Metabolic dysfunction Associated Steatotic Liver Disease (MASLD)

What the diabetologist needs to know

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Financial Disclosures

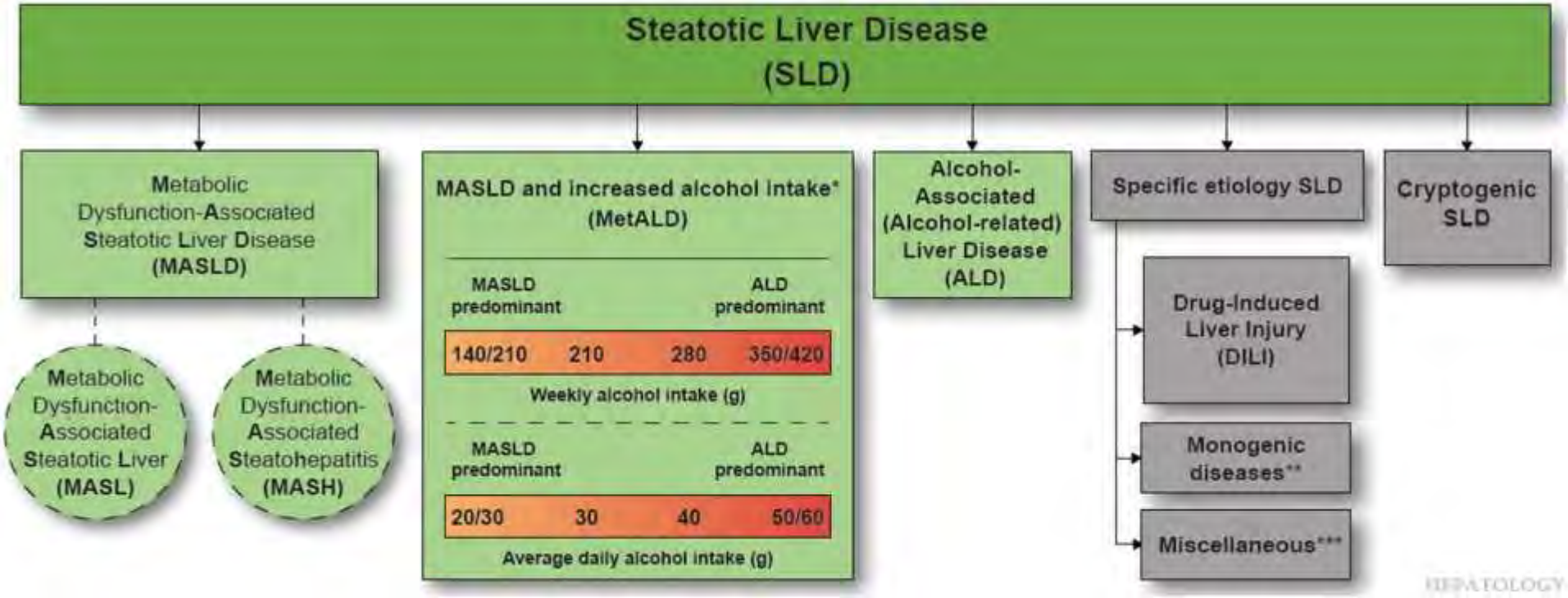
I have no financial relationships with commercial interests to disclose.

Some tables and figures may contain previous terminology referring to metabolic dysfunction-associated steatotic liver disease (MASLD). These are extracted from articles/guidelines written before the change was made to a more scientifically accurate and destigmatizing terminology. Old terminology should no longer be used.

Objectives

- Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD): update on the new nomenclature and definition
- Who should be suspected of having MASLD?
- Who should be evaluated for clinically significant/ “at risk” (F ≥ 2) fibrosis?
- How to manage MASLD?

What's in a Name?



Kanwal et al, Hepatology, November 2023

Definition

MASLD

ALL disease grades and stages

≥5% of hepatocytes display macrovesicular steatosis in the absence of an alternative cause of steatosis

