Non-alcoholic Steatohepatitis: MASHing It All Up and Putting Back Together Again

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Faculty Disclosures:

- I have served/serve on speaker's bureaus or advisory boards sponsored by Gilead, Abbvie, Intercept, GSK, Madrigal

- I have received research support paid directly to the institution from Durect Pharmaceuticals and Ocelot Bio

- There are no off label discussions

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48 y/o obese male with new diagnosis of Type 2 diabetes comes for intake assessment and management. He drinks 2 glasses of wine per night. Labs show: ALT 49, AST 52, tbili 0.9, plts 184K, fasting glu 146, hgb a1c 7.6%. He is on no therapy. He reports his mother had a liver transplant at age 64 for unknown reasons. An ultrasound is performed showing a large fatty liver. Which next best test is likely to help predict his risk for underlying liver fibrosis.

A. Liver biopsy
B. Fibroscan
C. FIB4
D. MR elastrography

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A 64 y/o long standing type 2 diabetic male, now well controlled, comes to you for follow up. He is on metformin and an insulin pump. Hgba1c is 6.4%. His BMI is 34 and is gaining weight over the last 3 years, now has gained 34 lbs in 3 years. His LDL is 114 on atorvastatin 20mg daily. A FIB4 was performed showing 1.94. A fibroscan is performed at an open access center with the result of 10.3 Kpa (Stage 3 fibrosis) and a CAP score of 310 (marked/severe steatosis). Which of the following agents could be considered to help manage his medical issues?

A. Metformin dose increase
B. Pioglitazone
C. Semaglutide SC
D. Simvastatin
E. Vitamin E

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Term	Definition
Non-alcoholic fatty liver disease (NAFLD)	Presence of ≥ 5% hepatic steatosis without evidence of hepatocellular injury in the form of hepatocyte ballooning or evidence of fibrosis. The risk of progression to cirrhosis and liver failure is minimal
Non-alcoholic steatohepatitis (NASH)	Presence of ≥ 5% hepatic steatosis with inflammation and hepatocyte ballooning with or without fibrosis. This can progress to cirrhosis, liver failure, and rarely liver cancer. Note: NASH can be present without fibrosis.
NASH cirrhosis	Presence of cirrhosis with current or previous histological evidence of steatosis or steatohepatitis
NAFD activity score (NAS)	An unweighted composite of steatosis, lobular inflammation, and ballooning scores on liver biopsy. NAS is used to measure changes in histology in clinical trials. Fibrosis is scored separately from NAS

Chalasani et al Hepatology 2018;67:328-357

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In with the New Nomenclature

HEPATOLOGY

Outline

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EDITORIALS

A call for unity: The path towards a more precise and patient-centric nomenclature for NAFLD

American Association for the Study of Liver Diseases, Latin American Association for the Study of the Liver, European Association for the Study of the Liver

Author Information

Hepatology 78(1):p 3-5, July 2023. | *DOI:* 10.1097/HEP.0000000000000412

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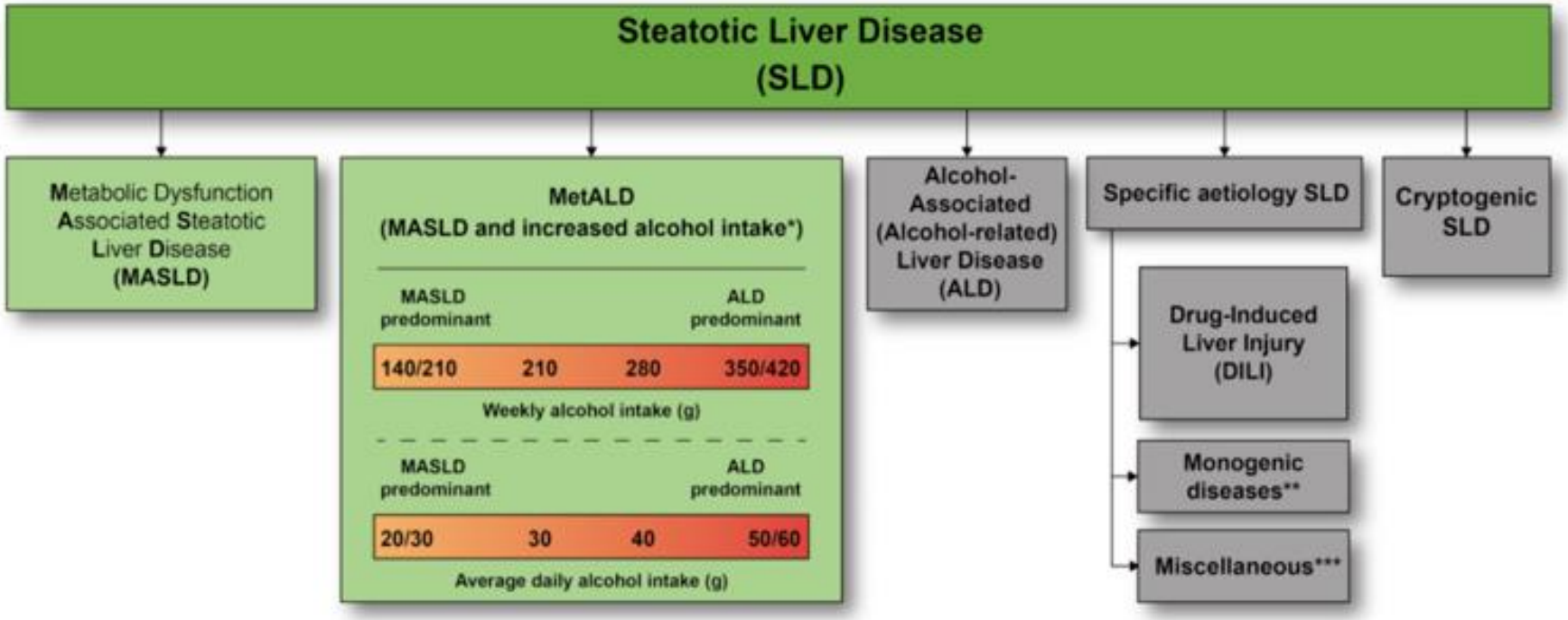
Steatotic Liver Disease Sub-classification



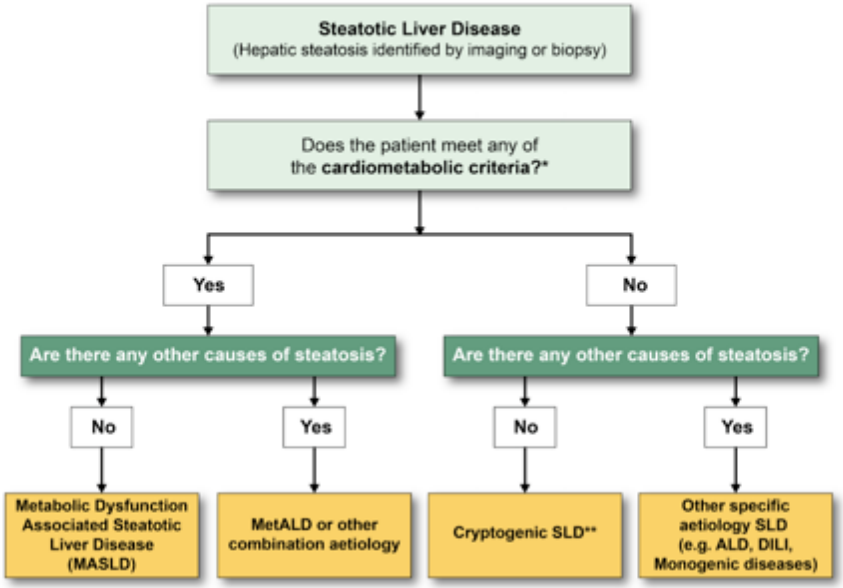
*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease

This depicts the schema for Steatotic Liver Disease (SLD) and its sub-categories. SLD, diagnosed histologically or by imaging, has many potential etiologies. MASLD, defined as the presence of hepatic steatosis in conjunction with one CMRF and no other discernible cause, ALD, and an overlap of the 2 (MetALD), comprise the most common causes of SLD. Within the MetALD group there exists a continuum across which the contribution of MASLD and ALD will vary. To align with current literature, limits have been set accordingly for weekly and daily consumption, understanding that the impact of varying levels of alcohol intake are evolving. Other causes of SLD need be considered separately, as is already done in clinical practice, given their distinct pathophysiology. Multiple etiologies of steatosis can coexist. If there is uncertainty and the clinician strongly suspects metabolic dysfunction despite the absence of CMRF then the term possible MASLD can be considered pending additional testing (e.g., HOMA-IR, OGTT). Those with no identifiable cause (cryptogenic SLD) may be recategorized in the future pending developments in our understanding of disease pathophysiology. Lastly, the ability to provide an affirmative diagnosis allows for the coexistence of other forms of liver disease with MASLD, e.g., MASLD + autoimmune hepatitis or viral hepatitis.

