2.08 (0.78–5.53)	0.1321	2.20 (0.79–6.10)	0.1204	2.97 (0.62–14.18)	0.1583	3.95 (0.74–21.05)	0.1003
High C-reactive protein	2.21 (1.30–3.76)	0.0063	2.25 (1.27–3.97)	0.0085	4.33 (1.78–10.53)	0.0031	4.53 (1.54–13.36)	0.0093
Overweight/obesity	2.18 (0.85–5.61)	0.0988	4.48 (1.26–15.89)	0.0232	1.41 (0.29–6.90)	0.6495	2.98 (0.31–28.18)	0.3168
T2DM	4.81 (3.28–7.07)	<0.0001	5.30 (3.59–7.81)	<0.0001	4.78 (1.94–11.75)	0.0021	5.17 (1.80–14.85)	0.0047
CKD	1.47 (0.77–2.81)	0.2184	1.38 (0.70–2.73)	0.3340	0.32 (0.10–0.99)	0.0483	0.30 (0.10–0.86)	0.0280
History of cancer	1.05 (0.43–2.58)	0.9060	1.07 (0.42–2.73)	0.8815	1.13 (0.33–3.86)	0.8333	1.18 (0.31–4.52)	0.7913
History of CVD	1.49 (0.81–2.76)	0.1846	1.54 (0.81–2.93)	0.1722	1.31 (0.51–3.40)	0.5509	1.18 (0.38–3.63)	0.7563
Sarcopenia	1.68 (0.98–2.87)	0.0576	1.58 (0.94–2.65)	0.0784	1.84 (0.71–4.75)	0.1892	1.45 (0.60–3.49)	0.3815
Severe risk for fibrosis[b]	4.20 (1.43–12.39)	0.0127	4.67 (1.37–15.83)	0.0169	5.17 (1.84–14.55)	0.0040	5.52 (1.62–18.82)	0.0096
Excess alcohol use	0.96 (0.33–2.78)	0.9308			1.81 (0.34–9.59)	0.4580		
ALD	0.99 (0.34–2.90)	0.9793			1.81 (0.33–9.89)	0.4650		

Younossi, et al. Hepatology. 2022;00:1–15.

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Clinical Implications

- Assessing metabolic co-morbidities is critical in patients with chronic liver disease
- ***Optimizing treatment of metabolic co-morbidities*** is important in both NAFLD and MAFLD
- Concurrent alcohol use is a major distinguishing feature in MAFLD vs. NAFLD definitions, but bigger picture is the importance of ***accurate assessment of alcohol use and identification of unhealthy alcohol*** in all patients with liver disease
- Raising ***awareness of fatty liver*** in general as a major contributor to liver-related morbidity and mortality among patients and providers
- Need to improve early disease identification, linkage to care, reduce patient stigma, and expand resources to help improve management of co-morbidities as well as unhealthy lifestyles

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Take Home Points

- Despite differences in NAFLD vs. MAFLD nomenclature, there is significant overlap in disease epidemiology and clinical characteristics
- MAFLD prevalence is higher than NAFLD prevalence in some populations due to less restrictive MAFLD definition
- Metabolic co-morbidities are important risk factors for disease progression and mortality among both NAFLD and MAFLD
- Higher mortality seen in patients with MAFLD in some studies are likely driven by patients with unhealthy alcohol use and concurrent alcohol-related liver disease
- There is ongoing discussion regarding ideal nomenclature in this area.

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AT THE FOREFRONT
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Emerging therapy for NAFLD and Alcohol related liver disease

American College of Gastroenterology

2022/2023

Mary E. Rinella, MD
Professor of Medicine, Division of Gastroenterology & Hepatology
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Disclosures

- **Consulting past 12 months:** Boehringer Ingelheim, Cytodyn, Intercept Pharmaceuticals, GSK, Madrigal, NGM Biopharmaceuticals, Novo Nordisk, Sonic Incytes
- ***All consulting contracts cancelled as of 2021 during writing of the NAFLD guidelines***

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Active clinical trials in NASH

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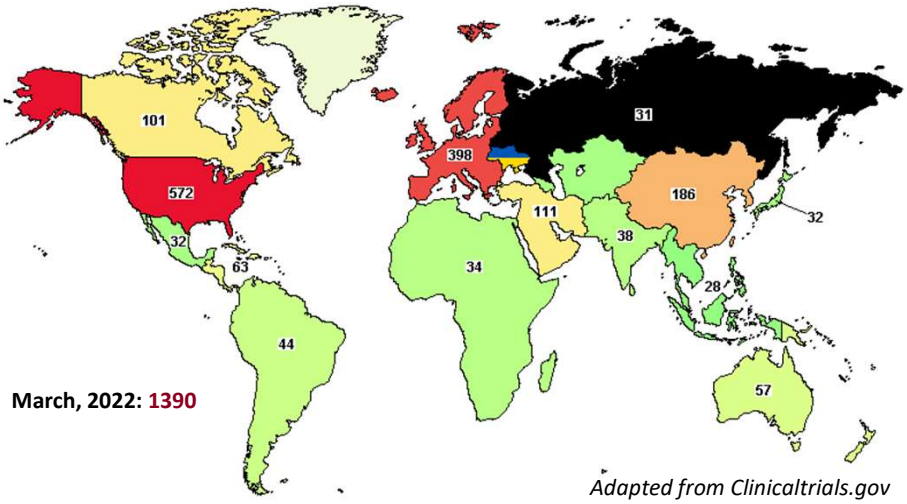

March, 2022: 1390

Adapted from Clinicaltrials.gov

Colors indicate the number of studies with locations in that region
Least — Most
Labels give the exact number of studies

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NASH: Agents in Phase 3 2021

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METABOLIC AGENTS

ANTI-FIBROTIC AGENTS

AGENT	MoA (TARGET)	TRIAL, PATIENTS AND ENDPOINT(S)	
Obeticholic Acid (Ocaliva)	**Lipotoxicity/oxidative stress** (FXR agonist)	**REVERSE (n=540*, compensated cirrhosis) – Q3 2020**[2] (1) > Fibrosis improvement ≥1 stage without NASH worsening	**REGENERATE (n=2065*, fibrosis stage 1–3) – PRO: FEB 2019, final Completion: OCT 2022**[3] (1) (2) > Fibrosis improvement ≥1 stage without NASH worsening > NASH resolution without fibrosis worsening / All-cause mortality and liver-related events
Resmetirom (MGL-3196)	**Lipotoxicity** (THR-ß agonist)	**MAESTRO-NASH (n=2000*, fibrosis stage 2–3) – PRO: JUN 2021, final Completion: MAR 2024**[4] (3) (3) > NASH resolution without worsening of fibrosis	
Aramchol	**Fatty acid synthesis** (SCD1 inhibitor)	**ARMOR (NASH and fibrosis) – PRO: JUN 2022, final Completion: DEC 2024**[5] (4) (4) > Histological endpoint at 52 weeks > Composite of progression to cirrhosis, liver-related clinical outcomes and all-cause mortality	Hold
Semaglutide	**GLP-1 RA**	**N=1200, SQ OW** > Part 1: Histological endpoint at 72 weeks, Part 2: Clinical events > Part liver-related clinical outcomes and all-cause mortality	Enrolling
Lanifibranor	**Pan-PPAR**	**N=1200, 800mg, 1200mg** > Part 1: Histological endpoint at 72 weeks, Part 2: Clinical events > Part liver-related clinical outcomes and all-cause mortality	Enrolling
Belapectin (GR-MD-02) (P2/3 adaptive)	**Fibrosis** (Galectin-3 inhibitor)	**NASH-RX (n=500*, compensated NASH cirrhosis) – Q4 2022**[3] (2) > NASH resolution without worsening of fibrosis	Enrolling

PRIMARY and FINAL READOUT

*. **1**. ClinicalTrials.gov. NCT02704403; **2**. ClinicalTrials.gov. NCT03439254; **3**. ClinicalTrials.gov. NCT02548351;. **4**. NCT03900429; **5**. https://www.prnewswire.com/il/news-releases/galmed-pharmaceuticals-announces-successful-completion-of-end-of-phase-2-meeting-with-fda-and-plan-for-start-of-phase-3-300827912.html (accessed Sept 2019).*

Adapted from S. Harrison

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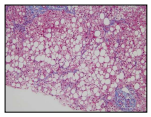
Currently accepted endpoints for non-cirrhotic NASH conditional approval

Resolution of NASH,
no worsening of fibrosis

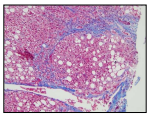
- ***Why?:*** NASH drives fibrosis
- ***Caveat:*** Resolution or improvement of NASH could reflect disease progression

Reduction in fibrosis,
no worsening of NASH

- ***Why?:*** Fibrosis linked to hard clinical outcomes
- ***Caveat:*** Can't worsen NASH, which drives disease



Stage 2-3



Stage 3-4

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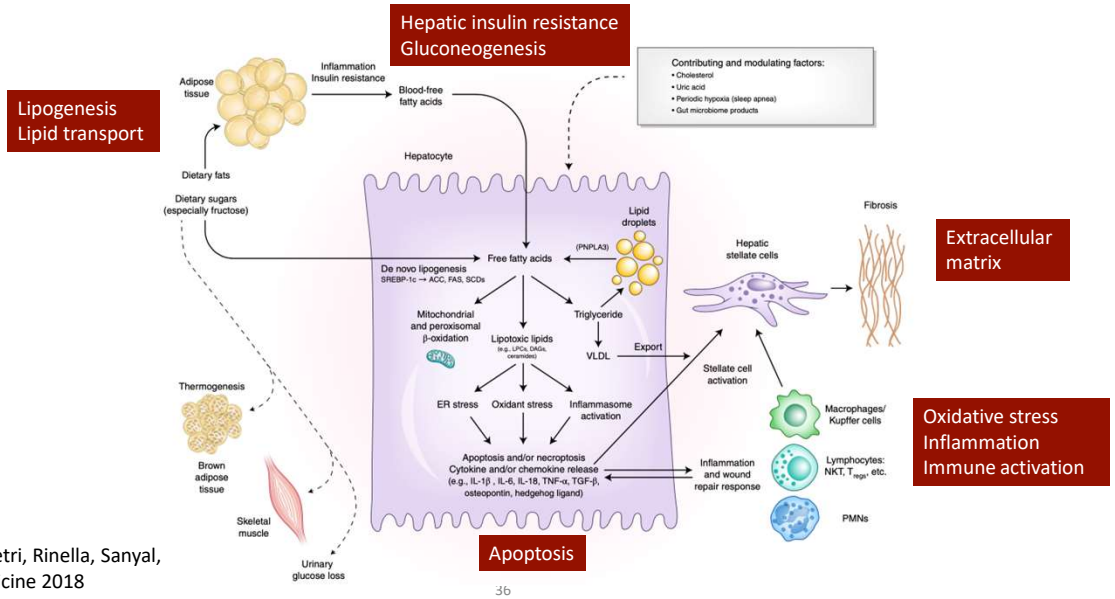
Overview of NASH pathogenesis



Friedman, Tetri, Rinella, Sanyal, Nature Medicine 2018

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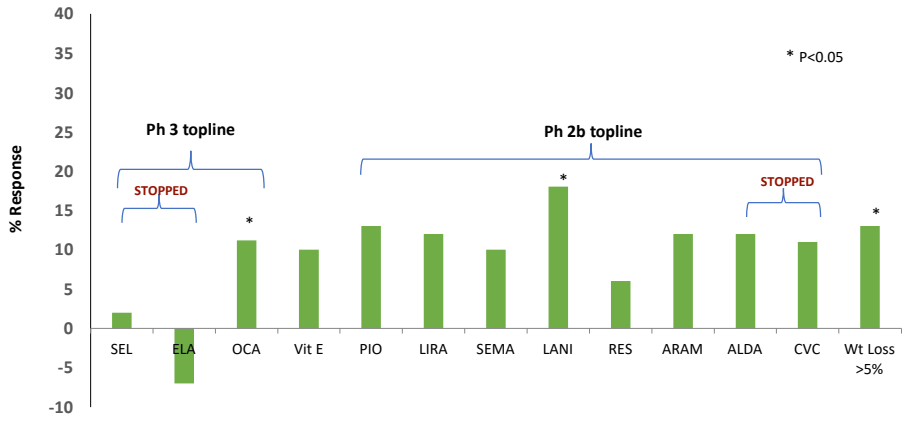
Fibrosis Improvement ≥1 Stage – Margin over Placebo



Harrison et al. STELLAR3/4; Sanyal et al NEJM 2010; Vilar-Gomez et al. Gastro 2015;149:367–78;Newsome et al NEJM 2020; AASLD #104; AASLD #LB4; Lawitz et al. EASL 2018 ; AASLD #14; Sanyal et al. *Lancet*, accepted; Petit et al. *Clin Endocrinol Metab*, February 2017; AASLD #736; AASLD #LB23; AAASLD #LB5; Loomba et al. *Hepatology* 2018 NGM bio press release
SHG = second harmonic generation digital image analysis;