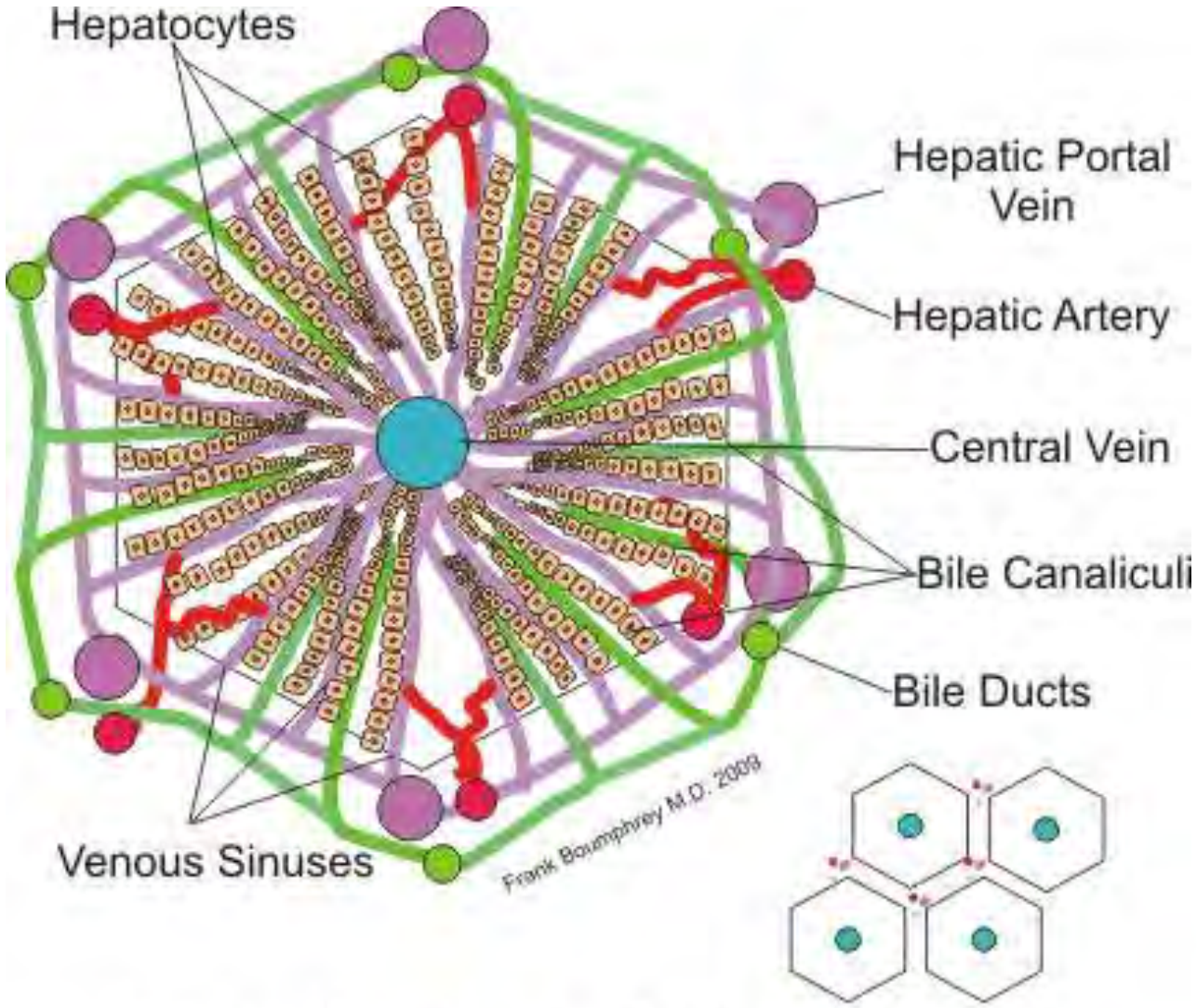
MASL

Macrovesicular hepatic steatosis with no to mild inflammation

MASH

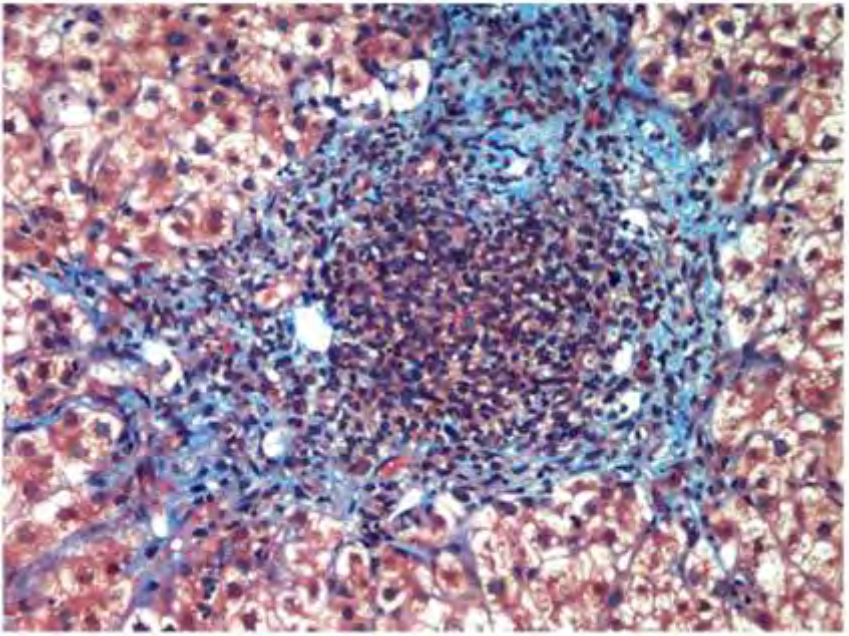
Presence of inflammation and cellular injury (ballooning) w or w/o fibrosis

CIRRHOSIS

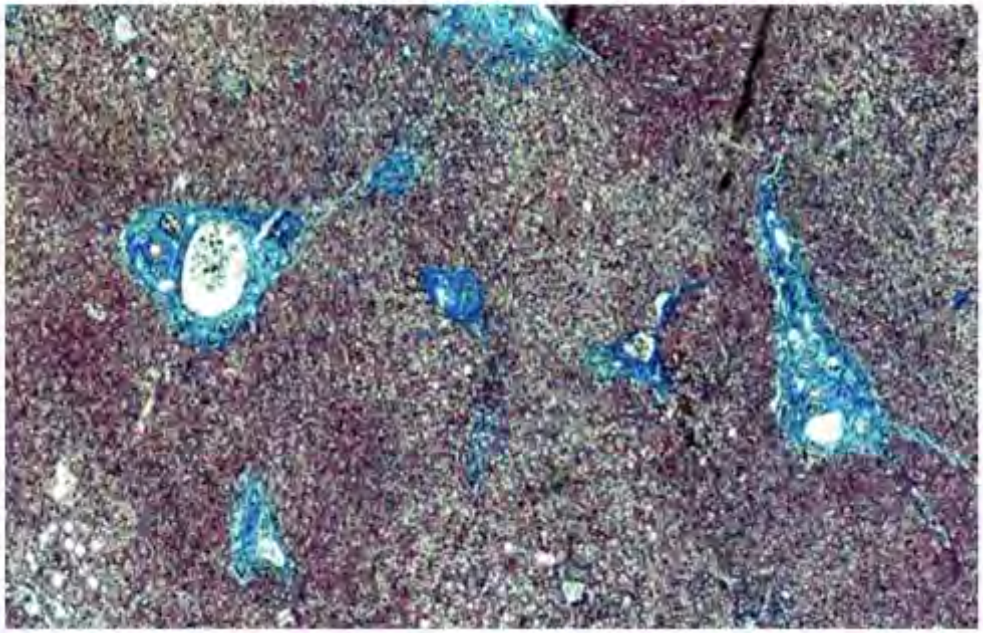


Basic Structure of Liver Lobule

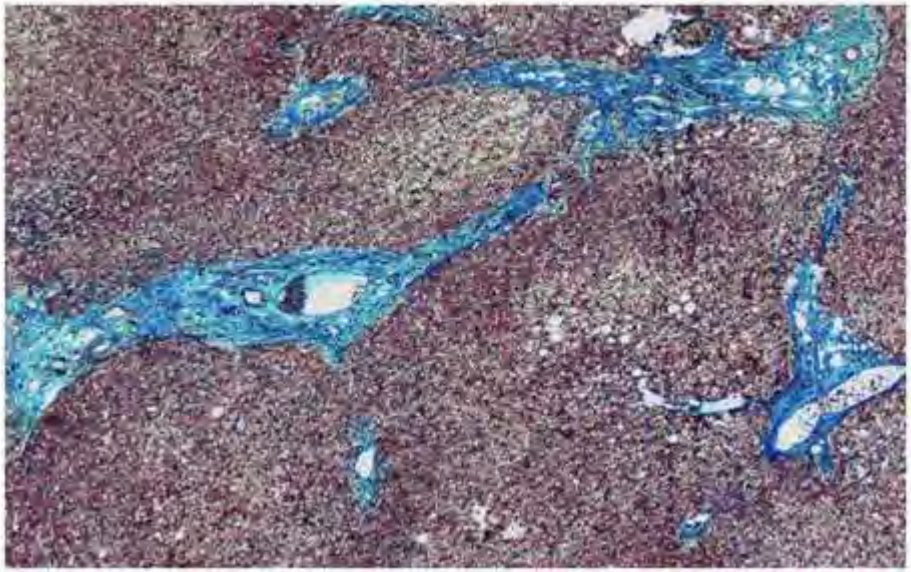
METAVIR F1 fibrosis: Portal fibrosis without fibrous septa



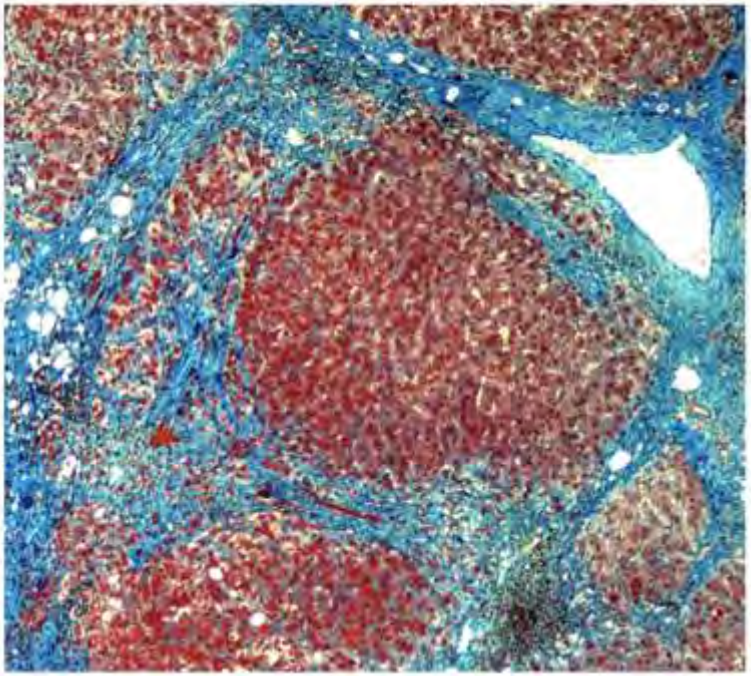
METAVIR F2 fibrosis: Portal fibrosis with few septa