Citation : Rinella ME, Lazarus JV, Ratziu V, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. *Hepatology*. Published online June 24, 2023. doi:10.1097/HEP.0000000000000520

Metabolic Associated Steatotic Liver Disease

MASLD Diagnostic Criteria



*Cardiometabolic criteria

Adult Criteria	Pediatric Criteria
At least 1 out of 5:	At least 1 out of 5:
☐ BMI ≥ 25 kg/m² [23 Asia] OR WC > 94 cm (M) 80 cm (F) OR ethnicity adjusted	☐ BMI ≥ 85th percentile for age/sex [BMI z score ≥ +1] OR WC > 95th percentile OR ethnicity adjusted
☐ Fasting serum glucose ≥ 5.6 mmol/L [100 mg/dL] OR 2-hour post-load glucose levels ≥ 7.8 mmol/L [≥140 mg/dL] OR HbA1c ≥ 5.7% [39 mmol/L] OR type 2 diabetes OR treatment for type 2 diabetes	☐ Fasting serum glucose ≥ 5.6 mmol/L [≥ 100 mg/dL] OR serum glucose ≥ 11.1 mmol/L [≥ 200 mg/dL] OR 2-hour post-load glucose levels ≥ 7.8 mmol [140 mg/dL] OR HbA1c ≥ 5.7% [39 mmol/L] OR already diagnosed/treated type 2 diabetes OR treatment for type 2 diabetes
☐ Blood pressure ≥ 130/85 mmHg OR specific antihypertensive drug treatment	☐ Blood pressure age < 13y, BP ≥ 95th percentile OR ≥ 130/80 mmHg (whichever is lower); age ≥ 13y, 130/85 mmHg OR specific antihypertensive drug treatment
☐ Plasma triglycerides ≥ 1.70 mmol/L [150 mg/dL] OR lipid lowering treatment	☐ Plasma triglycerides < 10y, ≥ 1.15 mmol/L [≥ 100 mg/dL]; age ≥ 10y, ≥ 1.70 mmol/L [≥ 150 mg/dL] OR lipid lowering treatment
☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [40 mg/dL] (M) and ≤ 1.3 mmol/L [50 mg/dL] (F) OR lipid lowering treatment	☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [≤ 40 mg/dL] OR lipid lowering treatment

In the presence of hepatic steatosis, the finding of any of a cardiometabolic risk factor, would confer a diagnosis of MASLD if there are no other causes of hepatic steatosis. If additional drivers of steatosis are identified, then this is consistent with a combination etiology. In the case of alcohol this is termed MetALD. In the absence of overt cardiometabolic criteria, other etiologies must be excluded and if none is identified, this is termed cryptogenic SLD, although depending on clinical judgment could also be deemed to be possible MASLD and thus would benefit from periodic reassessment on a case-by-case basis.

Citation : Rinella ME, Lazarus JV, Ratziu V, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. *Hepatology*. Published online June 24, 2023. doi:10.1097/HEP.0000000000000520

Rinella et al. AASLD Practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 2023. AASLD.org

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Were the Endocrinologists Invited to the Naming?

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Fructose
+
Glucose

Acetyl CoA

De novo lipogenesis ("DNL")

ACC
FAS
SCDs

Lipotoxic lipids

Hepatocellular injury
⇅
Inflammation

"MASH"

Fibrosis

HCC

Muscle, Brown adipose tissue (BAT)

Liver free fatty acids

Carnitine
CPT1
CPT2

Mitochondrial beta-oxidation

PNPLA3?

Steatosis

MOGAT2
DGAT2

Circulating free fatty acids

Adipose IR

Adipose tissue

Triglyceride

Amino acids
Choline/PC

VLDL

Hypertriglyceridemia

Chylomicron triglyceride

(Courtesy of Dr Brent Tetri, SLU)

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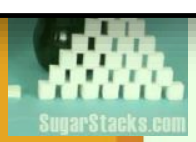
Energy Intake and Disposal



ctose
+
cose

Acetyl CoA

De novo lipogenesis ("DNL")

ACC
FAS
SCDs

Muscle, Brown adipose tissue (BAT)

Circulating free fatty acids

Adipose IR

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Lipotoxic lipids

Liver free fatty acids

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Steatosis

MOGAT2
DGAT2

Triglyceride

Amino acids
Choline/PC

VLDL

Hypertriglyceridemia

Hepatocellular injury
↓↑
Inflammation

"MASH"

Fibrosis

HCC

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(Courtesy of Dr Brent Tetri, SLU)

Energy Intake and Disposal

ctose
+
cose

Acetyl CoA

Muscle, Brown adipose tissue (BAT)

De novo lipogenesis ("DNL")

SREBP-1c

ACC
FAS
SCDs

OCA

Lipotoxic lipids

Hepatocellular injury
↓↑
Inflammation

"MASH"

Fibrosis

HCC

Liver free fatty acids

Carnitine
CPT1
CPT2

Mitochondrial beta-oxidation

MOGAT2
DGAT2

Triglyceride

Amino acids
Choline/PC

VLDL

Hypertriglyceridemia

Circulating free fatty acids

Adipose IR

Adipose tissue

Chylomicron triglyceride

Hepatic fatty acid metabolism

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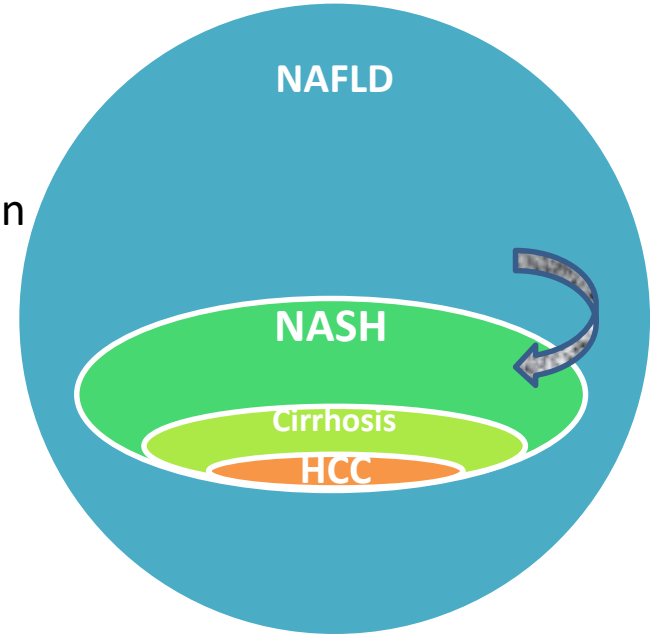
(Courtesy of Dr Brent Tetri, SLU)

- Wide spectrum of liver disease ranging from simple macrovesicular steatosis to steatohepatitis to cirrhosis
- 25% of Americans are affected
  - Hispanics > Caucasians > African Americans
- More common in males
- Accounts for up to ¾ cases of abnormal transaminases in the outpatient setting
- Most common cause of “cryptogenic” cirrhosis



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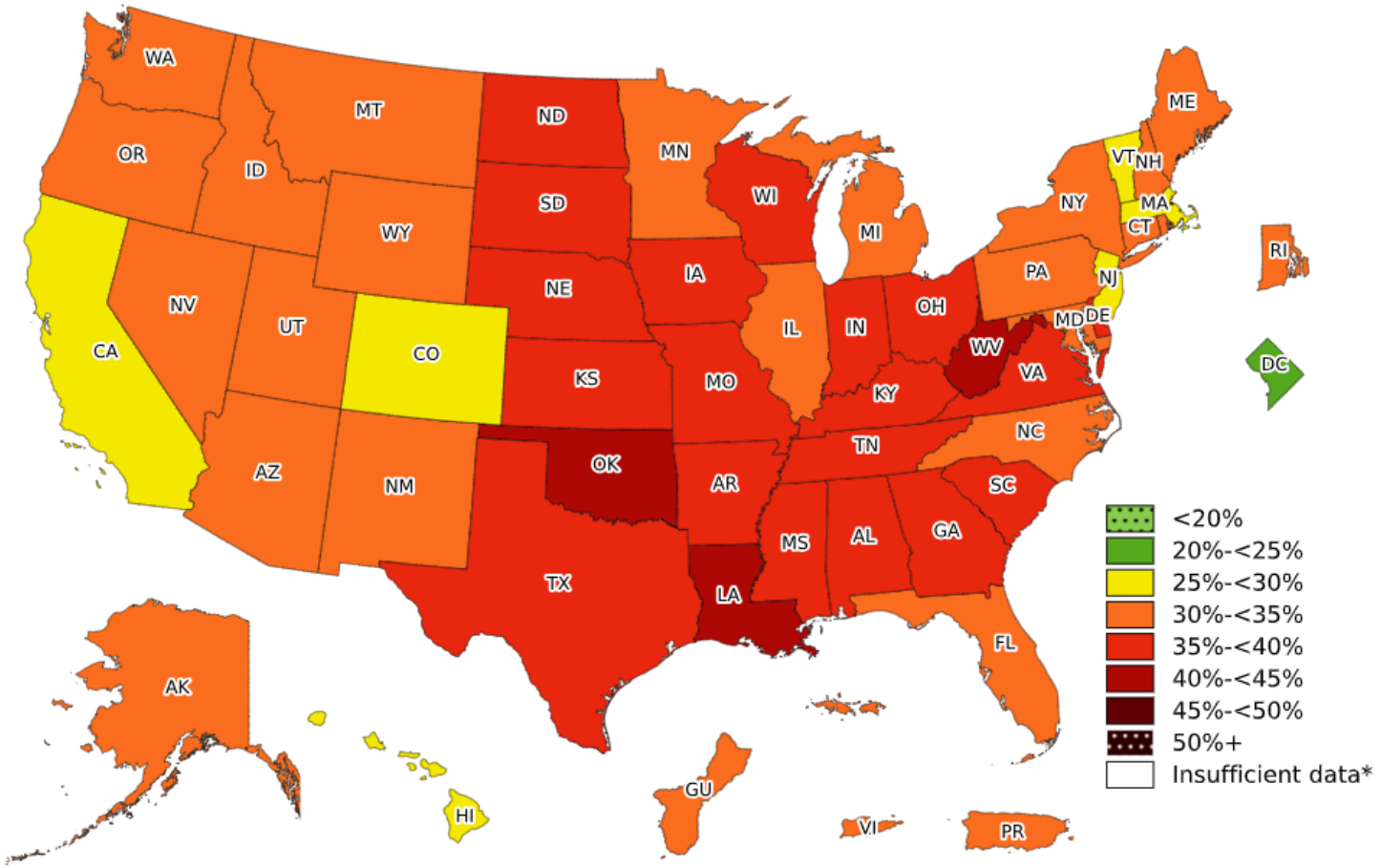
Risk Factors for MAFLD