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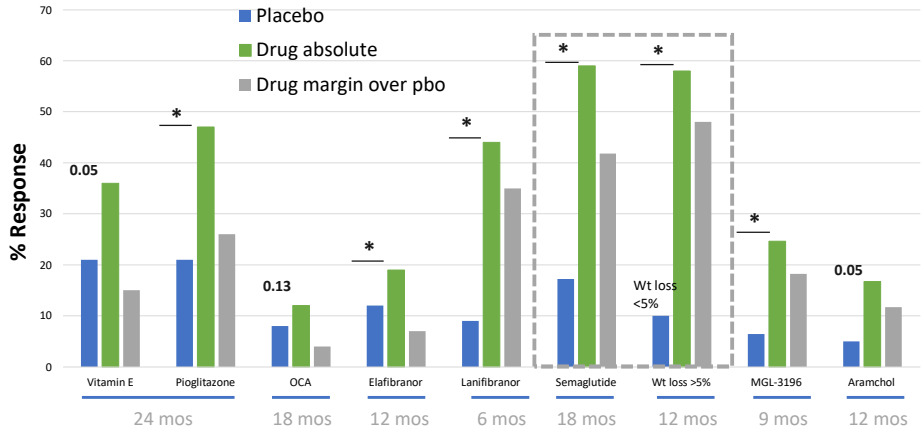
NASH Resolution



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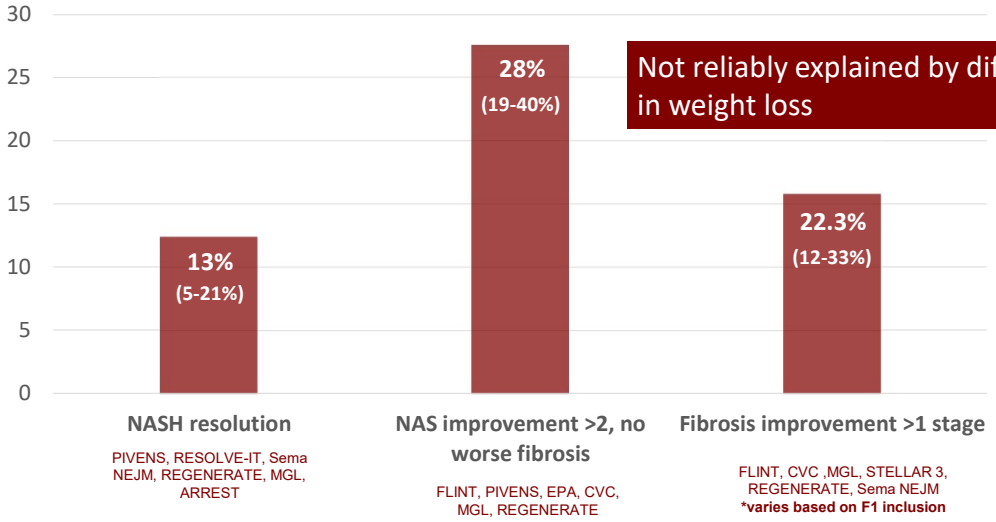
Expected 'placebo' response depends on the endpoint



Not reliably explained by differences in weight loss

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REGENERATE 18-month interim analysis: Fibrosis improvement by ≥1 Stage with no worsening of NASH (ITT, F2/3)

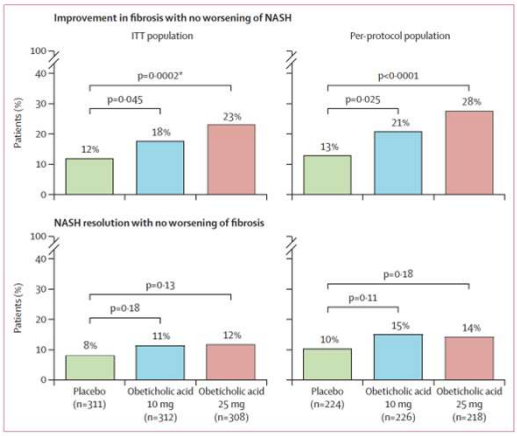
2480 patients
Randomization 1:1:1

Primary endpoint definition:
- Improvement in fibrosis by ≥1 stage (NASH CRN)

AND
- no worsening of lobular inflammation, hepatocellular ballooning **or steatosis**

OR
- Resolution of NASH

AND
- No worsening of fibrosis



Younossi Z*, Ratziu V*, Loomba R, Rinella ME, Anstee QM, Goodman Z, Bedossa P, Geier A, Beckebaum S, Newsome P, Sheridan D, Sheikh M, Trotter J, Knapple W, Lawitz E, Abdelmalek M, Kowdley K, Montano-Loza A, Boursier J, MathurinP, Bugianesi E, Mazzella G, Olveira A, Cortez-Pinto H, Graupera I, Orr D, Lotte L, Gluud, Dufour JF, Shapiro D, Campagna J, Zaru L, MacConell L, Shringarpure R, Harrison SA, Sanyal AJ, on behalf of the REGENERATE Study. Obeticholic Acid for the Treatment 1 of Nonalcoholic Steatohepatitis-Interim Analysis From a Multicentre, Randomised, Placebo-Controlled Phase 3 Study. ***Lancet*** 2019 Dec 14;394(10215):2184-2196.

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Obeticholic Acid – Updated analysis (press release)

The new interim analysis was based on a reassessment of the baseline and Month 18 liver biopsies using a consensus reading methodology. Consensus panels were comprised of three board-certified pathologists who demonstrated accuracy and reproducibility in their assessments of liver biopsies during proficiency testing. The consensus panels in this new interim analysis reviewed digitized whole slide images of the same glass slides of liver biopsy tissue that were evaluated in the original analysis using individual central readers.

The results of the new interim analysis from REGENERATE are shown in the following table:

		Placebo n=311	OCA 10 mg n=312	OCA 25 mg n=308
At least one stage of fibrosis improvement with no worsening of NASH*	9.6%	**14.1%** p=NS		**22.4%** p<0.0001
Resolution of NASH‡ with no worsening of liver fibrosis	3.5%	6.1% p=NS		6.5% p=NS

**Defined as no worsening of hepatocellular ballooning, no worsening of lobular inflammation and no worsening of steatosis*

‡Defined as the overall histopathologic interpretation of (i) no fatty liver disease or (ii) fatty liver disease (simple or isolated steatosis) without steatohepatitis AND a nonalcoholic fatty liver disease (NAFLD) activity score of 0 for ballooning and 0-1 for inflammation

(NASH). This is the second analysis in which OCA has met the primary endpoint for the intent-to-treat (ITT) population in REGENERATE and based on these results, Intercept will be re-submitting its NDA for OCA in liver fibrosis due to NASH.

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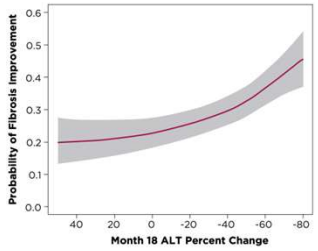
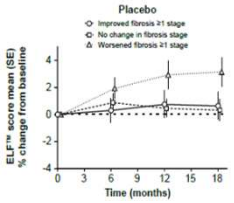
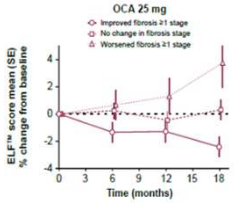
REGENERATE trial: Correlation of NITs with histological response

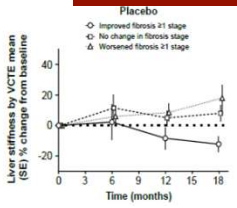


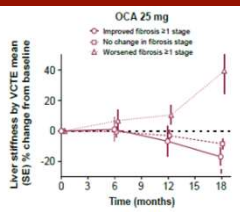
Histological response assessed by ELF





Histological response assessed by transient elastography





Rinella ME et al. *J Hepatology 2022*

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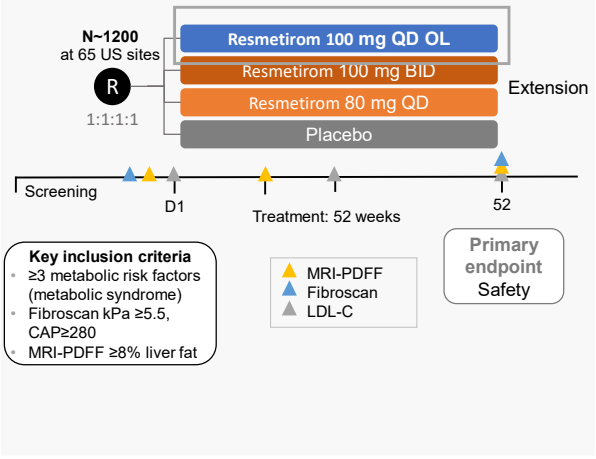
MAESTRO-NAFLD-1: Reduction in fibrosis and steatohepatitis imaging and biomarkers in Phase 3, 52-week resmetirom NASH trial

- Resmetirom is a liver-directed, orally active, selective THR-β agonist

Clinical trial	Preclinical	Phase 1	Phase 2	Phase 3	Description
Phase 2 MGL-3196-05	Completed				• **MRI-PDFF, liver biopsy: endpoints achieved** • 36 wks with 36-wk OLE
Phase 3 MAESTRO-NASH	Recruiting				• **Treatment of NASH F2-F3** • Serial liver biopsy • 52-wk Phase 3; 54-month outcomes
Phase 3 MAESTRO-NAFLD-1	Ongoing				• **Treatment of NASH** • **Safety, lipids and NASH biomarker and imaging study** • 52-wk • Enrolment of DB arms completed • **OL 100 mg arm; includes NASH cirrhotics**

Primary and key secondary endpoints of MAESTRO-NAFLD-1 include: safety, relative percent reduction of MRI-PDFF (week 16), LDL cholesterol (LDL-C) (week 24), Apolipoprotein B and triglycerides, PRO-C3 (week 52), and safety.

Study design



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Resmiterom program

- Resmetirom is a liver-directed, orally active, selective THR-β agonist

Clinical trial	Preclinical	Phase 1	Phase 2	Phase 3	Description
Phase 2 MGL-3196-05	Completed				• **MRI-PDFF, liver biopsy: endpoints achieved** • 36 wks with 36-wk OLE
Phase 3 MAESTRO-NASH	Ongoing				• **Treatment of NASH F2-F3** • Serial liver biopsy • 52-wk Phase 3; 54-month outcomes
Phase 3 MAESTRO-NAFLD-1	Ongoing				• **Treatment of NASH** • **Safety, lipids and NASH biomarker and imaging study** • 52-wk • Enrolment of DB arms completed • **OL 100 mg arm; includes NASH cirrhotics**

Primary and key secondary endpoints of MAESTRO-NAFLD-1 include: safety, relative percent reduction of MRI-PDFF (week 16), LDL cholesterol (LDL-C) (week 24), Apolipoprotein B and triglycerides, PRO-C3 (week 52), and safety.

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MAESTRO-NASH

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Study Design: Randomized, Double-Blind, Placebo Controlled

Inclusion/Exclusion

- ≥3 metabolic risk factors (Metabolic Syndrome)
- FibroScan **kPa consistent with F2-3**
- FibroScan **CAP ≥280**
- **≥8% liver fat** on MRI-PDFF
- **NAS≥4** with fibrosis stage 1A (up to 3%) 1B, total F1 up to 15%; F3, at least 50%, the rest F2

Dual Primary Endpoints – Week 52

- Dual: Resolution of NASH with at least 2-point reduction in NAS with no worsening of fibrosis

OR

- Reduction in fibrosis stage by 1-point with no worsening of NAS OR reduction in fibrosis stage with no worsening of NAS on Week 52 biopsy

Key secondary endpoints LDL-C lowering at Week 24

Composite liver-related outcome at 54 months [histologic evidence of cirrhosis on biopsy, MELD>=15, hepatic decompensation, liver transplant, all cause mortality]

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MAESTRO-NASH

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Baseline Characteristics (ITT)

	Resmetirom 80 mg (N=322)	Resmetirom 100 mg (N=323)	Placebo (N=321)	Overall (N=966)
Age	56 (12)	57 (11)	57 (11)	57 (11)
Female	182 (57)	182 (56)	178 (56)	542 (56)
White	291 (90)	291 (90)	281 (88)	863 (89)
Hispanic or Latino	71 (22)	81 (25)	52 (16)	204 (21)
BMI	36 (6)	36 (7)	35 (7)	36 (7)
Type 2 Diabetes	224 (70)	213 (66)	210 (65)	647 (67)
Hypertension	243 (76)	254 (79)	257 (80)	754 (78)
Dyslipidemia	230 (71)	236 (73)	223 (70)	689 (71)
Hypothyroid	38 (12)	46 (14)	45 (14)	129 (13)
FibroScan VCTE	13 (7)	14 (7)	13(6)	13 (7)
FibroScan CAP	346 (37)	349 (39)	347 (37)	348 (38)
MRI-PDFF	18 (7)	17 (7)	18 (7)	18 (7)
Baseline Liver Biopsy				
NAS >= 5	266 (83)	288 (89)	253 (79)	807 (84)
Fibrosis 1B	16 (5)	15 (5)	18 (6)	49 (5)
Fibrosis 2	107 (33)	100 (31)	112 (35)	319 (33)
Fibrosis 3	199 (62)	208 (64)	191 (60)	598 (62)

Data are mean (SD) or n (%)

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MAESTRO-NASH

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Liver Biopsy (ITT) at Week 52

- Reread of all baseline biopsies by 2 central pathologists
- ITT includes all patients with at least a baseline biopsy with appropriate fibrosis stage
- Eligible week 52 biopsies were included if conducted before 60 weeks; patients with biopsies after Week 60 were considered missing, 11 patients with a >Week 60 biopsy due to COVID were removed from the primary analysis population for liver biopsies (mITT, n=955)
- Biopsies rescored as F1A, C were considered exploratory and will be evaluated separately