METAVIR F3 fibrosis: Portal fibrosis with numerous septa without cirrhosis



METAVIR F4 fibrosis: Cirrhosis

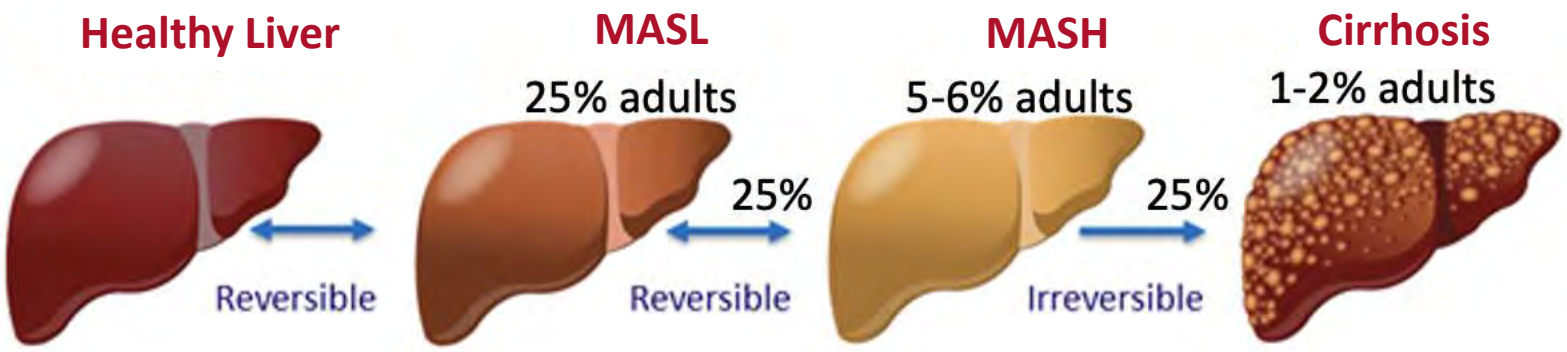


Epidemiology and Natural History

MASLD: worldwide estimated prevalence of 30% up from 17.6% (1990)
More common in the overweight/obese population (global prevalence 50%)
More common in the T2DM population (60%)

The prevalence of clinically significant fibrosis (stage 3 or 4) is increasing. As such, the incidence of hepatic decompensation, HCC, and death related to MASLD cirrhosis are likewise expected to increase 2- to 3-fold by 2030.

The total burden in the USA was $103 billion per year in direct costs.



Case Study

54 yo Hispanic male

Hypertension, type 2 diabetes, hyperlipidemia, BMI of 34

Complains of abdominal distress, fatigue and low libido

Frustrated that he has gained 20 lbs. over the past year despite attempts at healthy diet and exercise

3 months ago, glipizide was increased to 10 mg BID because of an A1c of 9.5%

Other medications:

Metformin 1000 mg BID

Rosuvastatin 10 mg daily

Lisinopril 10 mg daily

Case Study

Family History:
Mother with T2DM, HTN
Father with HTN, hyperlipidemia, myocardial infarction
No history of known liver disease

Social History:
Married with 3 kids
Desk job
Drinks alcohol a couple of times a week

Thoughts?

Multidisciplinary approach to this patient

Prevention > cure

Liver disease is silent until decompensation

Reflexes to have:
Older patient, at risk ethnic group, multiple metabolic risk factors → at risk of MASLD.
Is there a role for an ultrasound?
Does he have advanced liver fibrosis ?
Can he possibly have MetALD or other liver injuries?
Other causes of fatigue and low libido? Cirrhosis? Anemia? Hypothyroidism? Hypogonadism? Sleep apnea? Depression?

Case Study

Physical exam:

Vitals normal

Hepatomegaly

Waist circumference 40 inches (102 cm)

Labs:

Testosterone 500 ng/dL (normal)

HbA1c 8.7%

Platelets 155K

ALT 65, AST 55, Alkaline phosphatase 125 (1.3 x ULN), Bilirubin 1.2

Albumin 4.1

INR normal

Glucose 128

Creatinine 1.2, GFR 80 ml/min/1.73 m2

TSH normal

FLP normal

Thoughts?

No evidence of cirrhosis on physical exam but that does NOT r/o advanced fibrosis

Platelet trend is important

AST:ALT >=1
What if ALT was 40? Follow or evaluate now?

Liver injury vs liver function

Would you stop statin?

Can we optimize his diabetes regimen to benefit his liver?