- Visceral obesity
- Hypertriglyceridemia
- Type 2 diabetes mellitus
  - Insulin resistance
- Medications
  - Tamoxifen, methotrexate, corticosteroids, amiodarone
- No apparent cause in 20-40%
  - This number will decrease when we have a better understanding of relevant genetic polymorphisms

Prevalence† of Obesity Based on Self-Reported Weight and Height Among U.S. Adults by State and Territory, BRFSS, 2022



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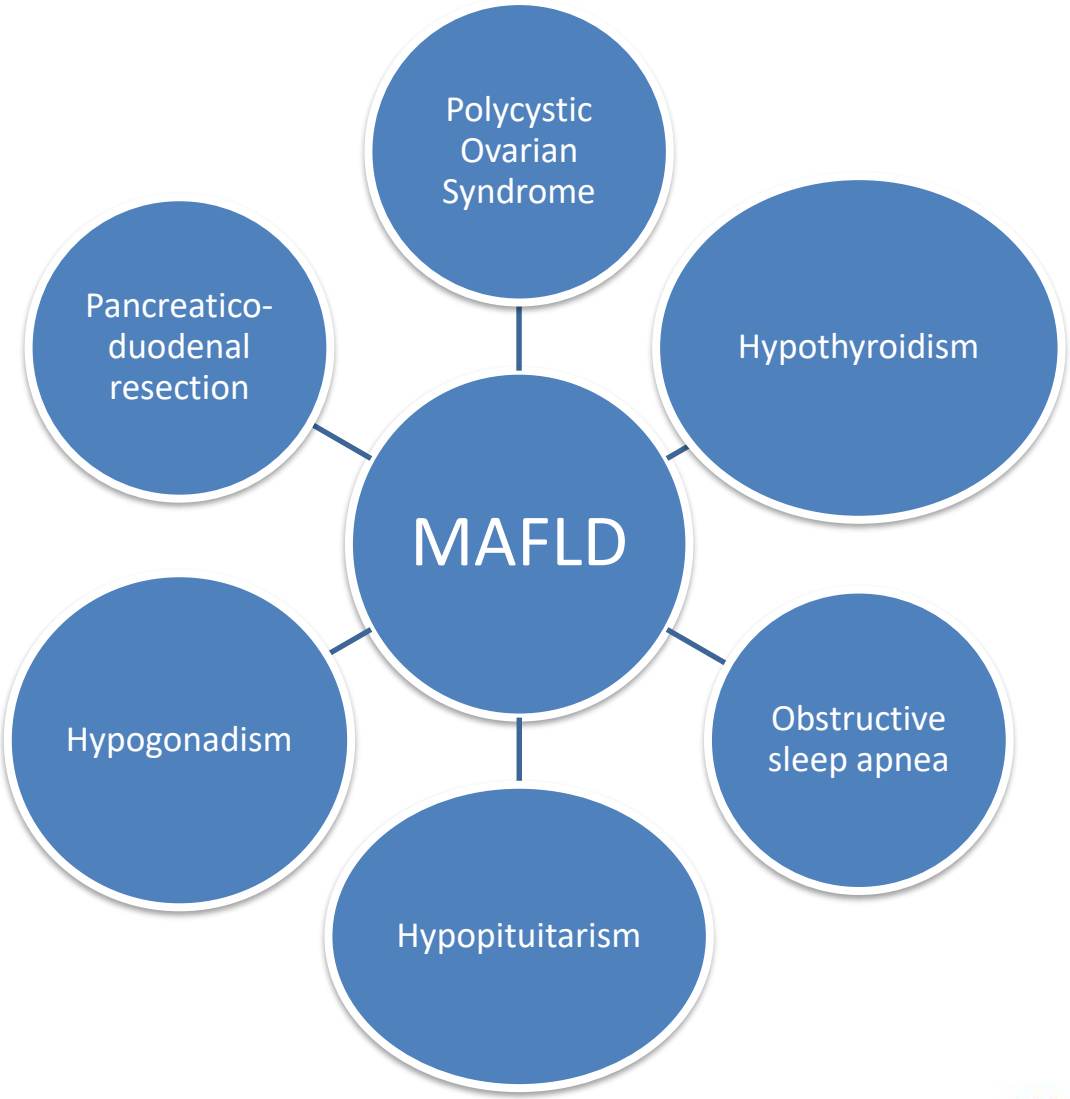
https://www.cdc.gov/obesity/data/prevalence-maps.html#overall

Conditions Associated with MAFLD



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Familial Association with MAFLD

- 18% of patients with MASH have a similarly affected first degree relative (Willner Am J Gastroenterol 2001)
- Patients with NAFLD have a higher % of relatives with cirrhosis than matched controls (Abdelmalek 2006 Clin Gastroenterol Hep)
- Conclusive studies are lacking
- Systematic screening of relatives of patients with MAFLD is not recommended