- All baseline and Week 52 biopsies were read independently by two central pathologists (glass slides) for the primary analysis read
  - Each pathologist's scores showed a similar statistically significant magnitude of response at both doses for both primary liver biopsy endpoints
  - The results were combined statistically to generate a single treatment effect

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MAESTRO-NASH (Primary Statistical Model)

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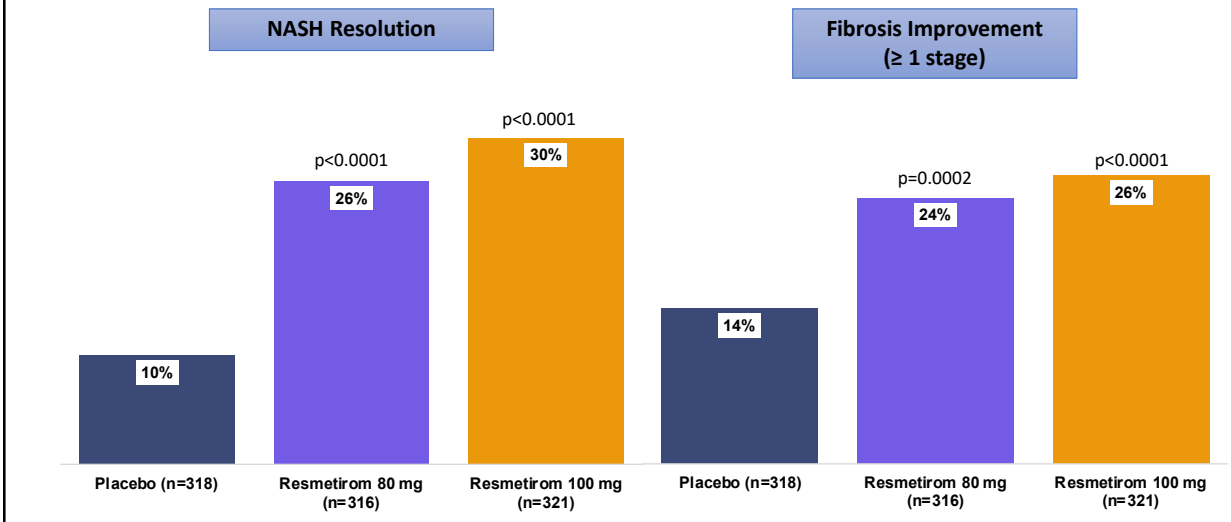
Liver Biopsy (ITT) at Week 52



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MAESTRO-NASH

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Liver Biopsy (ITT) at Week 52

- **Primary endpoint was met independently of baseline fibrosis stage or diabetes status**
- Other secondary liver biopsy endpoints were achieved at both doses:
  - ≥2 point reduction in NAS (with a reduction in ballooning or inflammation) and no worsening of fibrosis
  - ≥2 point reduction in NAS (with a reduction in ballooning or inflammation) AND ≥1-stage improvement in fibrosis
  - reduction in all 3 NAS components[1] without worsening of fibrosis
  - NASH resolution (with ≥2 point reduction in NAS) and ≥1-stage improvement in fibrosis
  - a 2-stage reduction in fibrosis without worsening of NAS

[1] the steatosis component response included either a ≥1 point reduction in steatosis grade or a PDFF response (≥30%); grade 1 steatosis is a large range (5-33%) and significant fat reduction may occur without a reduction in steatosis grade if the baseline steatosis score is grade 1

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Primary Endpoints After Consensus Assessment

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Primary Endpoint	Resmetirom 80 mg (n=316)	p-value	Resmetirom 100 mg (n=321)	p-value	Placebo (n=318)
NASH resolution (ballooning 0, inflammation 0,1) with ≥2-point reduction in NAS and no worsening of fibrosis	24%	<0.0001	28%	<0.0001	8%
≥1-stage improvement in fibrosis with no worsening of NAS	24%	<0.0001	26%	<0.0001	12%

As a supportive analysis, a consensus read of digitized images was conducted in cases where the two pathologists scores disagreed as to whether the there was a response for either NASH Resolution (ballooning 0,1; 2-pt NAS reduction and no worsening of fibrosis) OR >=1 stage Fibrosis reduction with no worsening of NAS (primary endpoints)

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MAESTRO-NASH

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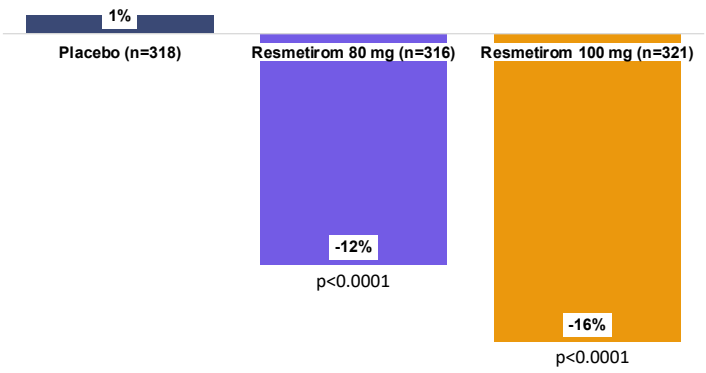
Key Secondary Endpoint LDL-c at Week 24 (ITT)



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MAESTRO-NASH

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Safety Summary

AE Term	Resmetirom 80 mg (n=316)	Resmetirom 100 mg (n=321)	Placebo (n=318)
SAEs	11.8%	12.7%	12.1%
Study discontinuation for AEs	2.8%	7.7%	3.7%
Diarrhea	28%	34%	16%
Nausea	22%	19%	13%

- Resmetirom was **safe and well-tolerated**
- Consistent with previous Phase 2 and Phase 3 data, the most common adverse events reported with greater frequency in the resmetirom groups vs placebo were an excess of generally mild and transient diarrhea and generally mild nausea at the beginning of therapy

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Therapy to counter substrate overload in NASH

Nutritional therapies have lacked Sustainability and attainability (≤15% at one year)

GLP1 RAs

- Decreased glucagon concentrations
- Improved insulin sensitivity
- Decreased A1C
- Slowed gastric emptying
- Increased satiety
- Decreased free fatty acid concentrations
- Decreased body weight

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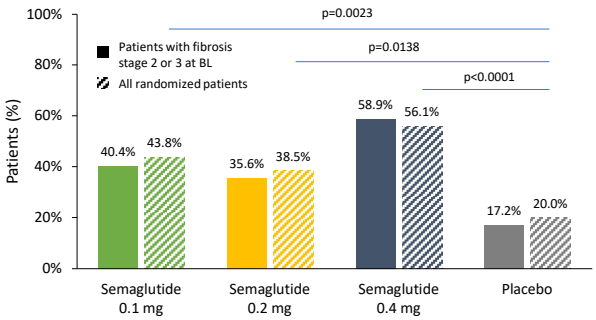
Efficacy and Safety of Semaglutide SC QD vs PBO in patients with NASH

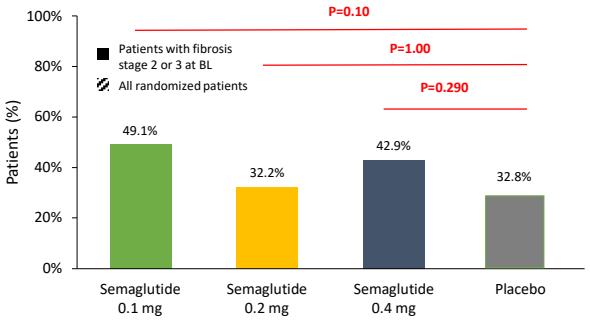
Resolution of steatohepatitis and no worsening in liver fibrosis

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* 2021 ;384(12):1113-1124.

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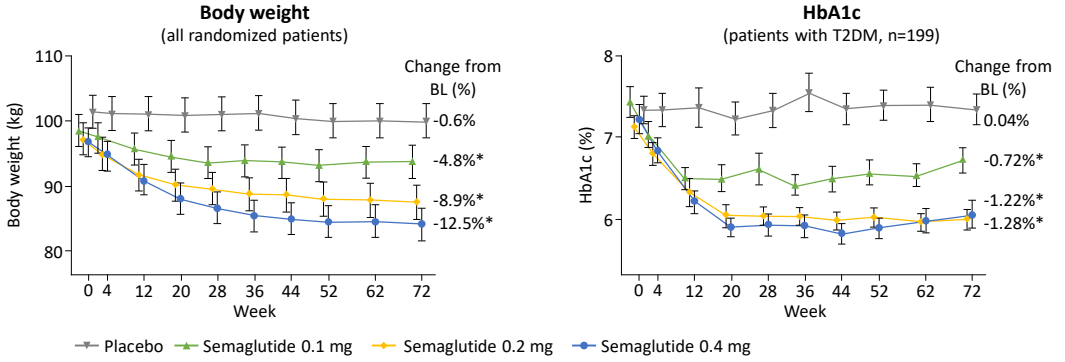
Impact of semaglutide versus placebo on body weight and HbA1c



- SEMA 0.4 mg resulted in increased HDL-C and decreased free fatty acids, triglycerides, and VLDL-C versus placebo

Data are observed means with standard error of the mean.
*p<0.05 for estimated treatment difference versus placebo.

- Safety profile: Major AEs were nausea, constipation, and vomiting, no drug discontinuation due to AEs

Newsome PN, et al. *NEJM* 2021 ;384(12):1113-1124.

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NATIVE Phase 2b trial: Impact of lanifibranor on NASH resolution and fibrosis regression after 24 weeks

PPARα/δ/γ agonist

N=247

Screening
Liver biopsy

24-week treatment + 4-week follow-up
Double-blind, randomized, placebo-controlled

n=81	Placebo	n=74
n=83	Lanifibranor 800 mg QD	n=77
n=83	Lanifibranor 1200 mg QD	n=77

End of treatment
Liver biopsy

Randomization 1:1:1
Stratification on T2DM
Once daily oral administration
Main inclusion criteria: Patients with biopsy-proven NASH confirmed by central reader having SAF scores of 1–3 for steatosis, 3–4 for activity, and <4 for fibrosis

Compound	$PPAR_{\alpha}$ EC50 (nM)	$PPAR_{\delta}$ EC50 (nM)	$PPAR_{\gamma}$ EC50 (nM)
Lanifibranor[1]	**1630**	**850**	**230**
Fenofibrate	2400	-	-
Pioglitazone	-	-	263
Rosiglitazone	-	-	13
Elafibranor[2]	10	100	-
Seladelpar[3]	-	2	-

1. Inventiva Company data; 2. Hanf R et al. Diabetes and Vascular Dis Res. 2014; 3. Cymabay company presentation.

Primary endpoint:

- **Decrease from baseline to Week 24 of ≥2 points of inflammation and ballooning (as measured by SAF-Activity score) and no worsening of fibrosis**

Secondary endpoints:

- Resolution of NASH and no worsening of fibrosis
- Improvement of fibrosis by ≥1 stage and no worsening of NASH
- Decrease from baseline to Week 24 of ≥2 points of the NAS CRN score and no worsening of fibrosis
- Resolution of NASH and improvement of fibrosis by ≥1 stage
- Change in parameters of glycemic control (fasting glucose, insulin, HOMA index, HbA1c, …)
- Change in liver enzymes (ALT, AST, GGT, ALP, total bilirubin)
- Change in main plasma lipid parameters (TC, HDL-C, calculated LDL-C, TG, …)

Other outcome measures:

- Change in inflammatory markers (fibrinogen, hs-CRP, alpha2 macroglobulin, haptoglobin, …)
- Change in fibrosis markers (TIMP-1, TIMP-2, HA, PIIINP, NFS, FIB-4 score, ELF score, Pro-C3, …)

Data are mean ± SD or n (%).
By using SAF Activity ≥3 as inclusion criterion rather than NAS ≥4, NATIVE selected a higher percentage of patients with severely active steatohepatitis associated with advanced fibrosis (although no *a priori* minimum fibrosis criterion was set).

Francque SM, et al. NEJM

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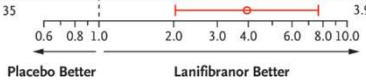
PPAR α/δ/γ agonist Lanifibranor: Impact on histology

End Point	Placebo	Lanifibranor	Risk Ratio (95% CI)	P Value
	percent of patients with response			
Primary end point: reduction of ≥2 points in SAF-A score and no worsening of fibrosis				
Lanifibranor, 800 mg	33	48	1.45 (1.00–2.10)	0.07
Lanifibranor, 1200 mg	33	55	1.69 (1.22–2.34)	0.007
Secondary end point: resolution of NASH without worsening of fibrosis				
Lanifibranor, 800 mg	22	39	1.70 (1.07–2.71)	
Lanifibranor, 1200 mg	22	49	2.20 (1.49–3.26)	
Secondary end point: improvement in fibrosis stage of ≥1 without worsening of NASH				
Lanifibranor, 800 mg	29	34	1.15 (0.72–1.85)	
Lanifibranor, 1200 mg	29	48	1.68 (1.15–2.46)	
Composite secondary end point: resolution of NASH and improvement in fibrosis stage of ≥1				
Lanifibranor, 800 mg	9	25	2.57 (1.20–5.51)	
Lanifibranor, 1200 mg	9	35	3.95 (2.03–7.66)	



Francque et al, *N Engl J Med* 2021; 385:1547-1558.