Always ask about herbs/ OTC/ supplements

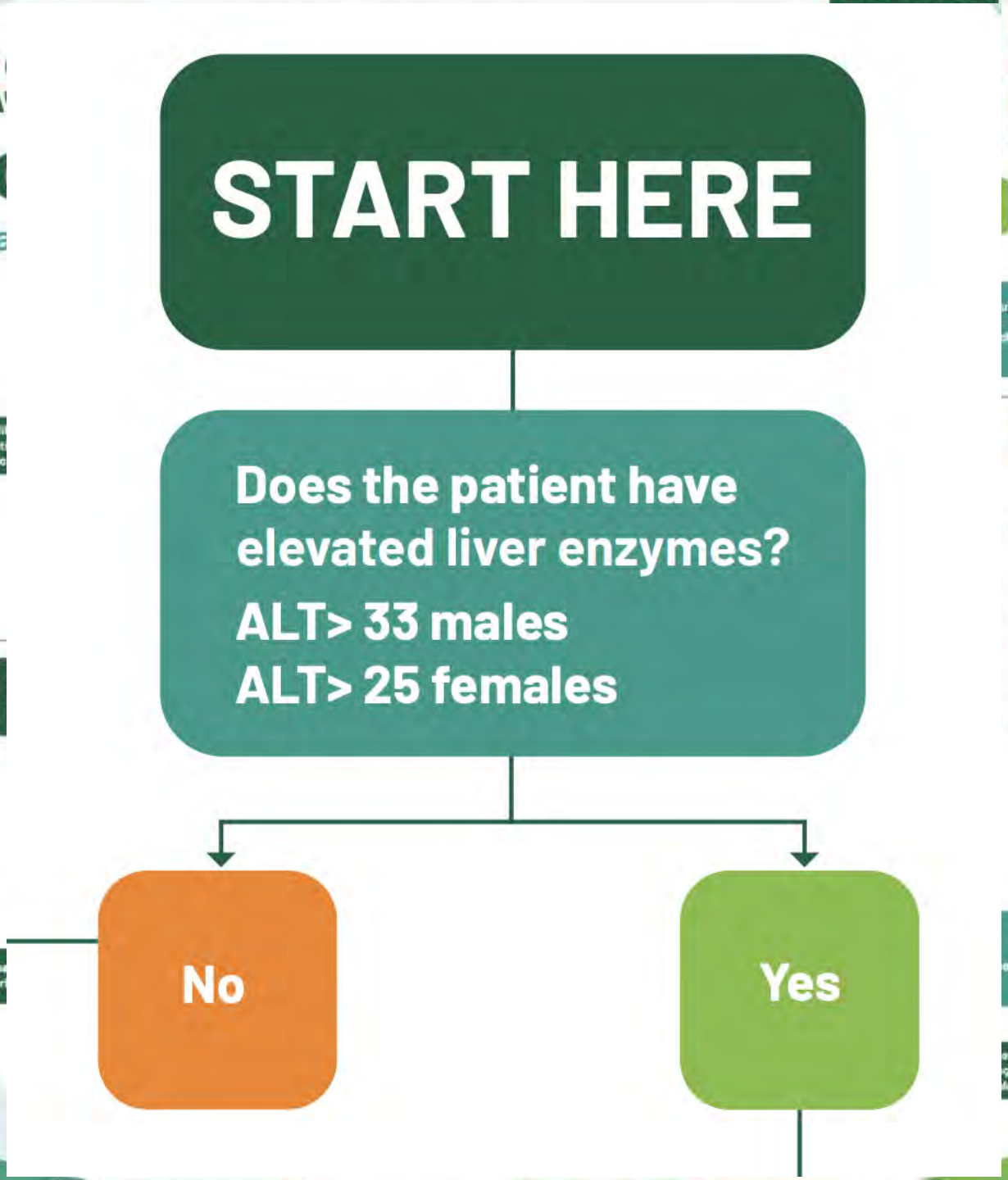
Screening for MASLD

General population-based screening for MASLD is not advised.

Although standard ultrasound can detect hepatic steatosis, it is not recommended as a tool to identify hepatic steatosis due to low sensitivity across the MASLD spectrum.

MASLD may be suspected in patients who fulfill any of the following criteria:

- Liver steatosis on imaging
- Unexplained elevation in liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST])


START HERE
Does the patient have elevated liver enzymes?
ALT> 33 males
ALT> 25 females
No
Yes

Screening for MASLD

MASLD may be suspected in patients who fulfill any of the following criteria:

- One or more cardiometabolic risk factors or MASLD co-morbidities (e.g., obstructive sleep apnea OSA, hypothyroidism, hypogonadism, polycystic ovarian syndrome PCOS)
- First-degree relative of a patient with MASLD cirrhosis

Adult Criteria

At least 1 out of 5:

- ☐ BMI ≥ 25 kg/m² [23 Asia] **OR** WC > 94 cm (M) 80 cm (F) **OR** ethnicity adjusted equivalent
- ☐ 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
- ☐ Blood pressure ≥ 130/85 mmHg **OR** specific antihypertensive drug treatment
- ☐ Plasma triglycerides ≥ 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

Screening for “at risk” fibrosis

At risk fibrosis = clinically significant fibrosis = ≥ F2

Targeted screening of populations at increased risk for advanced liver disease is advised:

- Patients with T2DM
- Obesity with metabolic complications
- Family history of cirrhosis
- Significant alcohol use (> 20 g / day in F, > 30 g / day in M)

Screening for “at risk” fibrosis

TABLE 4 - Screening for advanced fibrosis in high-risk populations

Screening recommended[a]	Prevalence of advanced fibrosis, %	References
T2DM	6–19	10,112,113,115,118,280–284
Medically complicated obesity	4–33	256–262,473–480
NAFLD in context of moderate alcohol use	17	285–291,300–307
First-degree relative of a patient with cirrhosis due to NAFLD/NASH	18	292,293

Abbreviation: T2DM, type 2 diabetes mellitus.

[a]Prevalence of advanced fibrosis in background population 0.9%–2%.[14,302,303,305]

Rinella et al, Hepatology, May 2023

MD CALC

Search "QT interval" or "QT" or "EKG"

Fibrosis-4 (FIB-4) Index for Liver Fibrosis

Noninvasive estimate of liver scarring in HCV and HBV patients, to assess need for biopsy

When to Use ^ | Pearls/Pitfalls v | Why Use v

- Patients with any known risk factors for liver disease, including chronic hepatitis, alcoholic liver disease, and the cholestatic and metabolic liver diseases.
- Patients with known liver fibrosis should have their fibrosis trended over time to evaluate for progression or stabilization.

Age Use with caution in patients <35 or >65 years old, as the score has been shown to be less reliable in these patients		years
AST Aspartate aminotransferase	Norm: 15 - 41	U/L
ALT Alanine aminotransferase	Norm: 1 - 35	U/L
Platelet count	Norm: 150 - 350	$\times 10^3/\mu L$

Result:

Please fill out required fields.

» Next Steps | Evidence | Creator Insights

AST to Platelet Ratio Index (APRI) ☆

Determines the likelihood of hepatic fibrosis and cirrhosis in patients with hepatitis C.

When to Use ^ | Pearls/Pitfalls v | Why Use v

Patients with hepatitis C being considered for liver biopsy to determine chance of fibrosis or cirrhosis.

AST	Norm: 15 - 41	U/L
AST upper limit of normal	40	U/L
Platelet count	Norm: 150 - 350	× 10^3/μL ⇋

NAFLD (Non-Alcoholic Fatty Liver Disease) Fibrosis Score ☆

Estimates amount of scarring in the liver based on several laboratory tests.

When to Use ⌄ | Pearls/Pitfalls ⌄ | Why Use ⌄

Age		years
BMI	Norm: 20 - 25	kg/m²
Impaired fasting glucose/diabetes	No 0 / Yes +1	
AST	Norm: 15 - 41	U/L
ALT	Norm: 1 - 35	U/L
Platelet count	Norm: 150 - 350	× 10³/μL ⇋
Albumin	Norm: 3.5 - 5.5	g/dL ⇋

BARD Score for NAFLD Fibrosis ☆

Predicts risk of advanced fibrosis in NAFLD patients.