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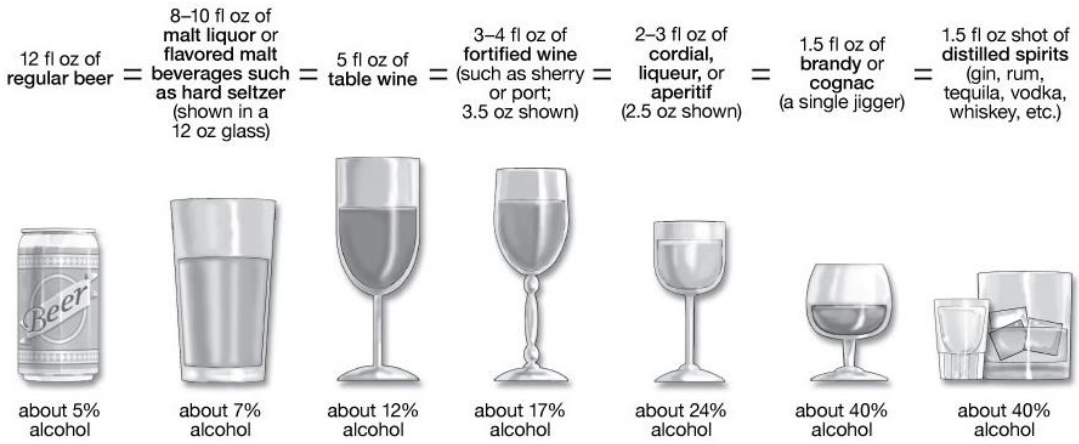
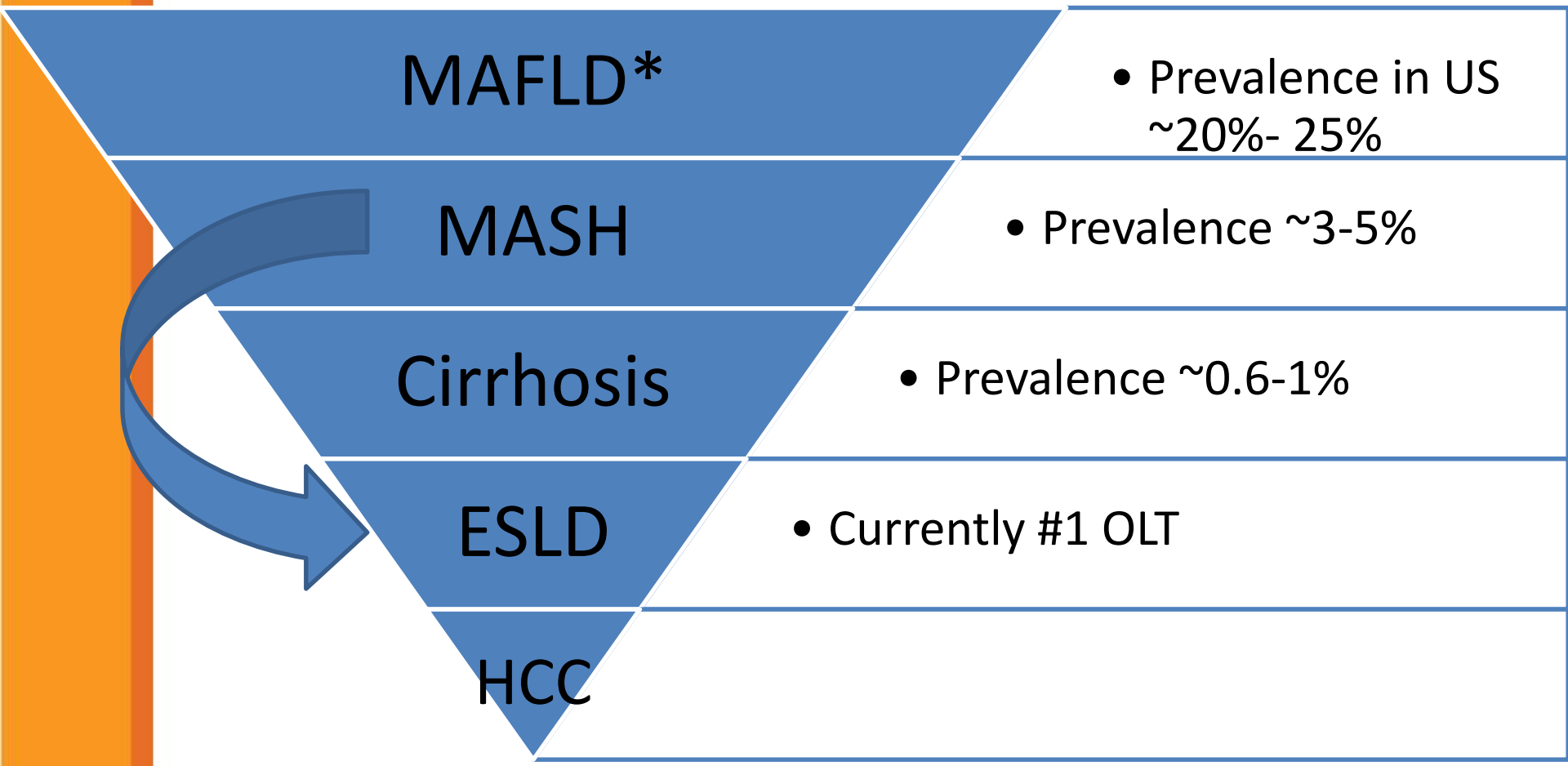
Diagnosis of MAFLD

- Diagnosis of Exclusion
  - Absence of alcohol excess
    - Women ≤1-2 equivalents/d, men ≤ 2-3/d
  - AST and ALT < 10 times upper limit of normal
  - No specific serologic markers
    - Anti-smooth muscle and anti- nuclear antibodies may be weakly positive
  - Ferritin may be mildly elevated





*MAFLD can spontaneously improve even without intervention

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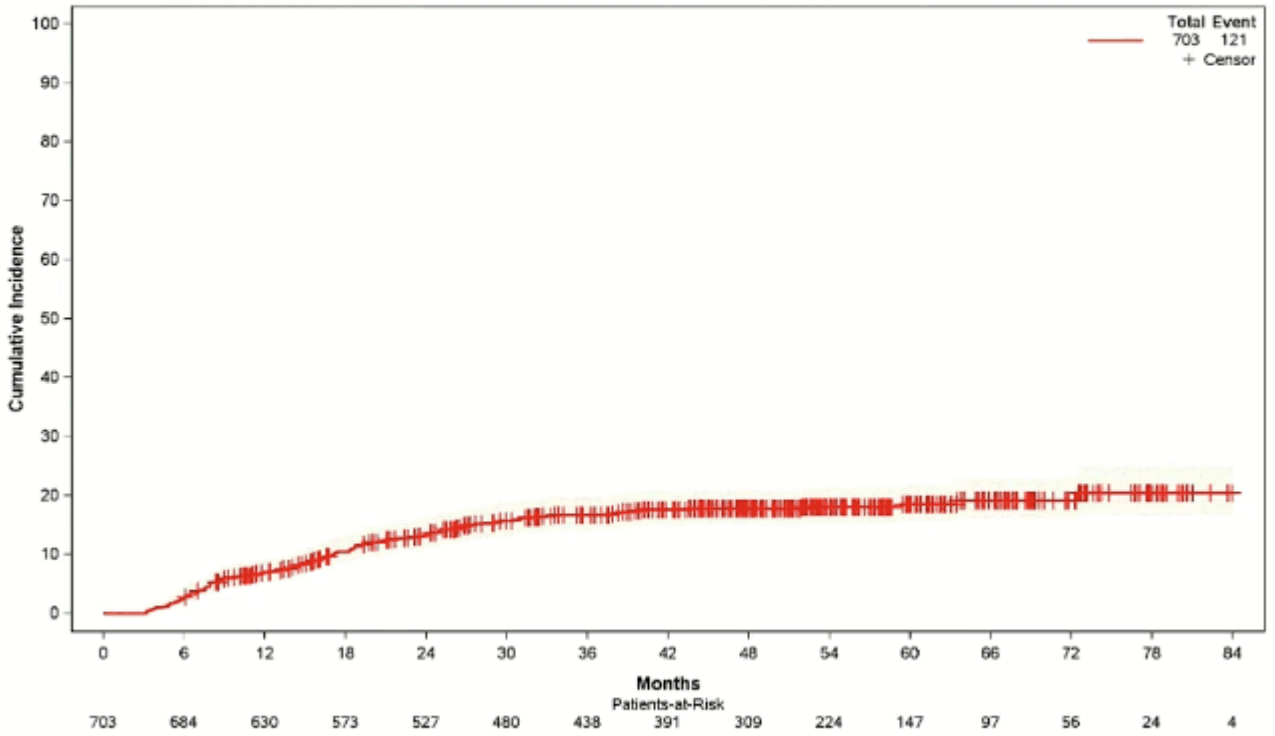
Non-alcoholic steatohepatitis disease progression in participants from the United States TARGET-NASH real world longitudinal observational study

17% progressed to cirrhosis in 4 years.

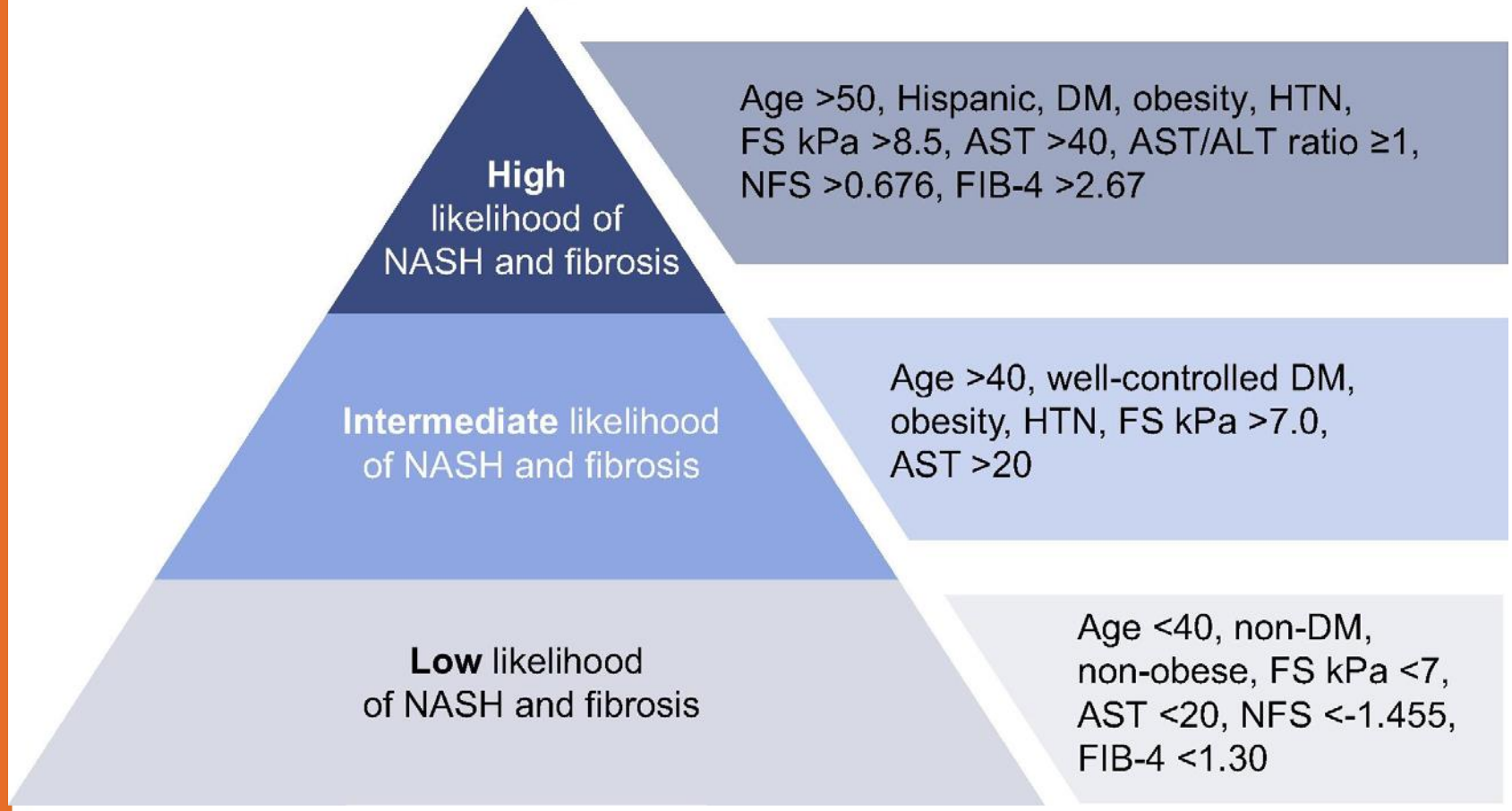
Cumulative Incidence for Disease Progression from NASH (F2-F3) to NASH Cirrhosis