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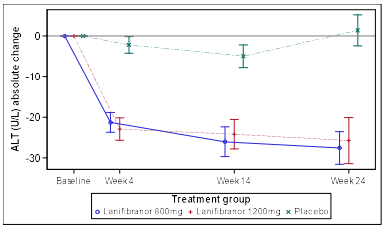
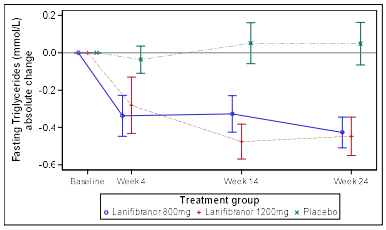
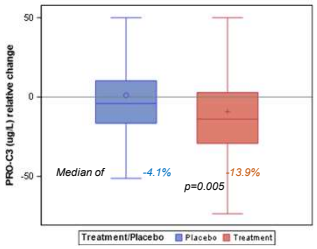
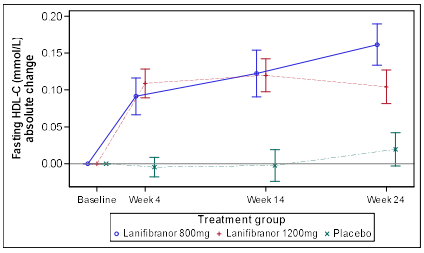
Impact of Lanifibranor on lipids and biomarkers (NATIVE Phase 2b)





* p<0.01 **p<0.001





Data are mean ± SD or n (%).
By using SAF Activity ≥3 as inclusion criterion rather than NAS ≥4, NATIVE selected a higher percentage of patients with severely active steatohepatitis associated with advanced fibrosis (although no *a priori* minimum fibrosis criterion was set).

Francque SM, et al. NEJM 2021
Anstee Q, et al. AASLD TLMdX2020. #LP36

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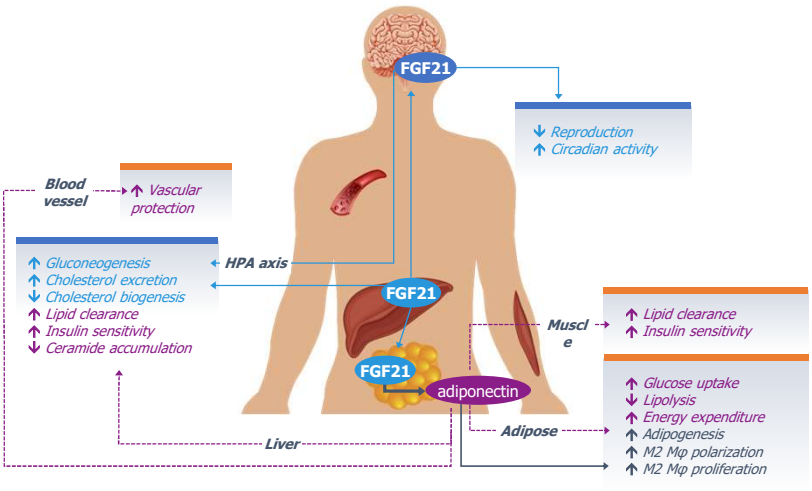
FGF-21 Has Potential to Be Mainstay of Therapy in NASH



Endogenous metabolic hormone that regulates energy expenditure and glucose and lipid metabolism

Reduces liver fat by action within liver and from periphery

Impacts liver fibrosis via metabolic pathway and upregulation of adiponectin

Native FGF21 has a **short half-life** of < 2 hours

Courtesy of S Harrison

Geng L, et al. Nat Rev Endocrinol. 2020 Nov;16:654-667.

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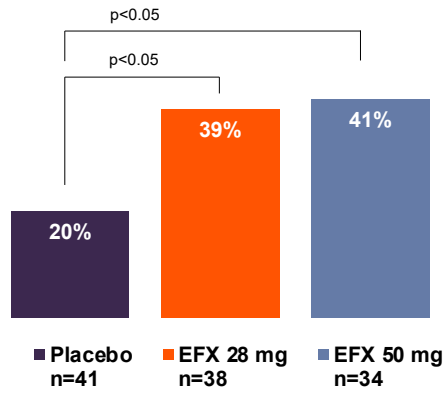
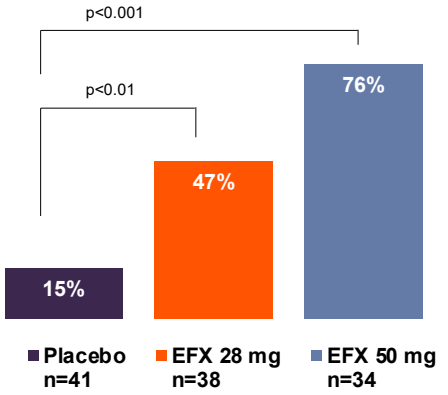
FGF-21 Has Potential to Be Mainstay of Therapy in NASH

Both EFX Doses Achieved Statistical Significance on Primary Endpoint (Fibrosis Improvement)



Both EFX Doses Achieved Statistical Significance on Key Secondary Endpoints (NASH Resolution)



Harrison S. Oral Presentation. AASLD 2023

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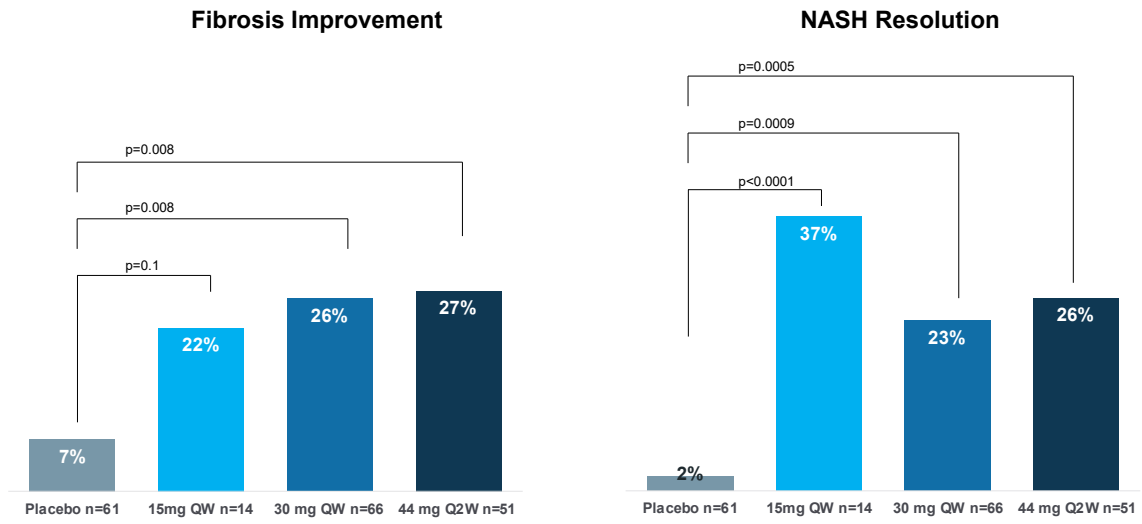
Pegozafermin – Phase 2 Efficacy Results



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Emerging therapies for Alcohol related liver disease

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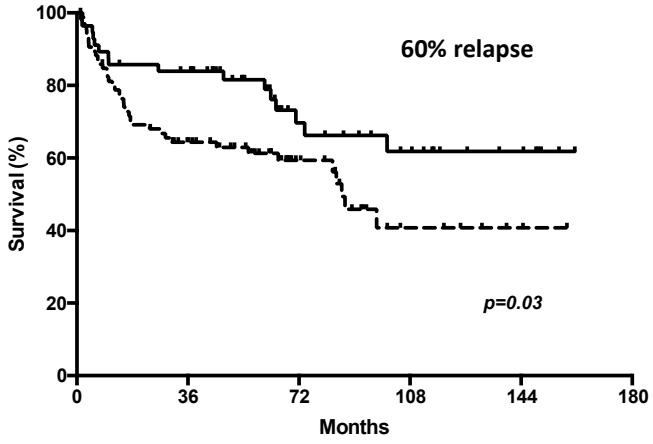
Most effective treatment for Alcohol related liver disease is abstinence



- Early follow-up outpatient clinic
- Multidisciplinary team in the clinic
- All team members should be trained

Altamirano et al, Hepatology 2017

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Prednisolone or Pentoxifylline for Alcoholic Hepatitis

Mark R. Thursz, M.D., Paul Richardson, M.D., Michael Allison, Ph.D., Andrew Austin, M.D., Megan Bowers, M.Sc., Christopher P. Day, M.D., Ph.D., Nichola Downs, P.G. Cert., Dermot Gleeson, M.D., Alastair MacGilchrist, M.D., Allister Grant, Ph.D., Steven Hood, M.D., Steven Masson, M.A., Anne McCune, M.D., Jane Mellor, M.Sc., John O'Grady, M.D., David Patch, M.D., Ian Ratcliffe, M.Sc., Paul Roderick, Ph.D., Louise Stanton, M.Sc., Nikhil Vergis, M.B., B.S., Mark Wright, Ph.D., Stephen Ryder, D.M., and Ewan H. Forrest, M.D., for the STOPAH Trial*

CORTICOSTEROID THERAPY IN SEVERE ALCOHOLIC HEPATITIS*

A Double-Blind Drug Trial

HENRIK P. PORTER, M.D., FRANCIS R. SIMON, M.D., CHARLES E. POPE, II, M.D., WADE VOLWILER, M.D., AND L. FREDERICK FENSTER, M.D.

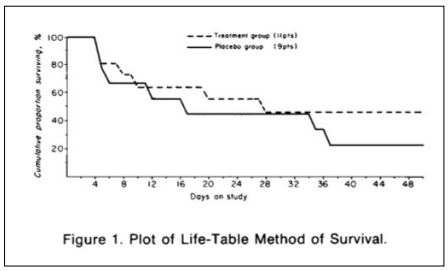
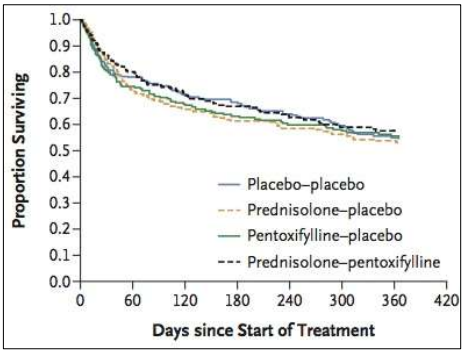


Figure 1. Plot of Life-Table Method of Survival.



1971 **2015**

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ORIGINAL ARTICLE

Early Liver Transplantation for Severe Alcoholic Hepatitis

Philippe Mathurin, M.D., Ph.D., Christophe Moreno, M.D., Ph.D., Didier Samuel, M.D., Ph.D., Jérôme Dumortier, M.D., Ph.D., Julia Salleron, M.S., François Durand, M.D., Ph.D., Hélène Castel, M.D., Alain Duhamel, M.D., Ph.D., Georges-Philippe Pageaux, M.D., Ph.D., Vincent Leroy, M.D., Ph.D., Sébastien Dharancy, M.D., Ph.D., Alexandre Louvet, M.D., Ph.D., Emmanuel Boleslawski, M.D., Ph.D., Valerio Lucidi, M.D., Thierry Gustot, M.D., Ph.D., Claire Francoz, M.D., Christian Letoublon, M.D., Denis Castaing, M.D., Jacques Belghiti, M.D., Vincent Donckier, M.D., Ph.D., François-René Pruvot, M.D., and Jean-Charles Duclos-Vallée, M.D., Ph.D.

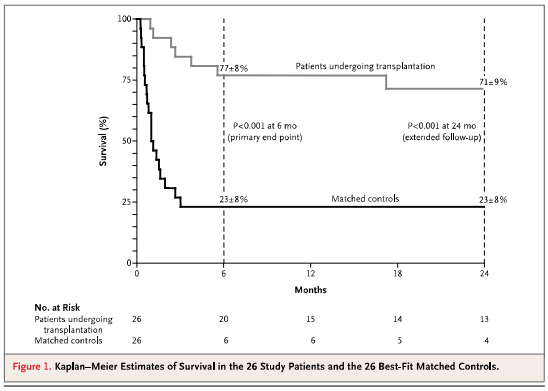

Figure 1. Kaplan–Meier Estimates of Survival in the 26 Study Patients and the 26 Best-Fit Matched Controls.

- Offered to **highly selected** patient with corticosteroid-resistant Alc Hep (< 2% admitted patients).
- Very **low relapse rate**: 3 out of 26 patients.