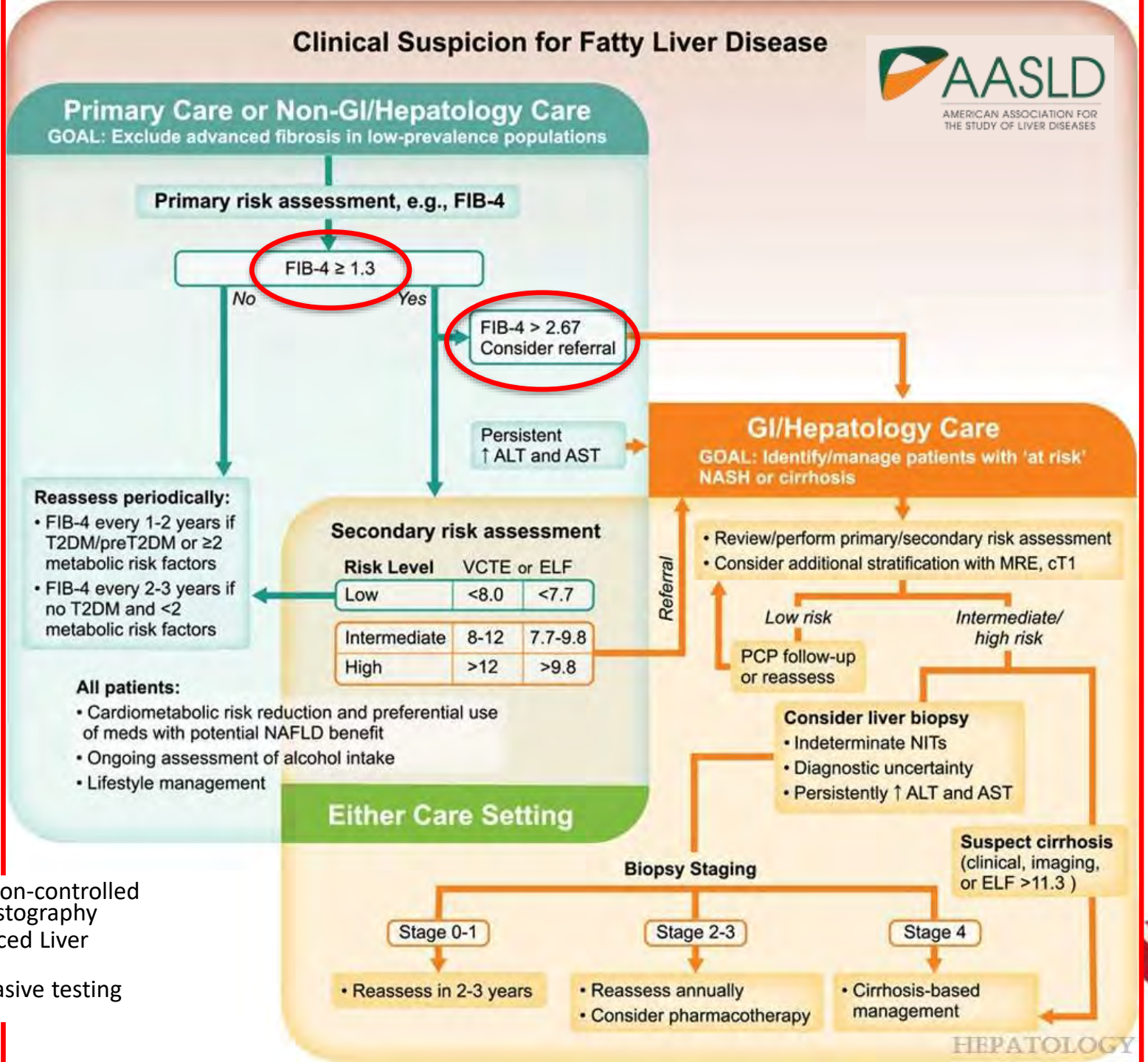
When to Use ⌄ | **Pearls/Pitfalls ^** | Why Use ⌄

- Strong negative predictive value for ruling out fibrosis (Raszeja-Wyszomirska 2010).
- Original study involved mostly Caucasian patients and therefore score may be less applicable in other populations.
- Doesn't predict fibrosis but rules out (high sensitivity).
- Helps differentiate adult patients with NAFLD from NASH who have not yet developed clinical stigmata of cirrhosis.

BMI ≥28	**No 0** / Yes +1
AST	Norm: 15 - 41 U/L
ALT	Norm: 1 - 35 U/L
Diabetes	**No 0** / Yes +1

Screening for “at risk” fibrosis

Aminotransferase levels are frequently normal in patients with advanced liver disease due to MASLD and should not be used in isolation to exclude the presence of MASLD with clinically significant fibrosis.