5 deaths included cardiac arrest, acute renal failure, 3 developed cirrhosis with ESLD & died, 1 renal failure

Sartini C et al. EASL 2023

Pre-screening criteria for NASH clinical trials



FS = FibroScan, NFS= NAFLD fibrosis score

Konerman et al, J Hepatol 2018

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- General population-based screening for NAFLD is not advised.
- All patients with hepatic steatosis or clinically suspected NAFLD based on the presence of obesity and metabolic risk factors should undergo primary risk assessment with FIB-4
- High-risk individuals, such as those with T2DM, medically complicated obesity, family history of cirrhosis, or more than mild alcohol consumption, should be screened for advanced fibrosis.
- In patients with pre-DM, T2DM, or 2 or more metabolic risk factors (or imaging evidence of hepatic steatosis), primary risk assessment with FIB-4 should be repeated every 1–2 years

Rinella et al. AASLD Practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 2023. AASLD.org

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- Ultrasound
- Labs – FIB4
- Fibroscan or US elastography
- MR elastography
- Sequential testing
- Liver biopsy

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Fibrosis-4 (FIB-4) Calculator

Share

The Fibrosis-4 score helps to estimate the amount of scarring in the liver. Enter the required values to calculate the FIB-4 value. It will appear in the oval on the far right (highlighted in yellow).

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count } (10^9/L) \times \sqrt{\text{ALT (U/L)}}} =$$

Interpretation:

Using a lower cutoff value of 1.45, a FIB-4 score <1.45 had a negative predictive value of 90% for advanced fibrosis (Ishak fibrosis score 4-6 which includes early bridging fibrosis to cirrhosis). In contrast, a FIB-4 >3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis. In the patient cohort in which this formula was first validated, at least 70% patients had values <1.45 or >3.25. Authors argued that these individuals could potentially have avoided liver biopsy with an overall accuracy of 86%.

Sources

Sterling RK, Lissen E, Clumeck N, et. al. Development of a simple noninvasive index to predict significant fibrosis patients with HIV/HCV co-infection. Hepatology 2006;43:1317-1325.

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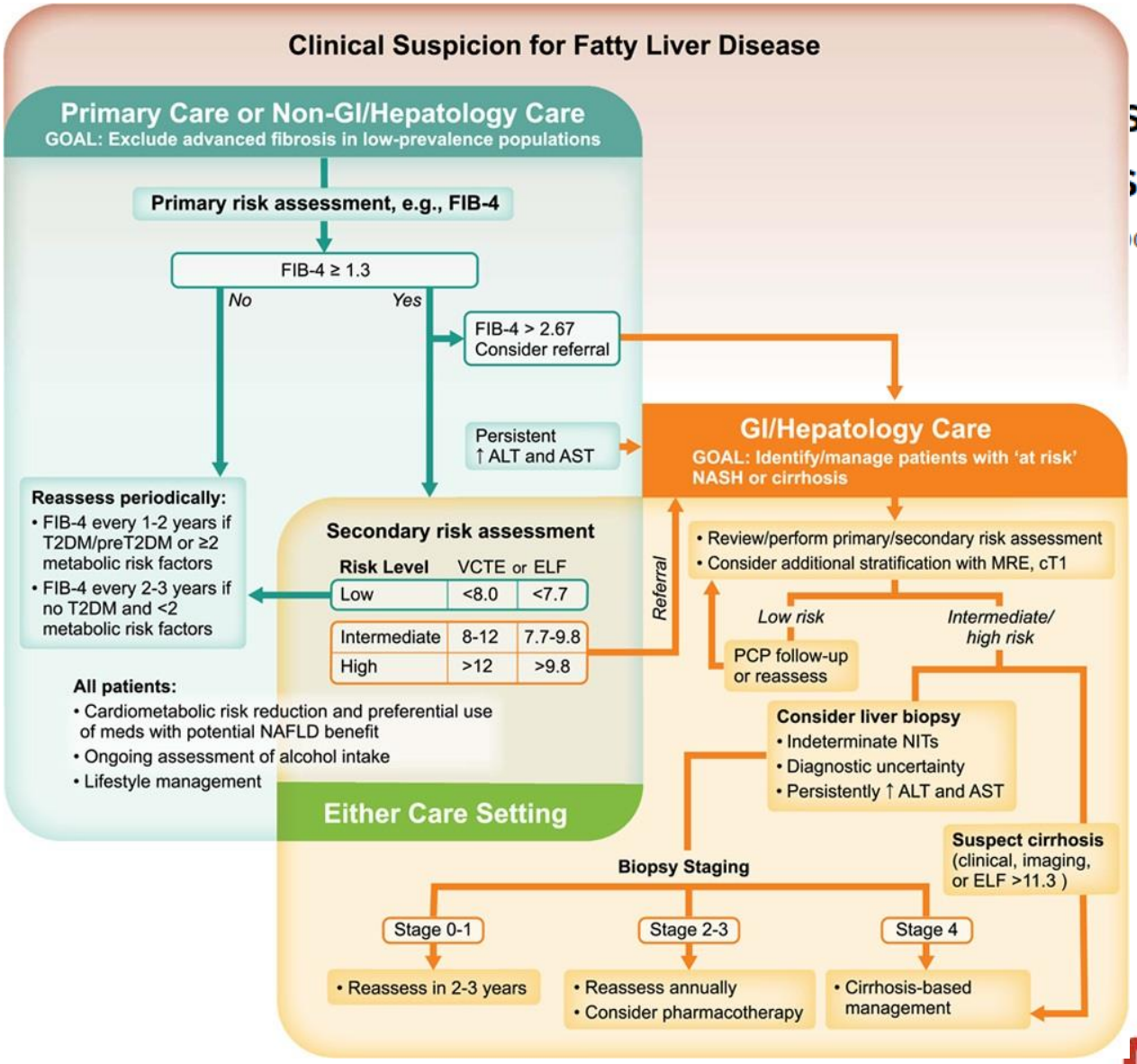

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Rinella et al. AASLD Practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 2023. AASLD.org