Mathurin et al. NEJM, 2011

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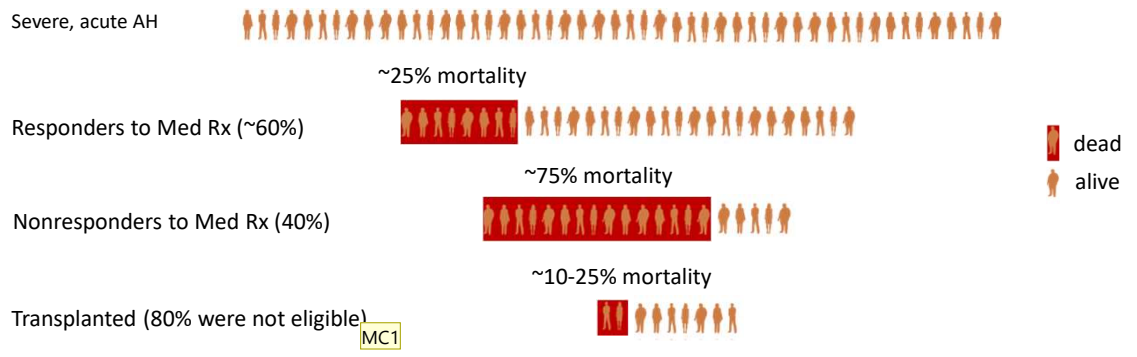
Liver transplantation confers dramatic survival benefit in severe medical-refractory alcoholic hepatitis



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Slide 66

MC1 Michael Charlton, 9/13/2021

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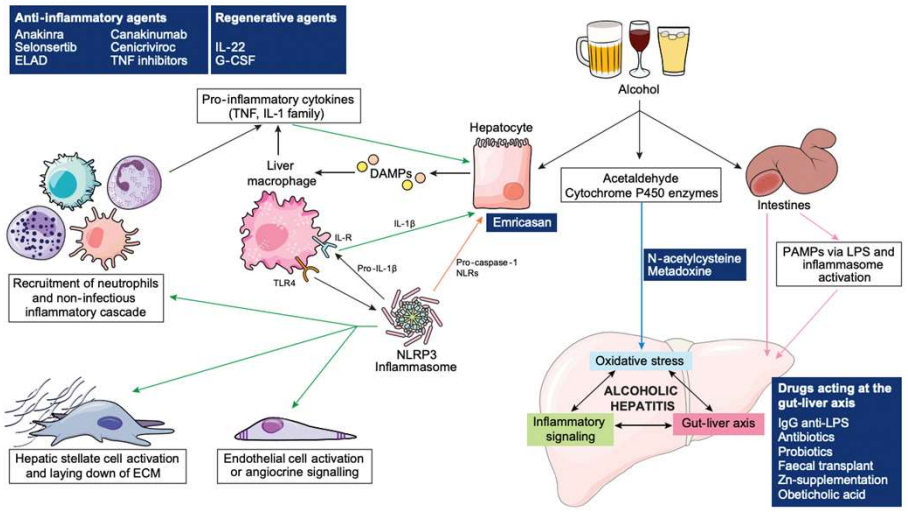
Pathophysiology and therapeutic targets in AH



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Ongoing studies on AH

	Characteristic	Observational	Interventional
Total number of trials		23 (5 multicenter)	77 (27 multicenter)
Funding source	Federal	5	14
	Industry	2	19
	Other	16	44
Completed trials		9	35
Clinical trial phase	Phase-1	NA	4
	Phase-2	NA	12
	Phase-3 and 4	NA	19
Active trials	Recruiting	8	12
	Not yet	2	4
Inactive trials	Suspended	0	1
	Terminated	0	9
	Unknown status	3	6
	Withdrawn	1	3
	Not yet recruiting	0	0

ClinicalTrials.gov accessed Sep. 22, 22

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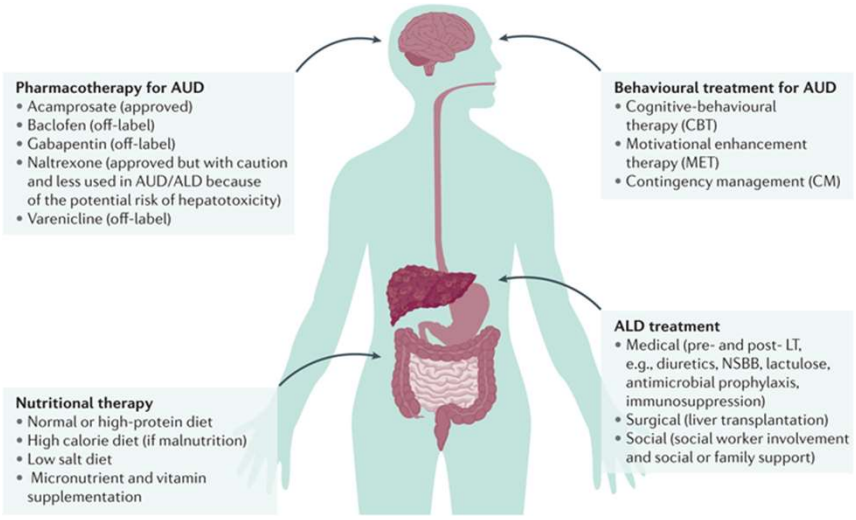
Pharmacotherapy will only help the acute phase of liver injury



Arab JP, Izzy M et al. Nat Rev Gastroenterol Hepatol. 2022 Jan;19(1):45-59.

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IL-1 receptor antagonist in combination with pentoxifylline and zinc for severe alcoholic hepatitis: A multicenter randomized double-bind placebo-controlled clinical trial

Aims: This study evaluated the safety and efficacy of the combination of recombinant human interleukin-1 receptor antagonist (anakinra), pentoxifylline (PTX), and zinc (Zn) sulfate in patients with AH. We targeted critical pathogenic elements of AH: inflammation (anakinra), protection from cellular injury (PTX), and gut leakiness (Zn).

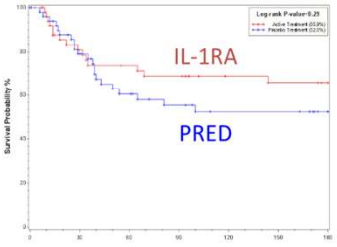
Methods: Subjects with clinical diagnosis of severe AH (MELD >20, MDF >32) were randomized to methyl prednisolone, 32 mg orally daily for 28 days (PRED) or a combination of anakinra, 100 mg daily subcutaneously for 14 days plus PTX 400 mg orally 3 times daily for 28 days plus Zn 220 mg orally daily for 180 days (IL-1RA). Endpoints included mortality at 30, 90, and 180 days. A Cox proportional regression analysis was used to identify variables associated with mortality.

Results:

- Fifty-three patients were randomized into the IL-1RA and 50 to the PRED arms.
- Baseline characteristics were comparable between treatment groups.
- Survival probability at 180-day post randomization, the primary outcome was 66.8% in the IL-1RA and 52.8% in the PRED group (HR=0.69; p=0.26).
- In Cox regression analysis, higher baseline MELD score was independently associated with mortality (p=0.003).
- No unexpected treatment-related severe adverse events were noted in either group. The incidence of infection was comparable in both groups.
- Survival at 180 days in subjects with initial MELD 20-25 (72.6%) was significantly higher than those with initial MELD 26-31 (45.2%) (HR=2.9, p=0.003).
- Both MELD strata (MELD 21-25; MELD 26-31) showed non-significant treatment effects in favor of IL-1RA.

Szabo G, et al., Abstract LB-1 (U01 AA0021893 DASH Consortium)

Kaplan-Meier survival curves through 180 days by treatment group



Conclusions: A combination of anakinra, PTX, and Zn provides comparable short-term and may provide long-term survival benefits compared to currently used PRED therapy in severe AH. Initial MELD is an important predictor of survival at 30, 90, and 180 days.

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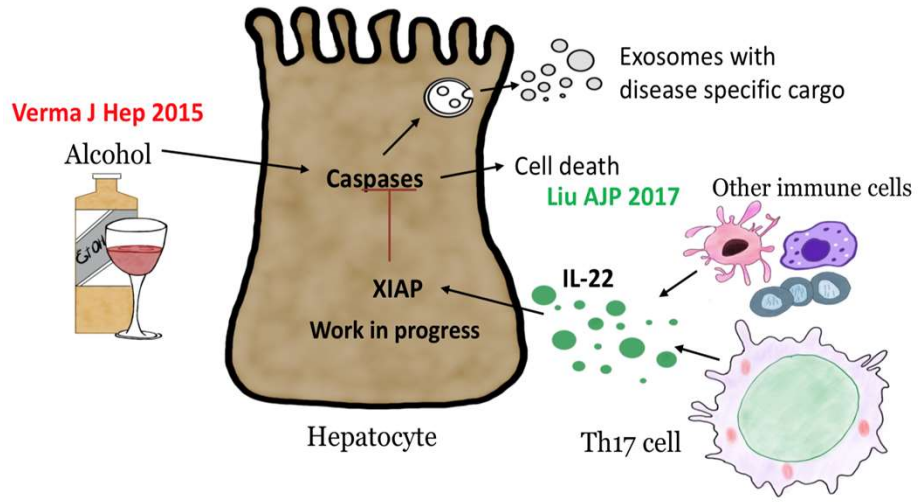
IL-22 attenuates alcohol induced caspase activation, cell death and extracellular vesical release



Verma VK, Li H, Wang R, Hirsova P, Mushref M, Liu Y, Cao S, Contreras PC, Malhi H, Kamath PS, Gores GJ, Shah VH.J Hepatol. 2016; Liu

Slide Courtesy of Vijay Shah MD

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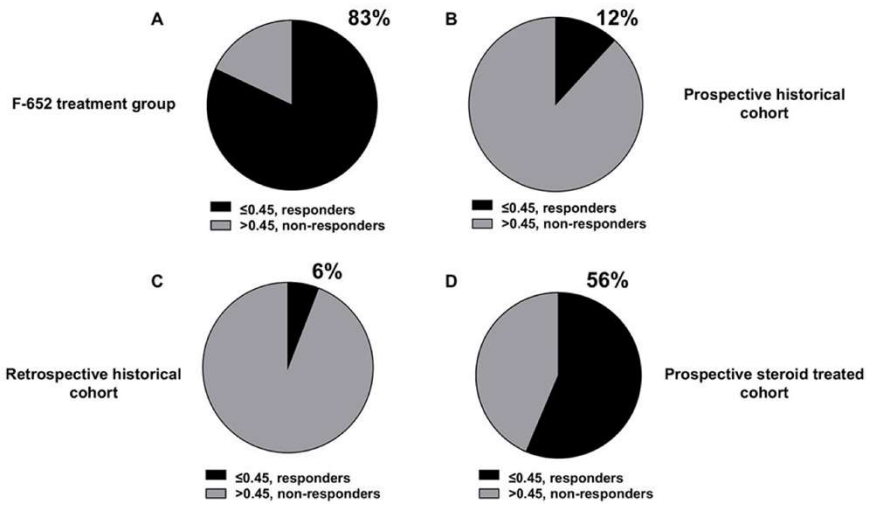
F-652 (IL-22 fusion protein) associated with higher response v. historical controls in patients with AH



Arab JP et al. Hepatology 2020

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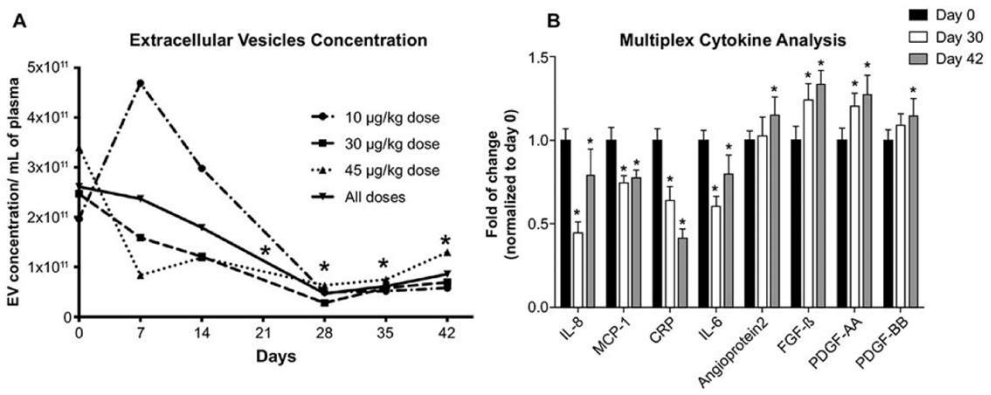
F-652 associated with higher response v. historical controls in patients with AH



Arab JP et al. Hepatology 2020

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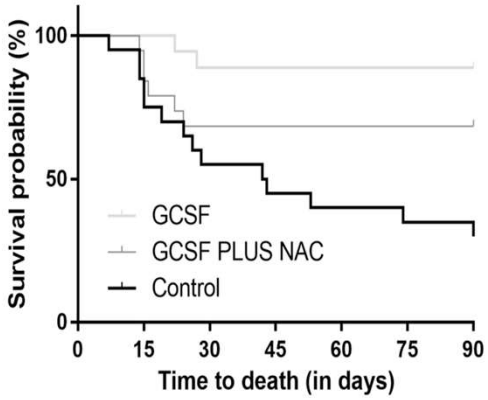
Possible survival benefit of G-CSF vs. SOC at 90 days

Potential MoA:
- Recruitment of bone marrow cells
- Stimulation of regeneration



Group	Number at risk						
Control	20	15	11	9	8	7	6
GCSF plus NAC	19	16	13	13	13	13	13
GCSF	18	18	16	16	16	16	16

Singh JP et al. Clin Gastroenterol Hepatol 2018

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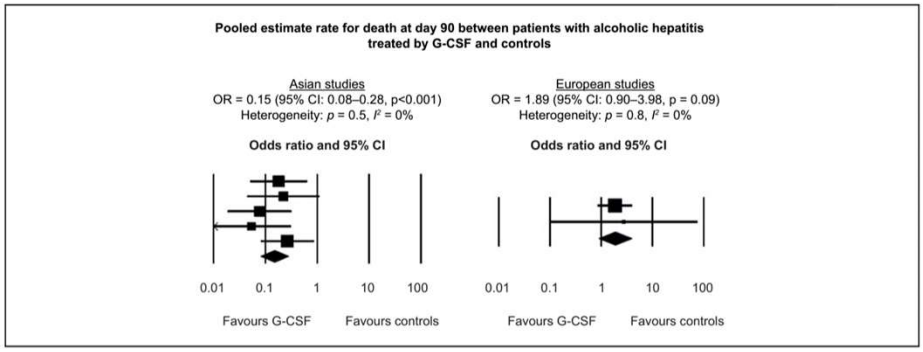
Meta-analysis of impact on GCSF on AH