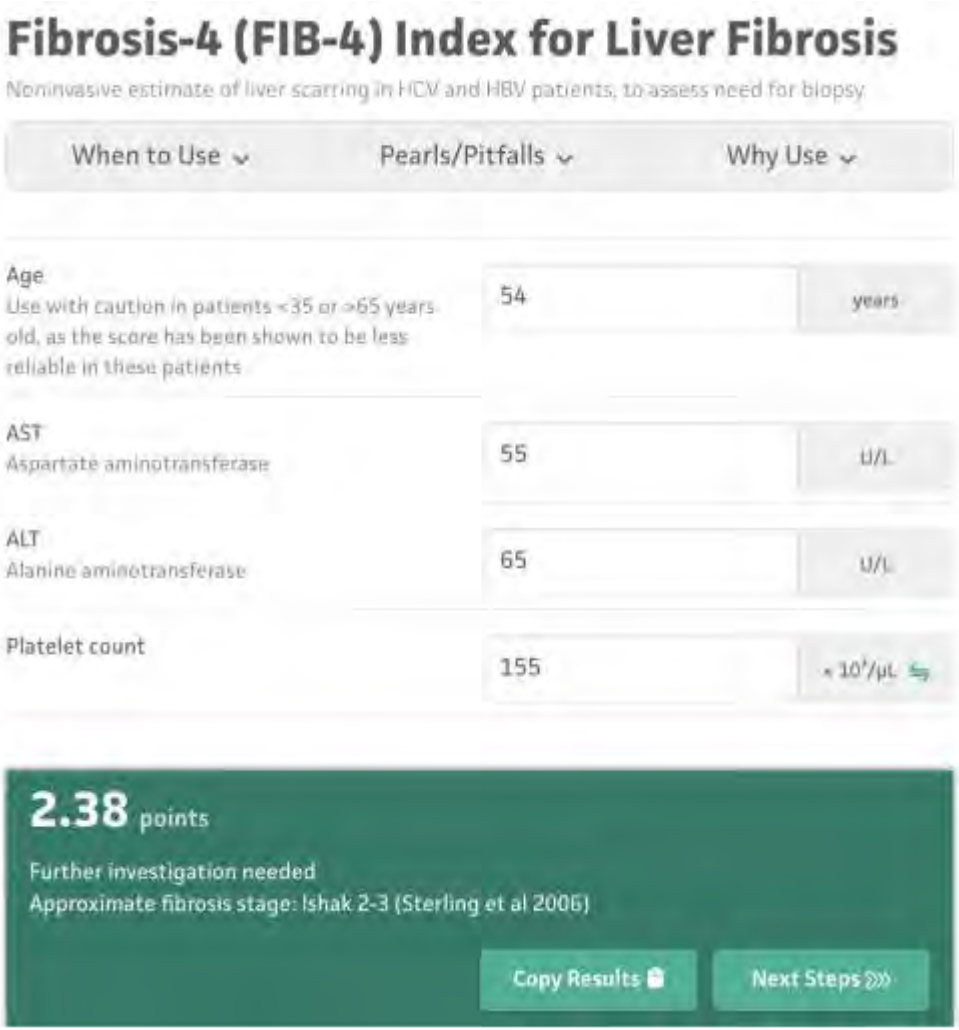


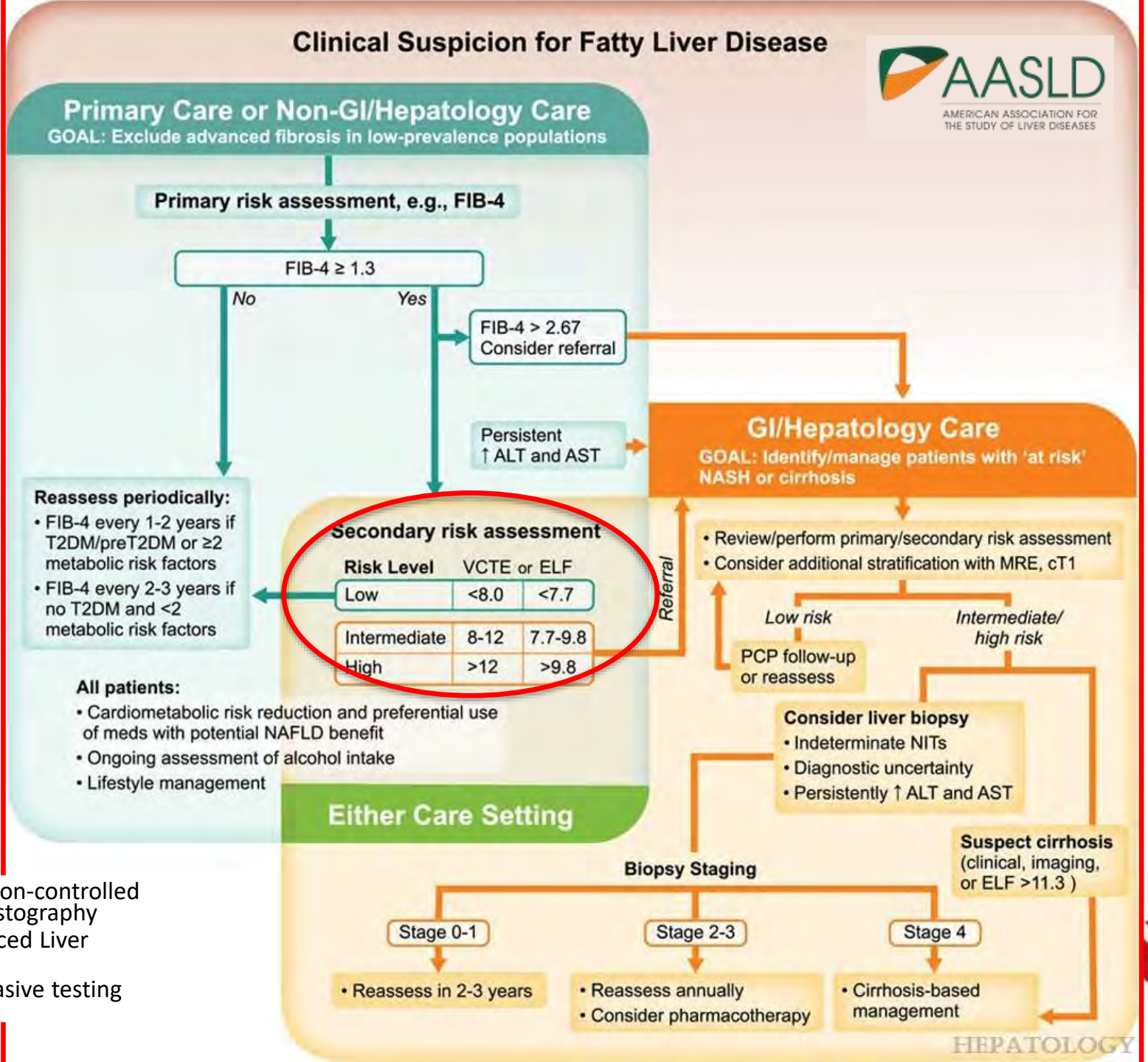
VCTE: Vibration-controlled transient elastography

ELF™: Enhanced Liver Fibrosis test

NIT: Non-invasive testing

Case Study


Fibrosis-4 (FIB-4) Index for Liver Fibrosis
Noninvasive estimate of liver scarring in HCV and HBV patients, to assess need for biopsy
When to Use
Pearls/Pitfalls
Why Use
Age
Use with caution in patients <35 or >65 years old, as the score has been shown to be less reliable in these patients
54
years
AST
Aspartate aminotransferase
55
U/L
ALT
Alanine aminotransferase
65
U/L
Platelet count
155
x 10³/µL
2.38 points
Further investigation needed
Approximate fibrosis stage: Ishak 2-3 (Sterling et al 2006)
Copy Results
Next Steps



VCTE: Vibration-controlled transient elastography

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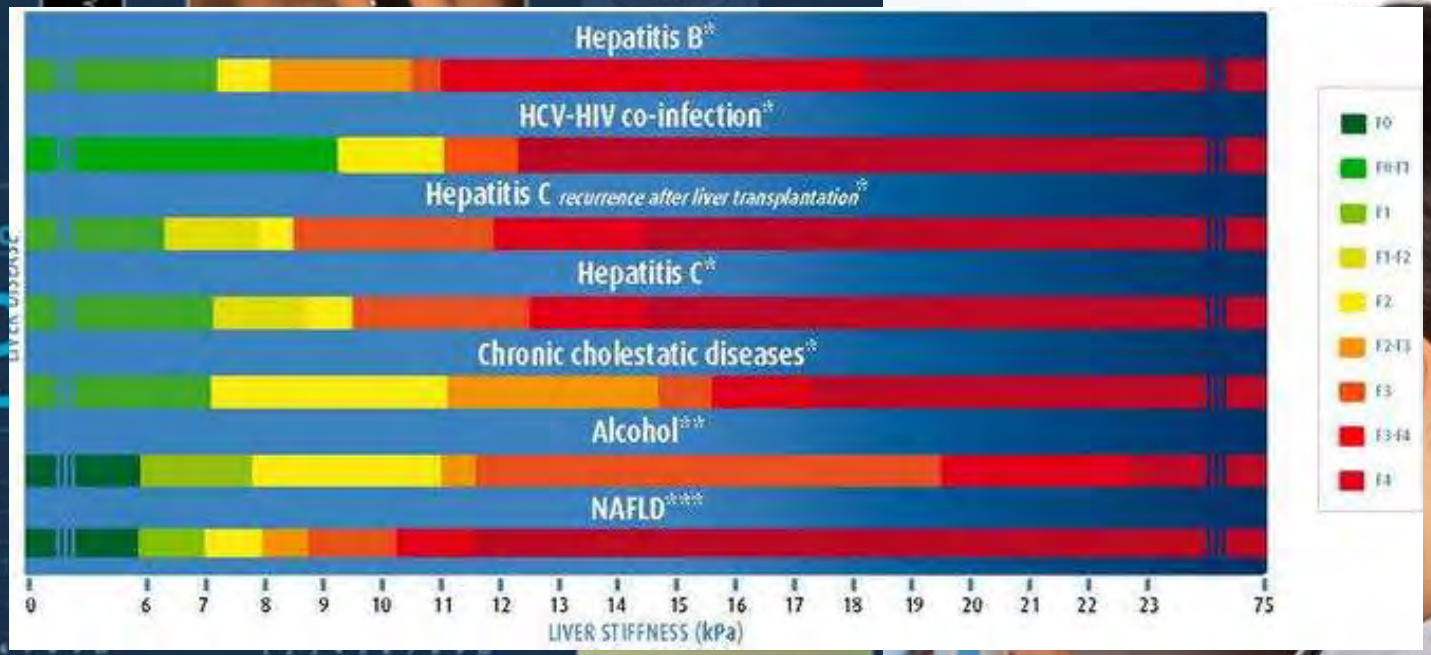
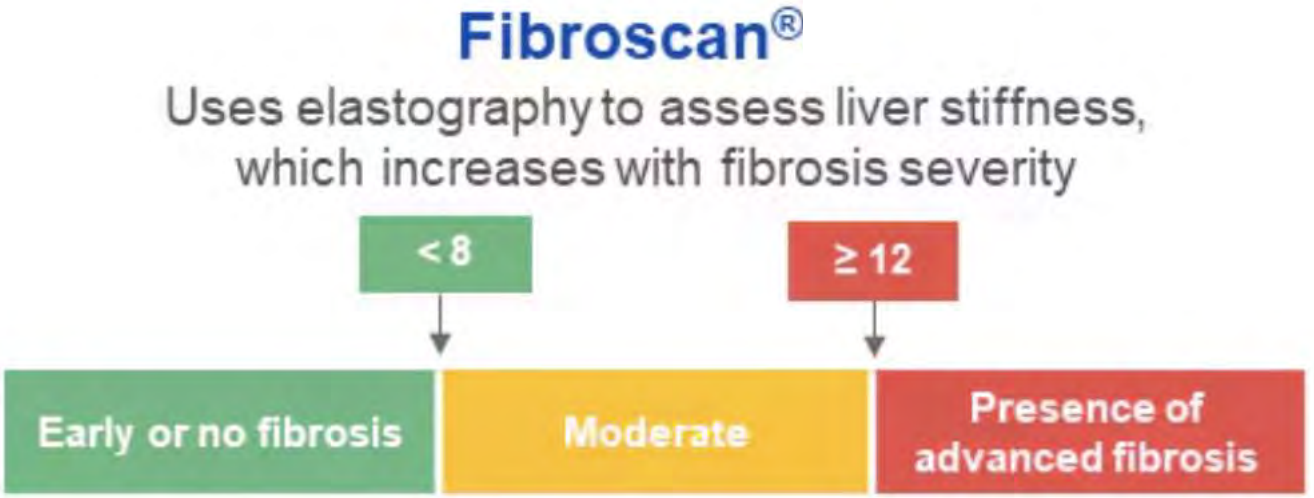
NIT: Non-invasive testing