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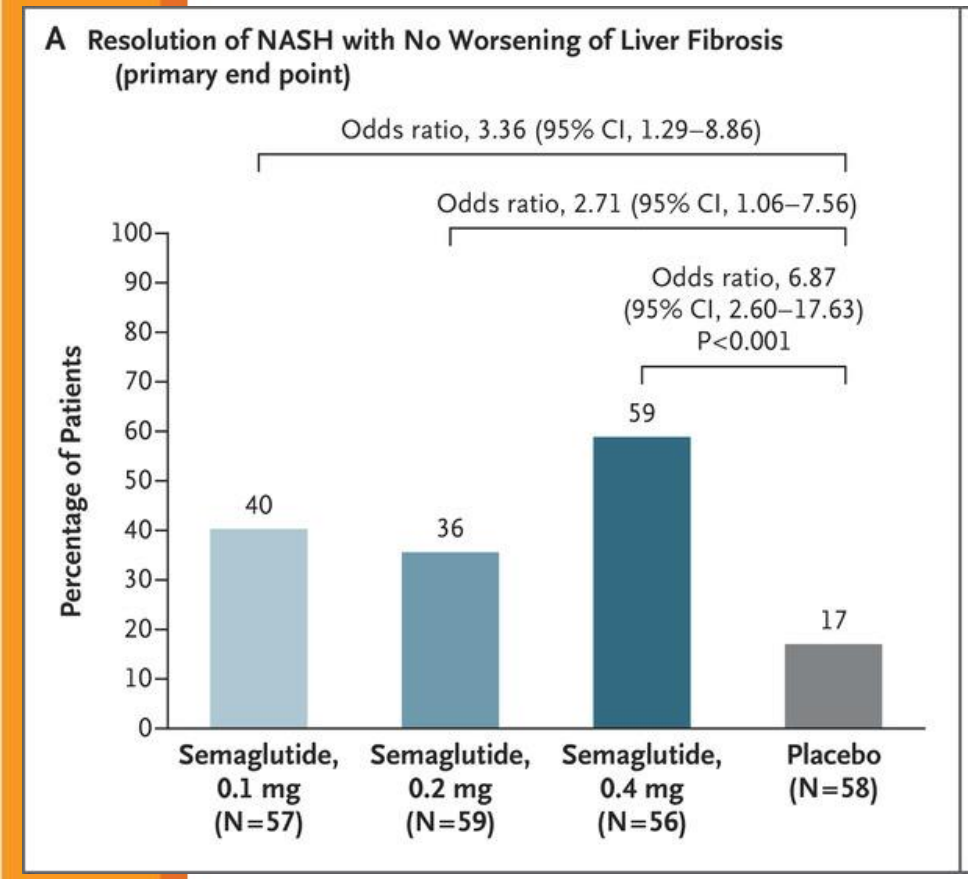
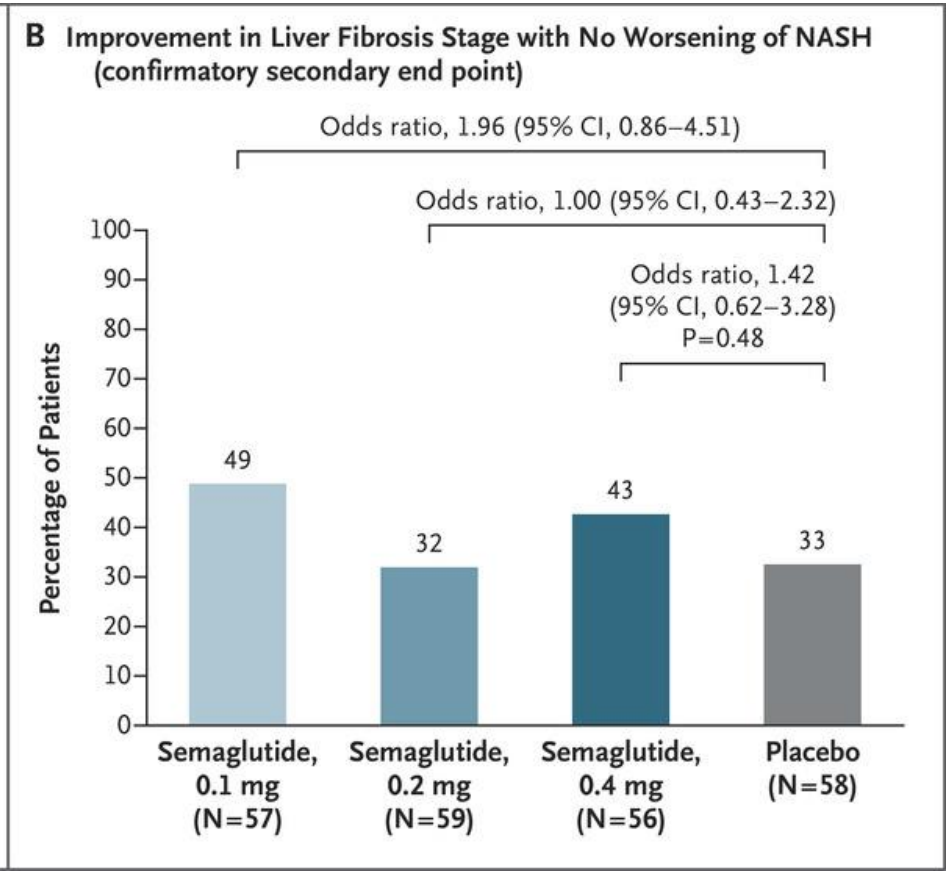
Selective Drug Therapies

- Pioglitazone?
- Semaglutide (GLP1 agonists)
- Resmitirom/VK2809 (THRβ agonists)
- Efruxifermin/Pegozafermin (FGF21 agonists)
- Denifanstat (FASN inhibitors)
- Combination therapies
  - Semaglutide +?





PN Newsome et al. N Engl J Med 2021;384:1113-1124.

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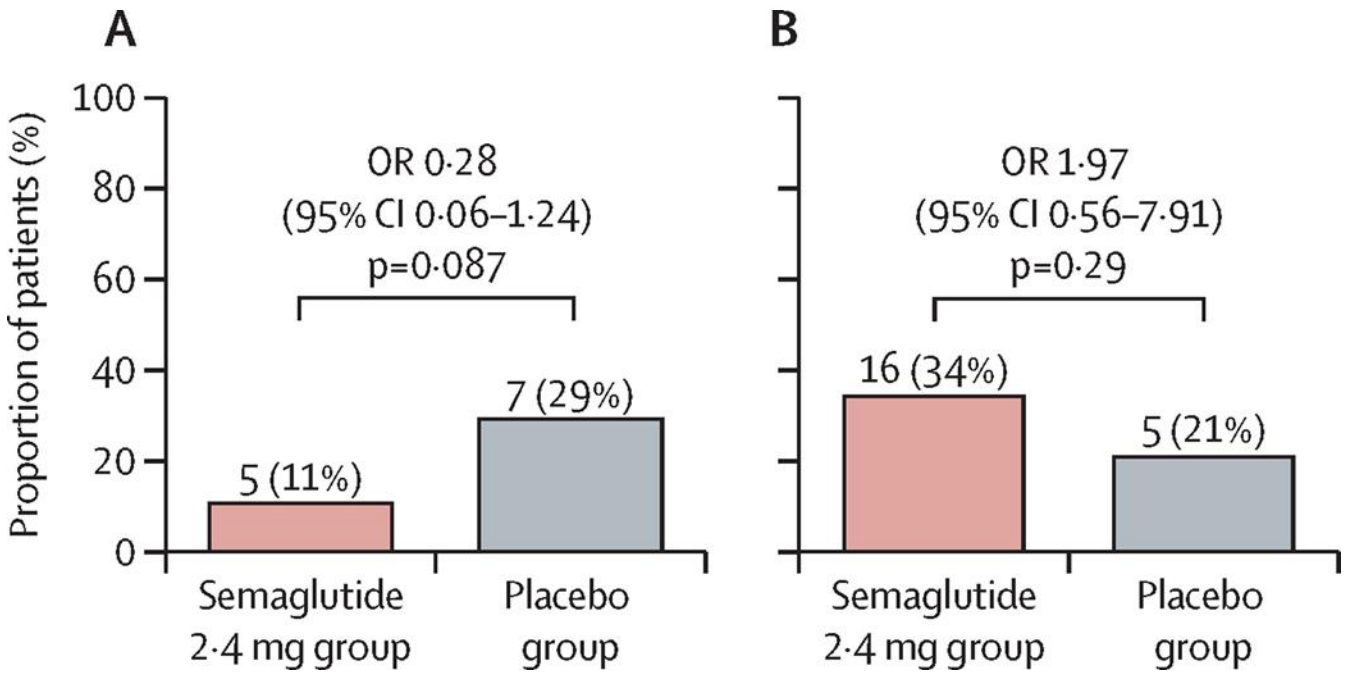

Improvement in liver fibrosis and no worsening of NASH (A) and resolution of NASH (B) at 48 weeks