Overall, 30% reduction in death over 90 days,
BUT high heterogeneity across studies



Requires confirmation in United States

Marotet al. Jhep reports 2020

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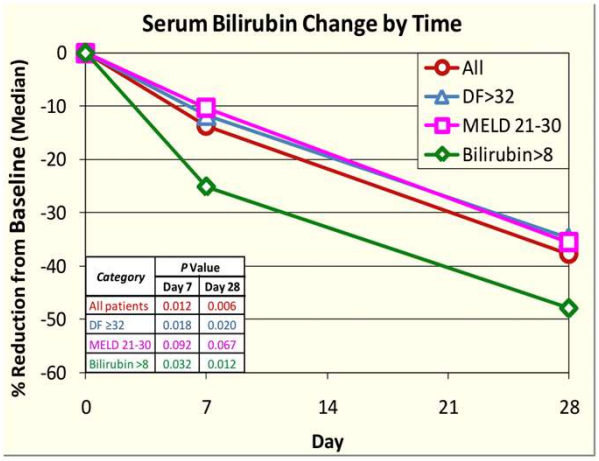
Phase 2a of DUR-928 for severe alcohol hepatitis

Open label, dose ranging
Inclusion:

- Clinical diagnosis of Alcoholic Hepatitis Guidelines definition for probable AH
- Serum bilirubin > 3 mg/dL AND AST > ALT, but less than 300 U/L
- MELD 11-30

Ph 2b, 300 pts, 30mg, 90mg vs Placebo/SOC, recruiting



Hassanein et al. Presented at The Liver Meeting Boston, 2019

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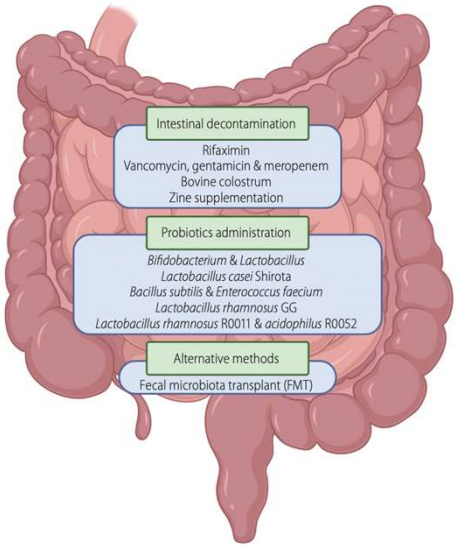
Targeting the gut-liver-axis in AH



Amox/Clavulonic acid Ph3 completed

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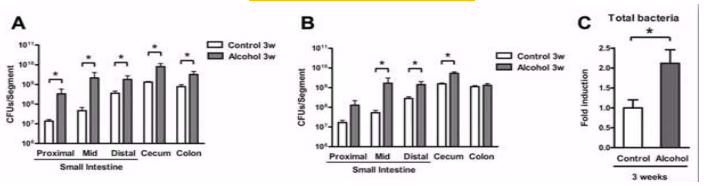
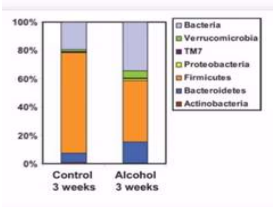
Changes in gut bacteria composition with alcohol

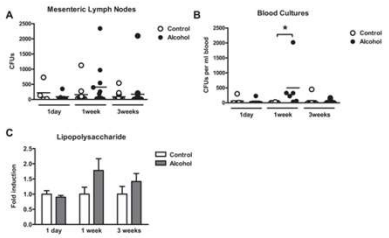
Bacterial overgrowth



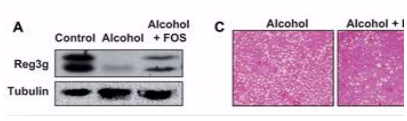
Bacteroidetes>>Firmicutes



Bacterial translocation



Prebiotic reverses alcohol induced reduction in Reg3g



Arthur W. Yan1, Derrick E. Fouts2, Johannes Brandl1,3, Peter Starkel4, Manolito Torralba2, Eckart Schott3, Hide Tsukamoto5, Karen E. Nelson2, David A. Brenner1, and Bernd Schnabl1, Hepatology 2011

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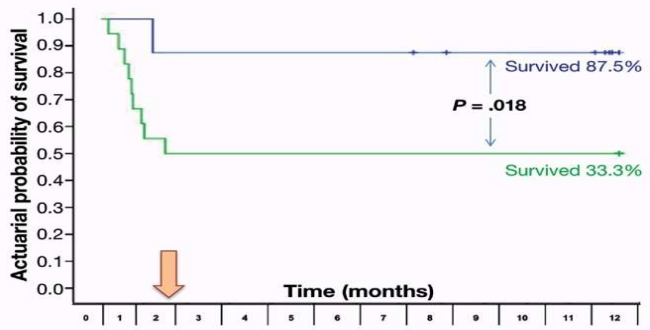
Fecal Transplantation in steroid refractory patients

Pilot study in 8 steroid ineligible Alcohol hepatitis [1]



Retrospective study in 51 patients [2]

Improved 1 and 3 mo survival after FMT vs. steroids, nutrition of PTX [2]

Retrospective study in 51 patients [3]

Reduced hepatic complications, less relapse and trend towards improved survival [3]

[1] Philips et al. Clin Gastro Hepatol 2017; [2] Philips et a. Indian Journal of Gastro 2018; [3] Philips et al. J of Clin and Exper Hepatol 2022

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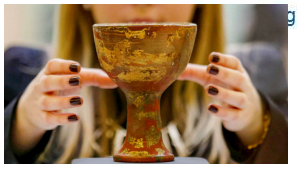
Take home points



NASH

- Promising therapeutic options are emerging
- Combination approaches
- Further validation of non-invasive tests and less reliance on histology to assess therapeutic efficacy
- Identification of NASH phenotypes →More precision driven care

Alcohol

- Abstinence is best medicine
- Increased acceptance of transplant for Alcohol hepatitis w good outcomes
- Anti-inflammatory targets, microbiome and genetic approaches hold promise

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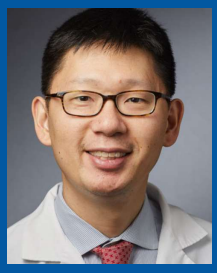
Fatty Liver Disease: In Search of the Optimal NAFLD Clinical Care Pathway

ACG Virtual Grand Rounds
June 15, 2023



Joseph K. Lim, MD, FACG
Professor of Medicine
Director, Clinical Hepatology
Vice-Chief, Section of Digestive Diseases
Yale University School of Medicine

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Lecture Objective

- Describe the effectiveness of optimal clinical care models in improving the NAFLD care cascade from early diagnosis to management

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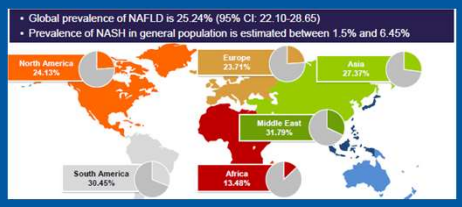
NAFLD is a Global Public Health Burden

- NAFLD is common – **global prevalence of 25.2%**
  - Middle East (31.8%)
  - South America (30.5%)
  - Asia (27.4%)
  - North America (24.1%)
  - Europe (23.7%) – estimated 52 million in EU
  - Africa (13.5%)



- Metabolic comorbidities are common: obesity (51.3%), type 2 diabetes mellitus (22.5%), hyperlipidemia (69.2%), hypertension (39.3%), metabolic syndrome (42.5%)
- Emerging cause of liver cirrhosis and liver failure
- #2 indication for liver transplantation in U.S.
- Associated with a significant increase in liver, cardiovascular, cancer, and all-cause mortality
- Associated with substantial cost: $103 billion (US), €35 billion (EU)

Younossi ZM, Koenig AB, Abdelatif D, et al. *Hepatology* 2016; 64:73-84; Adams LA, et al. Gastroenterology 2005; 129:113-21;

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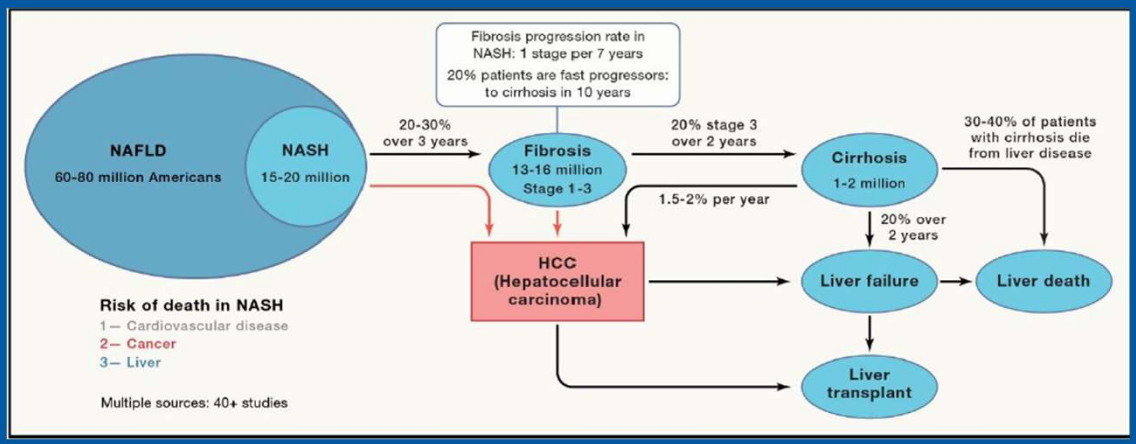
Natural History of NAFLD



Loomba R, Friedman S, Shulman G. Cell 2021.

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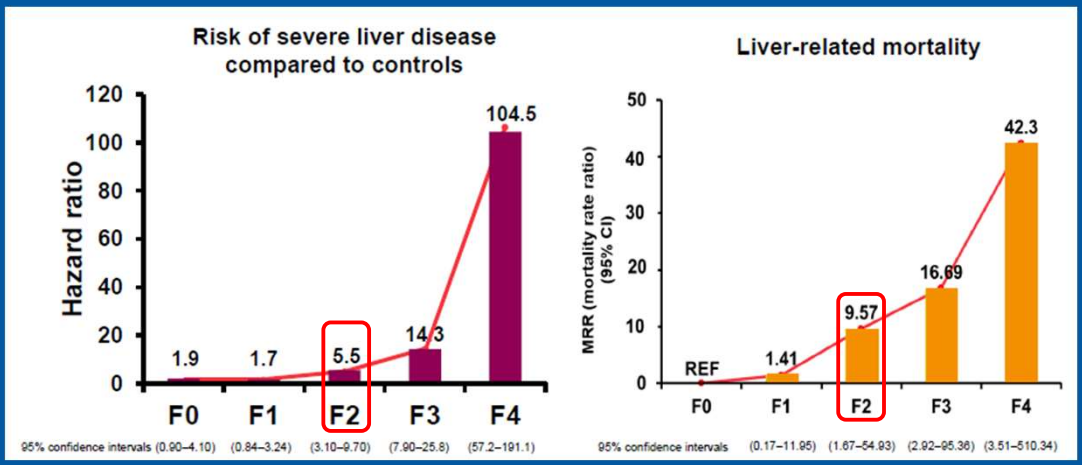
Fibrosis is Associated with Liver Mortality



Hagstrom H et al. J Hepatol 2017; Dulai PS et al. Hepatology 2017..