r Fibrosis

nt of hepatic fibrosis

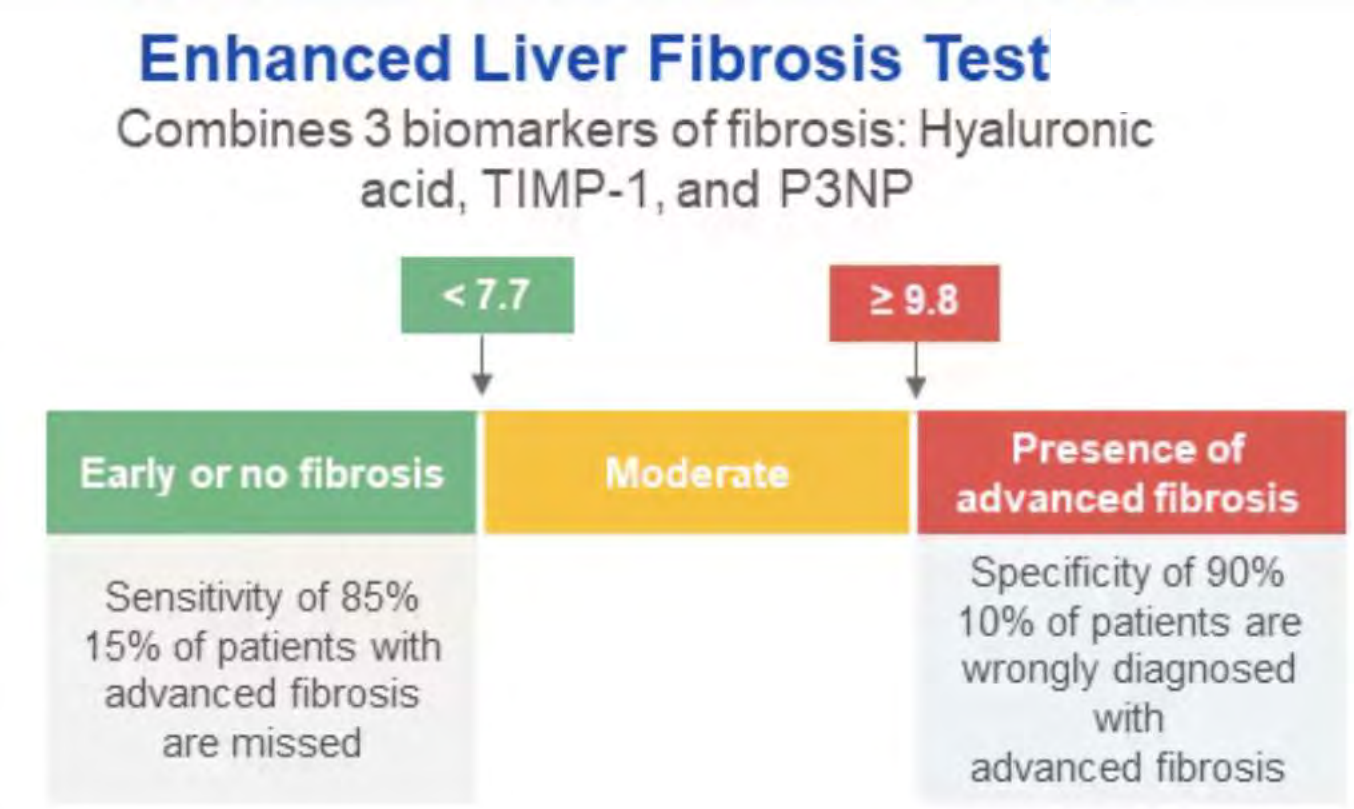


Assessing Liver Fibrosis



Rinella et al, Hepatology 2023

Assessing Liver Fibrosis



Rinella et al, Hepatology 2023

Does a liver biopsy still have a role?

When tests are discordant

When there are features that suggest a diagnosis other than steatotic liver disease

Case Study

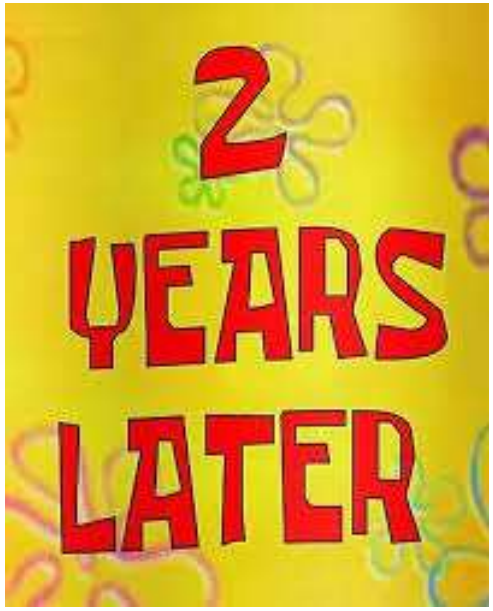
Steatosis Grade 0

Fibrosis Stage F0- F1

Next steps?

Case Study

Patient lost 10 lbs. on GLP-1
Still fatigued
AST 45, ALT 47
PLT 135 K
HbA1c 7 %



Fibrosis-4 (FIB-4) Index for Liver Fibrosis

Noninvasive estimate of liver scarring in HCV and HBV patients, to assess need for biopsy

When to Use | Pearls/Pitfalls | Why Use

Age Use with caution in patients <35 or >65 years old, as the score has been shown to be less reliable in these patients	56	years
AST Aspartate aminotransferase	45	U/L
ALT Alanine aminotransferase	47	U/L
Platelet count	135	× 10³/µL

2.72 points

Advanced fibrosis (METAVIR stage F3-F4) likely (McPherson 2017)
Approximate fibrosis stage: Ishak 2-3 (Sterling et al 2006)

Copy Results | Next Steps

Case Study

Fibroscan:

CAP 320 dB/s: steatosis grade S2

Liver stiffness 12 kPa: fibrosis stage F3

Management of MASLD

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HEPATOLOGY

Management of MASLD

A healthy diet and regular exercise form the foundation of treatment for the vast majority of those with MASLD: calorie deficit, diets with limited carbohydrates and saturated fat and enriched with high fiber and unsaturated fats.

Weight loss ≥ 7-10% improves steatosis, ballooning, inflammation, and fibrosis.