Loomba R et al. Lancet Gastro and Hep. Vol 8, June 2023

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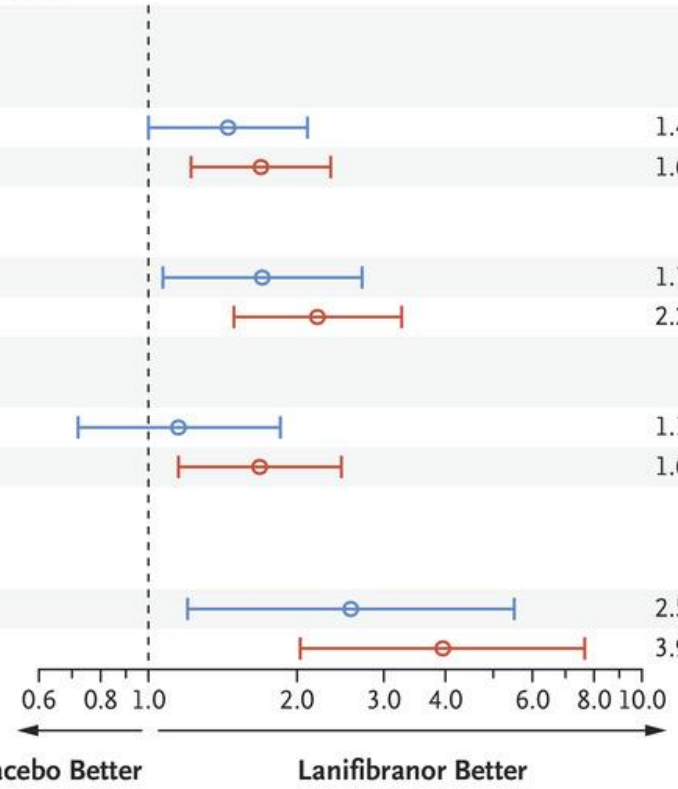
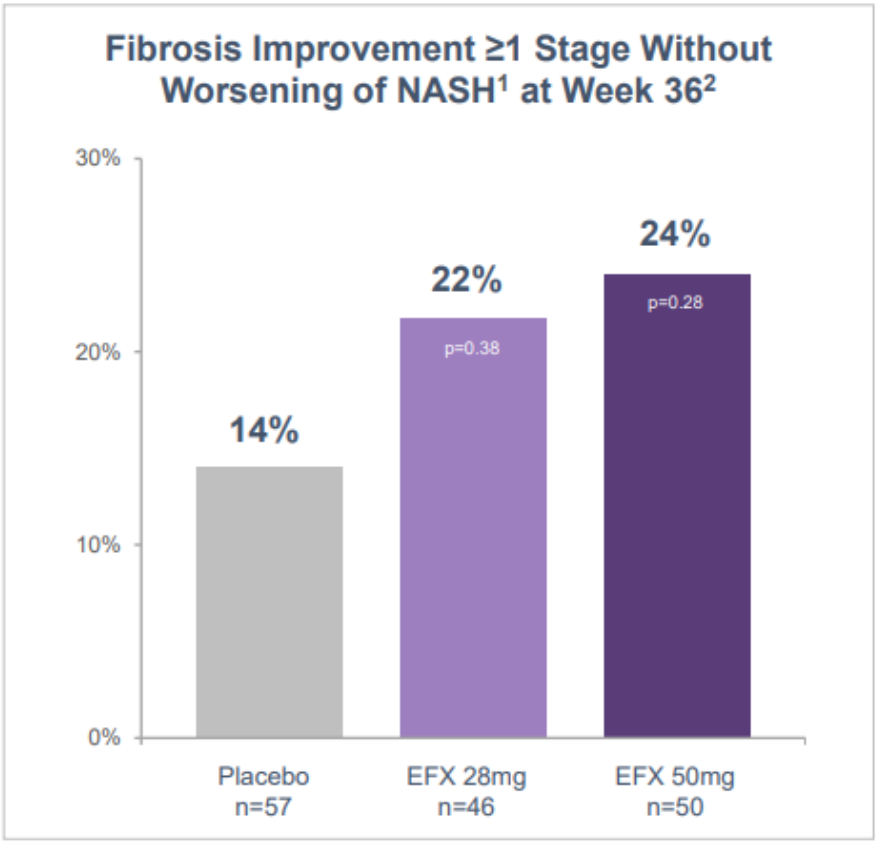
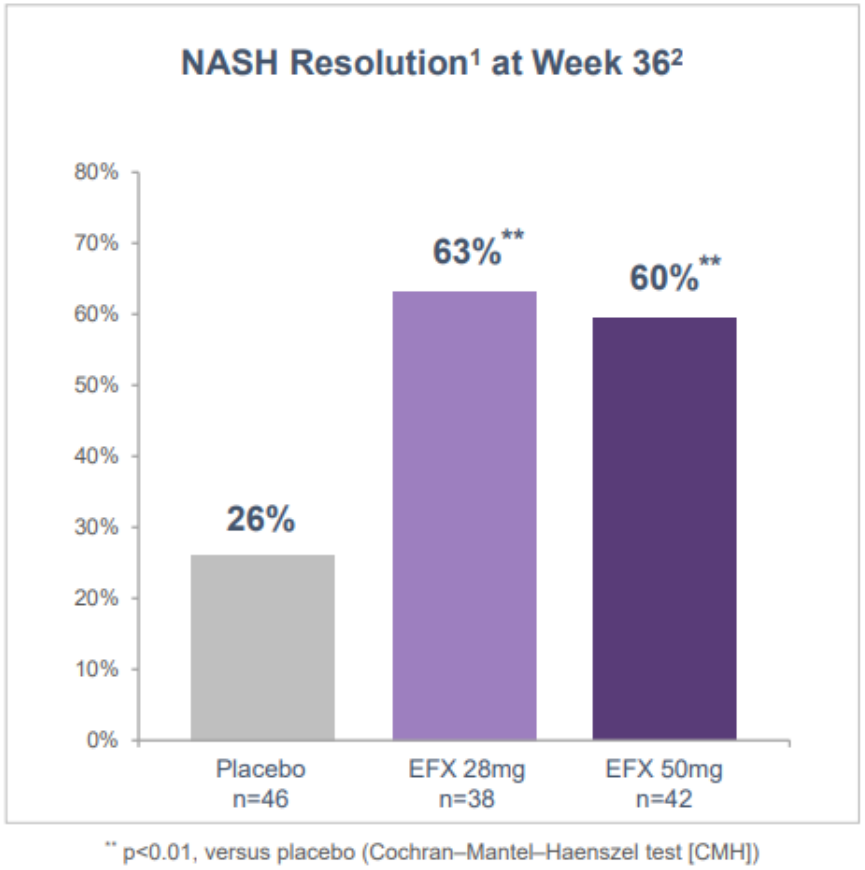
End Point	Placebo	Lanifibranor	Risk Ratio (95% CI)	P Value
	percent of patients with response			
Primary end point: reduction of ≥2 points in SAF-A score and no worsening of fibrosis				
Lanifibranor, 800 mg	33	48	1.45 (1.00–2.10)	0.07
Lanifibranor, 1200 mg	33	55	1.69 (1.22–2.34)	0.007
Secondary end 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)	



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





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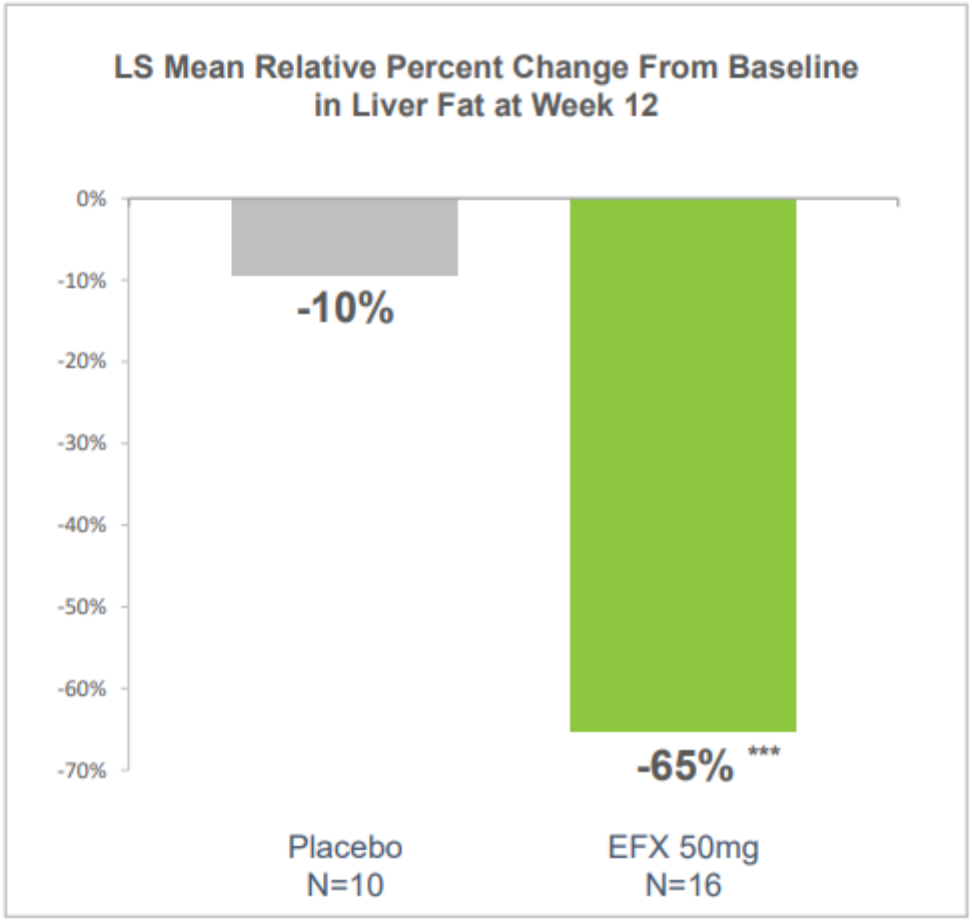

*** p<0.001, versus placebo (ANCOVA[1])

[1] Analysis of Covariance

Source Data: MRI-PDFF Analysis Set (all subjects with baseline and on-study measurements assessed by MRI-PDFF [N=26]); Topline preliminary data