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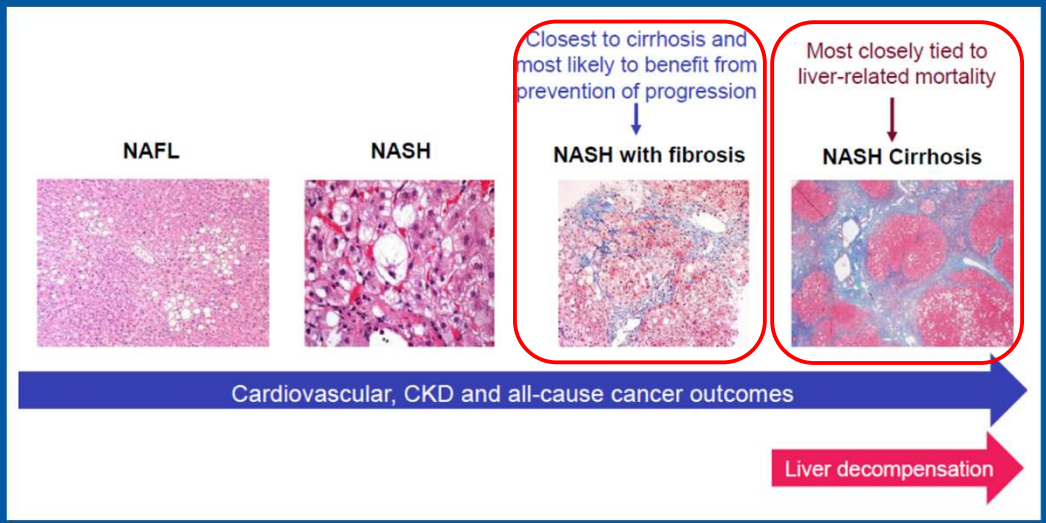
Aim of Case Finding: NASH with Fibrosis/Cirrhosis



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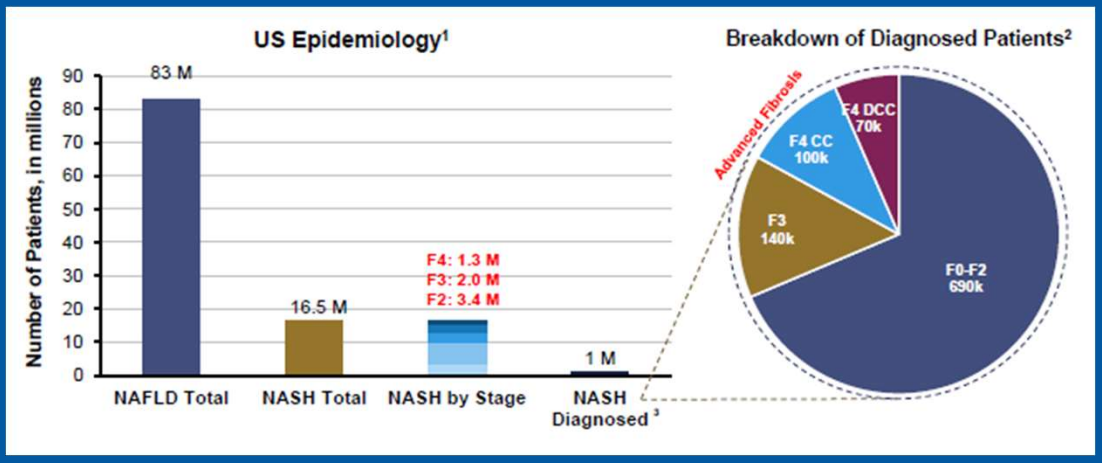
NAFLD in the U.S



Estes C et al. Hepatology 2017; NASH Epidemiology Study 2016 (Humedica, Pharmetrics, SHA).

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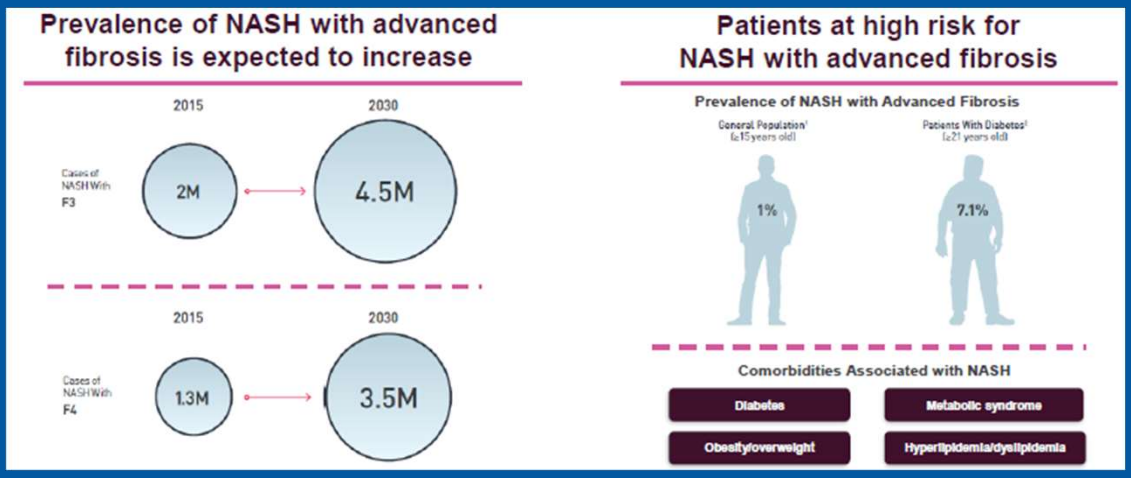
Models of Temporal Trends of NASH Fibrosis



Estes C et al. Hepatology 2017; Doycheva I et al. Aliment Pharmacol Therapy 2016.

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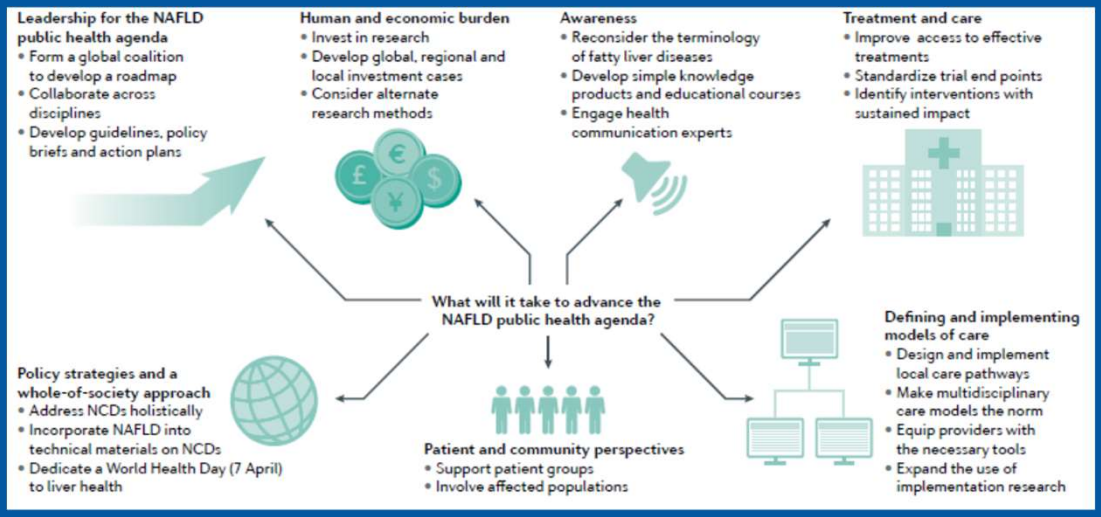
Public Health Policy Approach to Address NAFLD



Lazarus JV, et al. Nature Rev Gastro Hepatol 2022.

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Comprehensive Care Models for NAFLD

- Models of care (MoC) are setting-specific frameworks that outline how patients are managed along the cascade of care
- Principles for development of NAFLD care models:
  - Tailored to the position of each patient on the disease spectrum
  - Multidisciplinary with engagement of primary care and community services for disease prevention and mitigation
  - Articulate roles of primary and specialist clinicians
  - Establish co-location of services for NAFLD and comorbidities (obesity, T2DM, CVD)
  - Develop local guidance on screening and testing with non-invasive tests
  - Define composition and structure of multidisciplinary team and integration of care

Lazarus JV, et al. Nature Rev Gastro Hepatol 2021.

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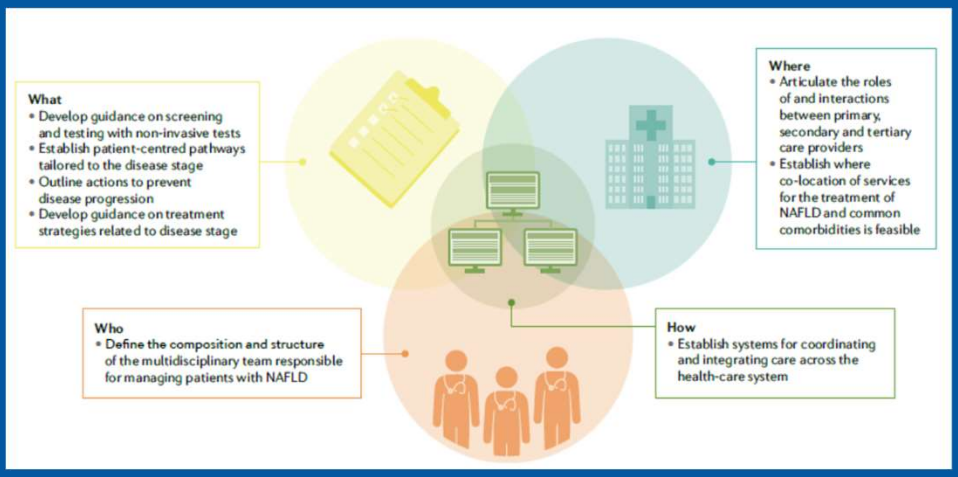
Comprehensive Care Models for NAFLD



Lazarus JV, et al. Nature Rev Gastro Hepatol 2021.

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Society Guidelines: NAFLD Diagnosis

American Diabetes Association. Diabetes Care

- "Patients with type 2 diabetes or prediabetes and elevated liver enzymes (alanine aminotransferase) or fatty liver on ultrasound should be evaluated for presence of nonalcoholic steatohepatitis and liver fibrosis"

AASLD

Screening for NAFLD in adults attending primary care clinics or high-risk groups attending diabetes or obesity clinics is not advised at this time due to uncertainties surrounding diagnostic tests and treatment options, along with lack of knowledge related to the long-term benefits and cost-effectiveness of screening

"In patients with T2DM, the presence of NAFLD should be looked for irrespective of liver enzyme levels…"

"Cardiovascular complications frequently dictate the outcome of NAFLD and screening of the cardiovascular system is mandatory in all persons, at least by detailed risk factor assessment"

Kanwal F, et al. Obesity 2021.

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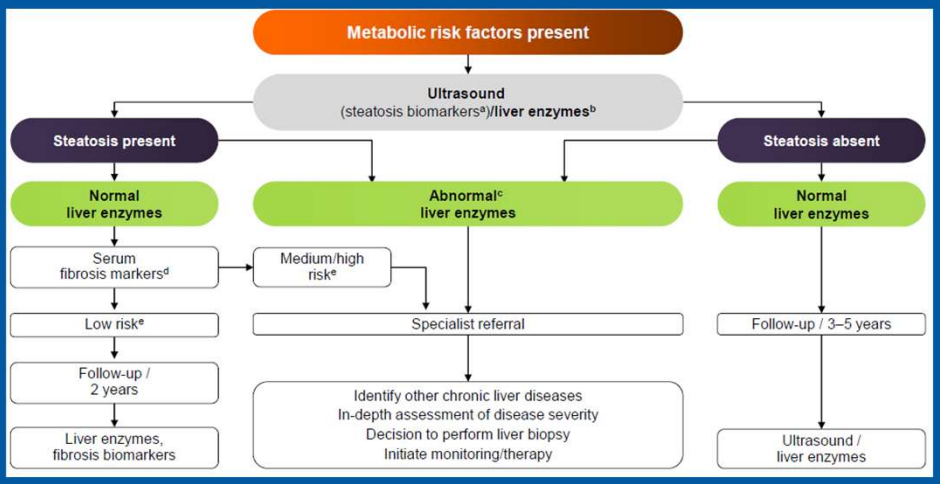
EASL-EASD-EASO Clinical Guideline 2016



EASL-EASD-EASO. J Hepatol 2016.

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Noninvasive Alternatives to Biopsy for Assessment of Liver Fibrosis

- No non-invasive gold standard – liver biopsy reference
- Serum indices (Indirect)
  - *Forms fibrosis index, APRI, FIB-4, NFS (NAFLD Fibrosis Score)*
- Serological markers (Direct)
  - *ELF, FibroTest*, *FibroSure*, *FibroSpect II*
- Liver stiffness measurement
  - US: Transient elastography (*FibroScan*)
  - US: ARFI (pSWE), 2D-SWE
  - MRI: MR elastography (MRE)
- Newer Modalities
  - Serum: ADAPT/ProC3, NIS4, MASEF
  - Imaging: Multiscan (cT1/PDFF)
  - Combination: FAST (CAP/LSM/AST), MAST (PDFF/MRE/AST), MEFIB (MRE/FIB4)

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Non-Invasive Test (NIT) Diagnostic Performance

Test	AUROC	Lower cut-off to rule out Advanced Fibrosis	Sensitivity for lower cut-off (%)	Upper cut-off to rule in Advanced Fibrosis	Specificity for upper cut-off (%)
Simple scores					
FIB-4[1]	0.78	<1.3	82	≥2.67	93
NFS[1]	0.74	<-1.455	89	≥0.676	89
APRI[2]	0.76	<0.57	90	>0.84	65
Proprietary serum tests					
FibroSure®[3]	0.83	≤0.31	84	>0.58	83
ELF[4,5]	0.86†	<7.7	85	≥9.8	90
Imaging techniques					
FibroScan®[6]	0.93	<7.9 kPa	91	≥9.6 kPa	92
MRE[7]	0.93‡	<2.97 kPa	85	>3.62 kPa	83
Histological tests					
Liver biopsy[8]	0.87	≤F2	85	≥F3	89

Anstee QM et al. Hepatology 2019; Siddiqui MS et al. Clin Gastro Hepatol 2019..

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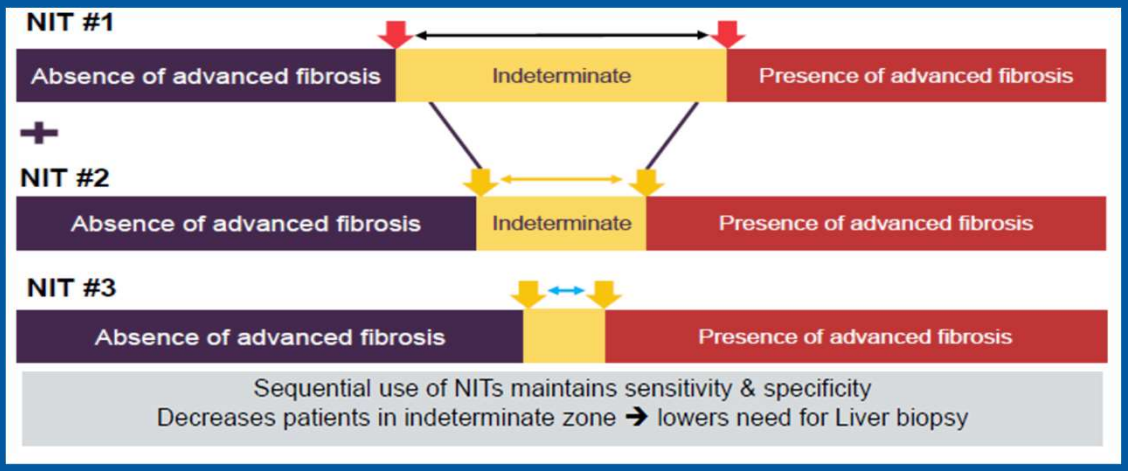
Sequential NIT Improves Risk Stratification



Anstee QM et al. Hepatology 2019; Srivastava A et al. BMC Gastroenerol 2019.

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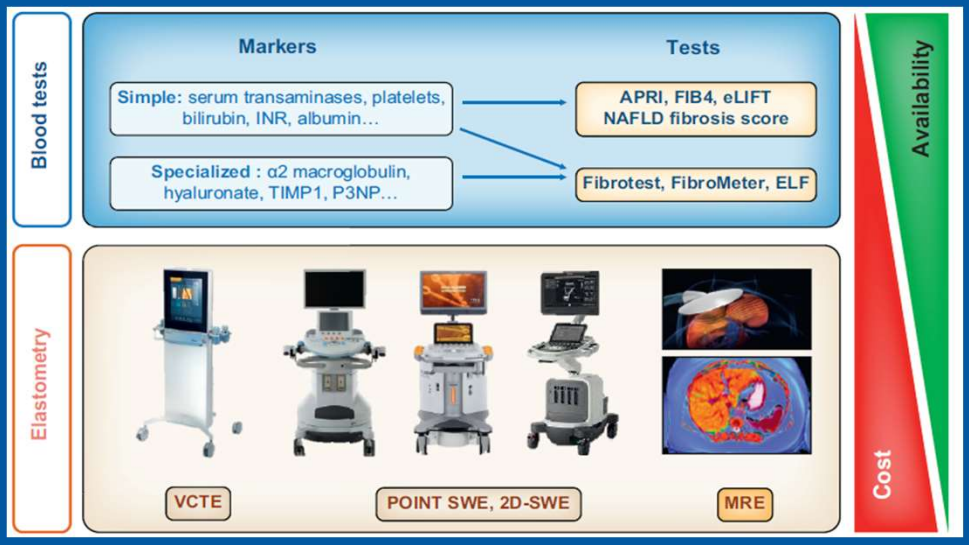
Balancing NIT Performance and Cost/Availability



Boursier J et al. JHEP Reports 2020.

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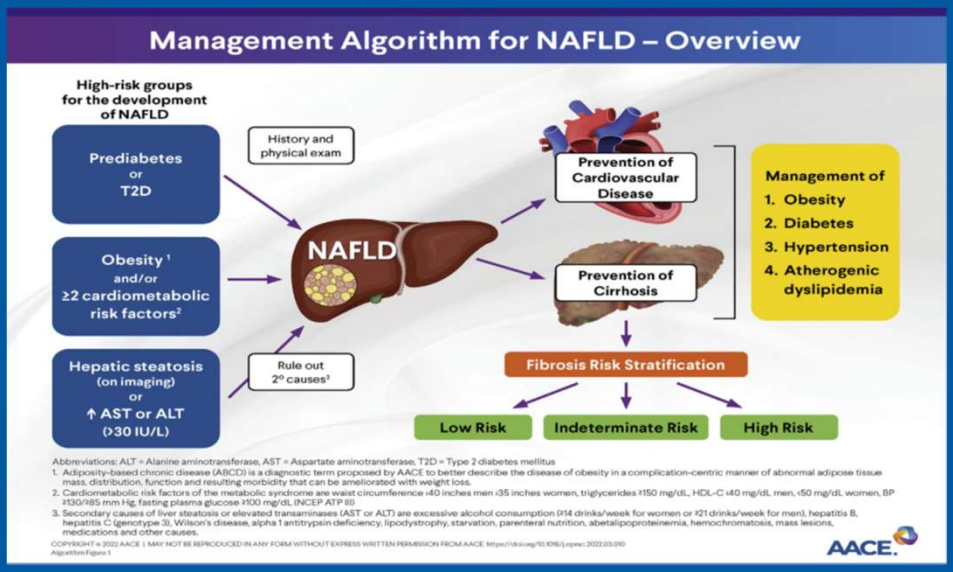
AACE NAFLD Guideline 2022



Cusi K et al. Endocrine Practice 2022.

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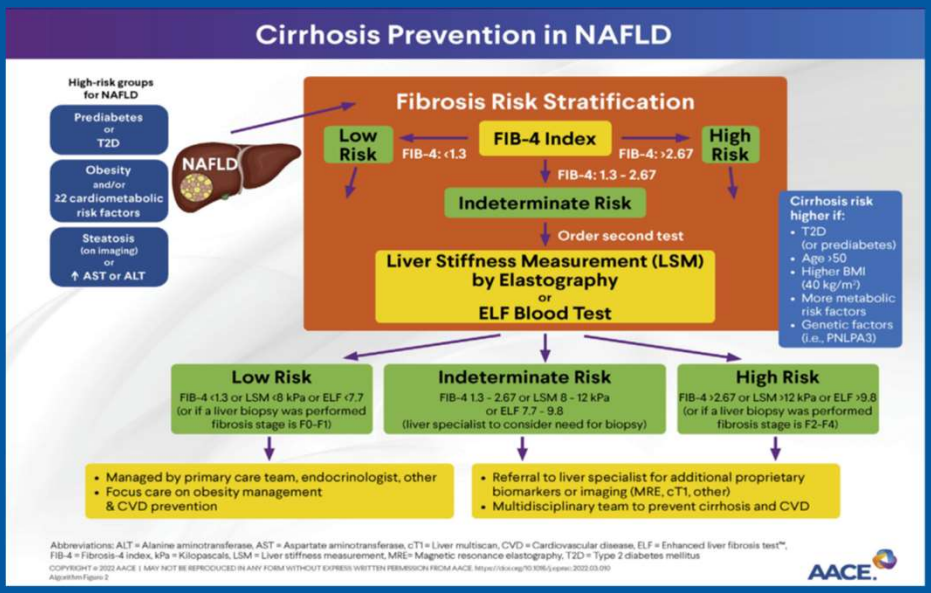
AACE NAFLD Guideline 2022



Cusi K et al. Endocrine Practice 2022.

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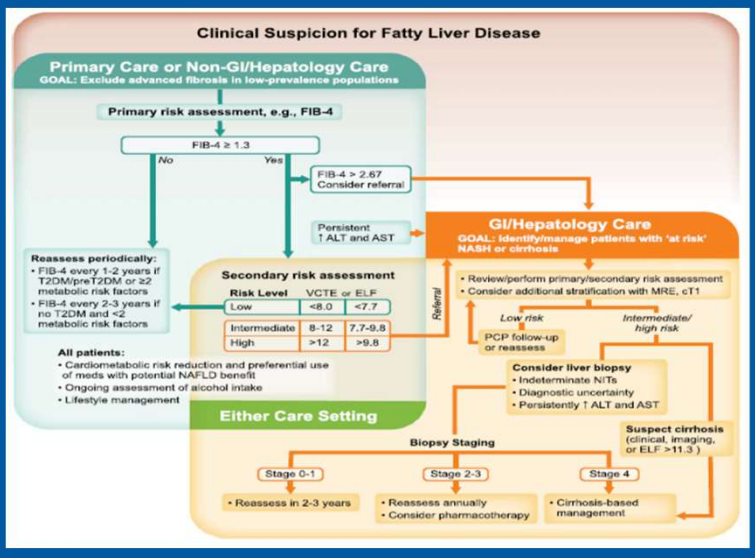
AASLD NAFLD Guidance 2023

TABLE 4 Screening for advanced fibrosis in high-risk populations

Screening recommended[a]	Prevalence of advanced fibrosis, %
T2DM	6–19
Medically complicated obesity	4–33
NAFLD in context of moderate alcohol use	17
First-degree relative of a patient with cirrhosis due to NAFLD/NASH	18



Rinella M et al. Hepatology 2023.

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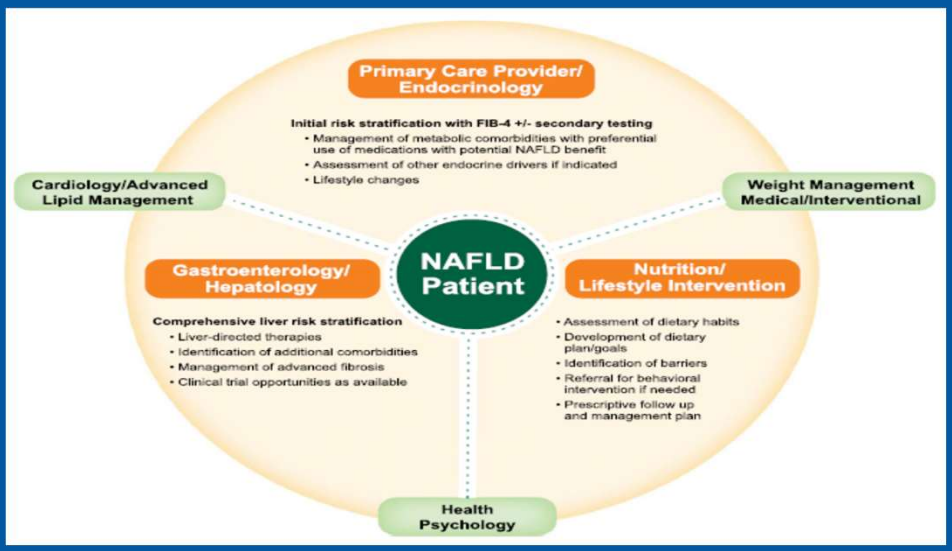
AASLD NAFLD Guidance 2023



Rinella M et al. Hepatology 2023.

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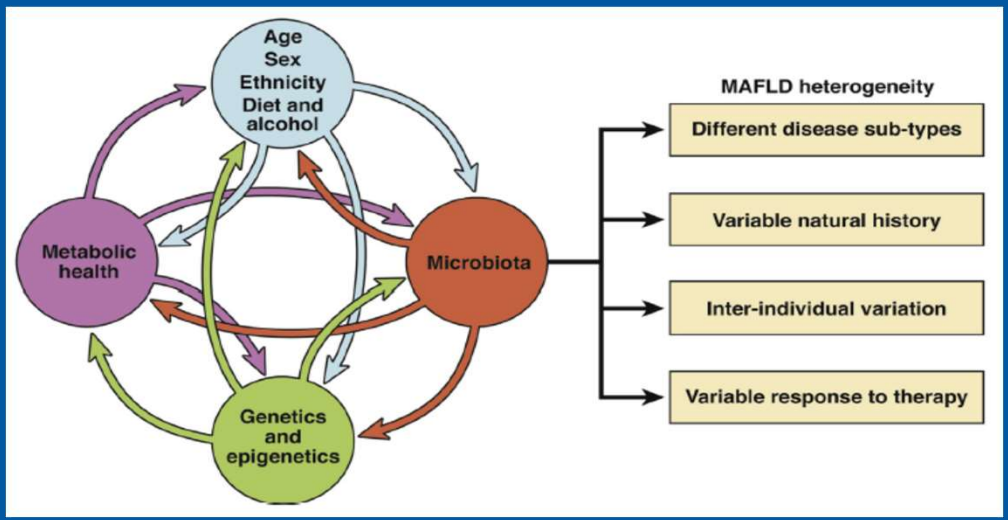
NAFLD Disease Heterogeneity



Eslam M, et al. Gastroenterology 2020.

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Conclusions

- Non-alcoholic fatty liver disease (NAFLD) represents a global public health burden and is associated with significant morbidity and mortality
- Liver fibrosis represents the leading predictor of clinical outcomes and mortality, and therefore case finding for NAFLD should prioritize identification of patients with NAFLD and significant/advanced liver fibrosis
- Significant deficits in the cascade of care for NAFLD persist in the U.S. and limit the potential to mitigate the clinical, public health, and societal cost of NAFLD-associated disease and impairment
- Comprehensive care models represent an important component of a multifaceted public health approach to addressing NAFLD at the local and population health levels, and should be patient-centered, multidisciplinary, and integrated within the healthcare system
- A stepwise approach using simple non-invasive serum and imaging-based tools at the primary care/endocrinology levels to identify high-risk patients for specialty referral may facilitate case finding of patients who may benefit from NASH-directed intervention
- Clinical care pathways for NAFLD by GI specialty societies may provide essential guidance to facilitate the development of comprehensive care models at the local level
- More research is needed to strengthen evidence-based approaches to improve each component of the NAFLD care cascade

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Questions

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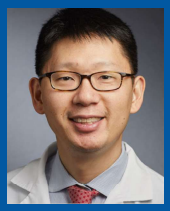

Joseph K. Lim, MD, FACG

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