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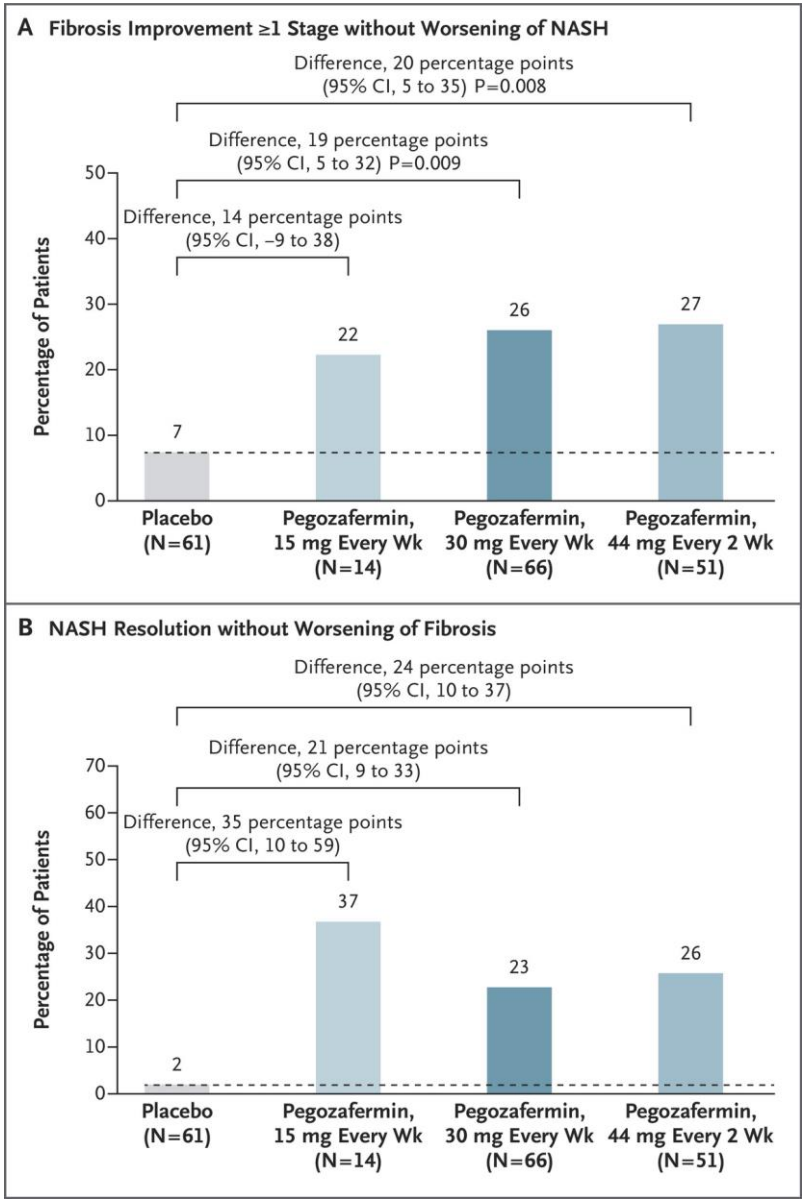
Akero. Symmetry phase 2, cohort D, data from akero.com



R Loomba et al. N Engl J Med 2023;389:998-1008.

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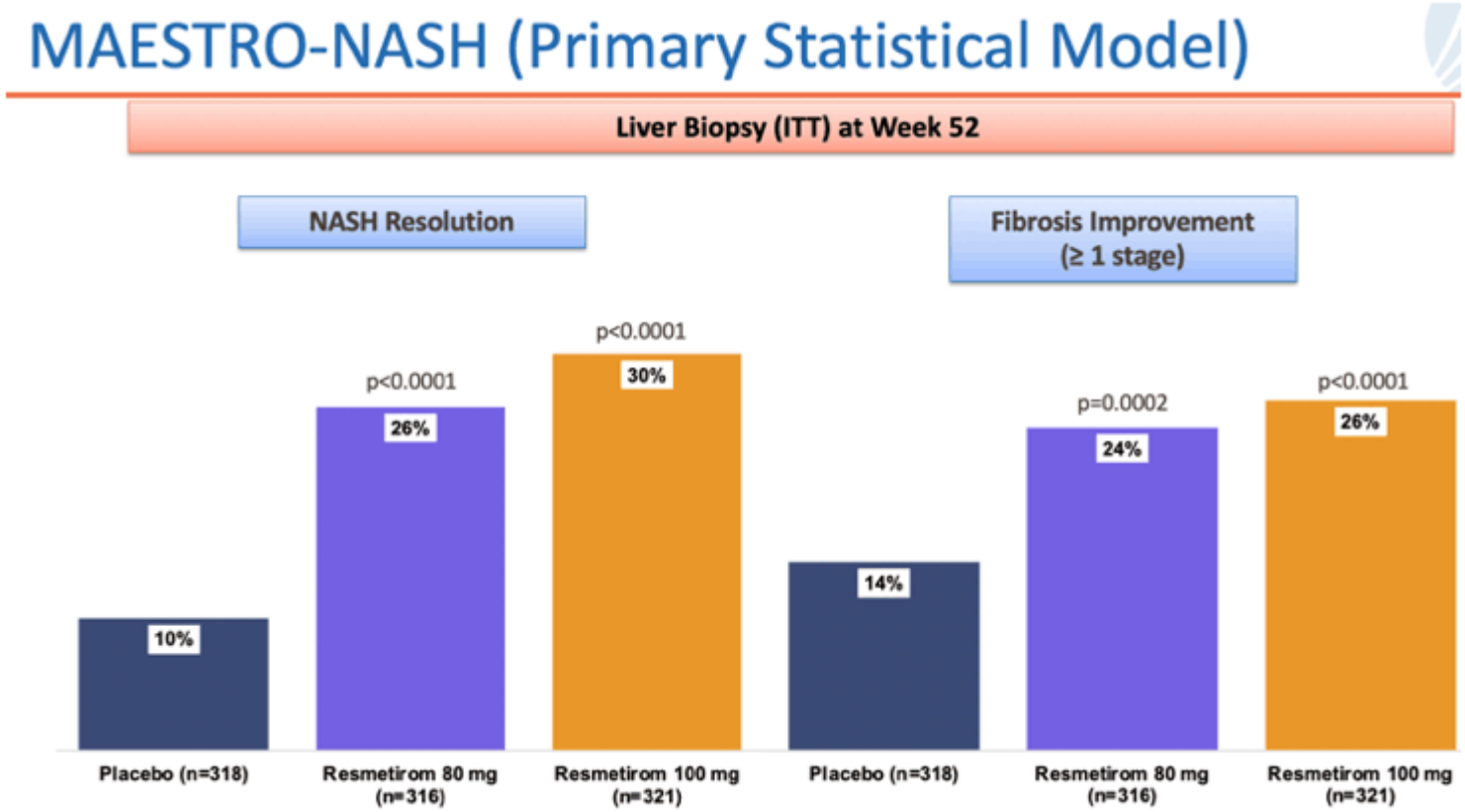
Resmitirom – Thyroid Receptor Beta Agonist



Courtesy Dr Stephen Harrison

- Lifestyle modifications
- Optimize management of co-morbidities
- Surveillance with non-invasive testing
- GLP-1 agonists when clinically indicated for other indications
- Consideration for clinical trials when F2-F4

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48 y/o obese male with new diagnosis of Type 2 diabetes comes for intake assessment and management. He drinks 2 glasses of wine per night. Labs show: ALT 49, AST 52, tbili 0.9, plts 184K, fasting glu 146, hgb a1c 7.6%. He is on no therapy. He reports his mother had a liver transplant at age 64 for unknown reasons. An ultrasound is performed showing a large fatty liver. Which next best test is likely to help predict his risk for underlying liver fibrosis.

A. Liver biopsy
B. Fibroscan
C. FIB4
D. MR elastrography

- Answer: C. FIB4 can be calculated from the labs provided above and is an easy assessment of liver fibrosis risk. Sequential testing of 2 fibrosis assessments is recommended when FIB4 > 1.3 and or multiple metabolic risks factors, obesity and DM type 2 in this case. So the best answer would have been FIB4 plus fibroscan if that was a choice. MRE is also a correct answer but no the cheapest or most available option. Liver biopsy is no longer recommended unless concerns for other liver disease or discrepancy in non-invasive testing results.

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A 64 y/o long standing type 2 diabetic male, now well controlled, comes to you for follow up. He is on metformin and an insulin pump. Hgba1c is 6.4%. His BMI is 34 and is gaining weight over the last 3 years, now has gained 34 lbs in 3 years. His LDL is 114 on atorvastatin 20mg daily. A FIB4 was performed showing 1.94. A fibroscan is performed at an open access center with the result of 10.3 Kpa (Stage 3 fibrosis) and a CAP score of 310 (marked/severe steatosis). Which of the following agents could be considered to help manage his medical issues?

A. Metformin dose increase
B. Pioglitazone
C. Semaglutide SC
D. Simvastatin
E. Vitamin E

Answer: C. There are no currently approved therapies directed at the liver fibrosis for MASH and no approved therapies for fatty liver disease. However, there are agents approved for use in the co-morbidities associated with MASH and should be considered in patients appropriately selected. Semaglutide is indicated in this patient for both obesity and diabetes. In addition, semaglutide has been associated with reduction in liver fat content. Metformin has not been shown to reverse fibrosis in MASH. Pioglitazone has shown limited MASH fibrosis improvement in some studies but it's beneficial effect can be counteracted by the adverse effect of weight gain. Patient is on a statin. Vitamin E has some data supporting its use but not recommended in this patient given possible association of stroke and prostate cancer

Thank you!

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