Management of MASLD

Abstain from alcohol

For patients without serologic evidence of immunity, vaccination for hepatitis A virus and hepatitis B virus

Standard, age-appropriate immunizations

Avoid OTC, herbs, supplements

Management of MASLD

Control of MASLD risk factors

TABLE 6 - Potential impact of available medications on patients with NAFLD

Medication	FDA indication	Patient population	Clinical benefits	Potential side effects	Cardiac benefit
Vitamin E (rrr-alpha) 800 IU daily[427,428]	NA	NASH without T2DM or cirrhosis	Liver related: improves steatosis, NASH resolution? No proven benefit on fibrosis	Hemorrhagic stroke, risk of prostate cancer?	No
Pioglitazone 30–45 mg po daily[429–431]	T2DM	NASH with and without T2DM	Liver related: improves steatosis, activity and NASH resolution, fibrosis improvement? Nonliver related: improves insulin sensitivity, prevention of diabetes, CV risk reduction and stroke prevention	Weight gain, risk of heart failure exacerbation, bone loss	Yes
Liraglutide[a] 1.8 mg s.c. daily (T2DM) 0.6–3 mg s.c. daily (obesity)[432]	T2DM, obesity	NASH without cirrhosis	Liver: improves steatosis, no proven impact on fibrosis. Nonliver related: improvement in insulin sensitivity, weight loss, CV risk reduction, may slow progression of renal disease	Gastrointestinal, gallstones (related to weight loss), pancreatitis	Yes
Semaglutide[b] 0.4 mg s.c. daily, 0.25–2.4 mg SQ weekly[433]	T2DM, obesity	NASH without cirrhosis	Liver related: improves steatosis, activity, and NASH resolution, no proven benefit on fibrosis, but may slow fibrosis progression. Nonliver related: improvement in insulin sensitivity, weight loss, improves CV and renal outcomes, stroke prevention	Gastrointestinal, gallstones (related to weight loss), pancreatitis	Yes
Tirzepatide[434,435]	T2DM	T2DM or obesity with NAFLD	Liver related: reduces steatosis on imaging. Nonliver related: improvement in insulin sensitivity, significant weight loss	Gastrointestinal, gallstones related to weight loss, pancreatitis	Unknown
SGLT-2i[436–438]	T2DM	T2DM and NAFLD	Liver related: reduction in steatosis by imaging. Nonliver related: may improve insulin sensitivity, improves CV and renal outcomes; benefit in heart failure, modest weight loss	Risk of genitourinary yeast infection, volume depletion, bone loss	Yes

Management of MASLD

Bariatric medicine

Dual GLP-1 and GIP receptor agonist approved for long-term use: Tirzepatide

GLP-1 agonists approved for long-term use: Semaglutide, Liraglutide

Combination phentermine-topiramate approved for long-term use

Combination naltrexone-bupropion approved for long-term use

Pancreatic lipase inhibitor approved for long-term use: Orlistat

Noradrenergic sympathomimetic drugs approved for short-term use: Benzphetamine, Diethylpropion, Phentermine, Phendimetrazine

Management of MASLD

Bariatric surgery

BMI ≥40 kg/m^2 irrespective of metabolic comorbid disease or BMI ≥35 kg/m^2 with comorbidities (T2DM or pre-DM, uncontrolled hypertension, osteoarthritis of hip or knee, urinary incontinence)

Effectively resolves MASLD or MASH in the majority of patients without cirrhosis and reduces mortality from CVD and malignancy.

Management of MASLD

Histological response may be tracked using non-invasive testing

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 8, 2024 VOL. 390 NO. 6

A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

S.A. Harrison, P. Bedossa, C.D. Guy, J.M. Schattenberg, R. Loomba, R. Taub, D. Labriola, S.E. Moussa, G.W. Neff, M.E. Rinella, Q.M. Anstee, M.F. Abdelmalek, Z. Younossi, S.J. Baum, S. Francque, M.R. Charlton, P.N. Newsome, N. Lanthier, I. Schiefke, A. Mangia, J.M. Pericàs, R. Patil, A.J. Sanyal, M. Noureddin, M.B. Bansal, N. Alkhouri, L. Castera, M. Rudraraju, and V. Ratziu, for the MAESTRO-NASH Investigators*

FDA NEWS RELEASE

FDA Approves First Treatment for Patients with Liver Scarring Due to Fatty Liver Disease

For Immediate Release: March 14, 2024

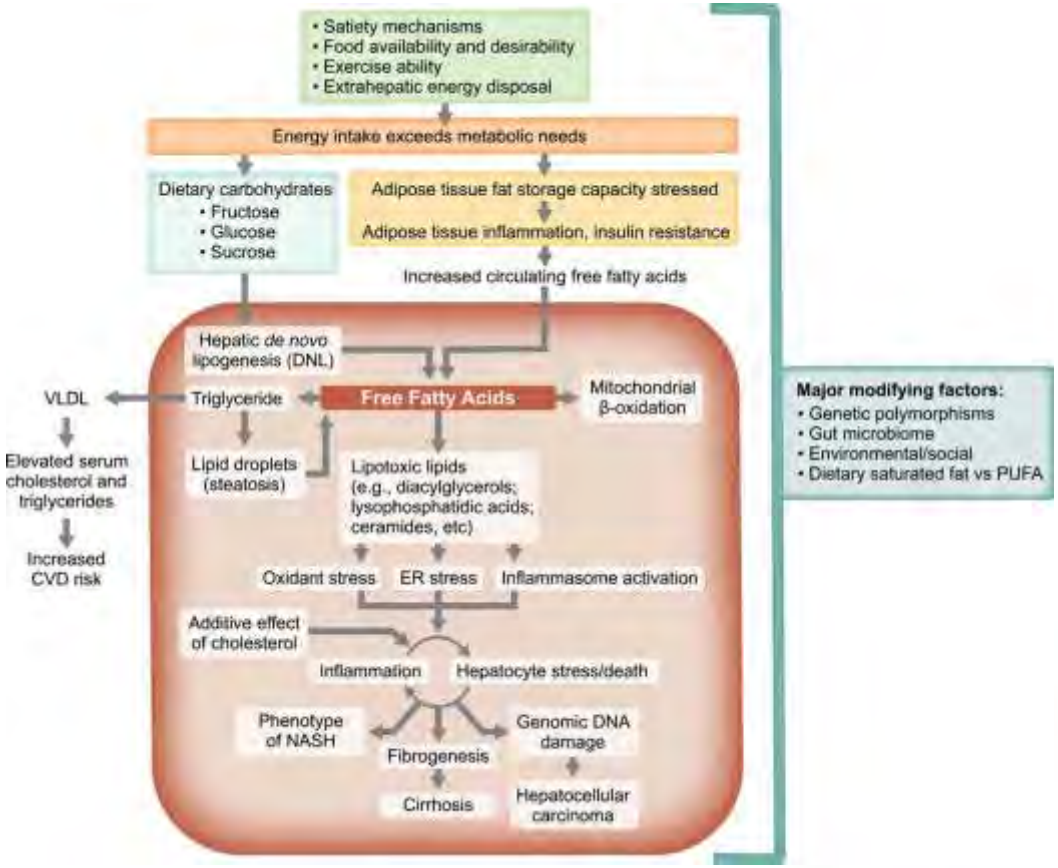
Today, the U.S. Food and Drug Administration approved Rezdiffra (resmetirom) for the treatment of adults with noncirrhotic non-alcoholic steatohepatitis (NASH) with moderate to advanced liver scarring (fibrosis), to be used along with diet and exercise.

Resmetirom- The Maestro Trial

Resemetirom: partial agonist of THR-β, which is the major form of thyroid hormone receptor THR in the liver.

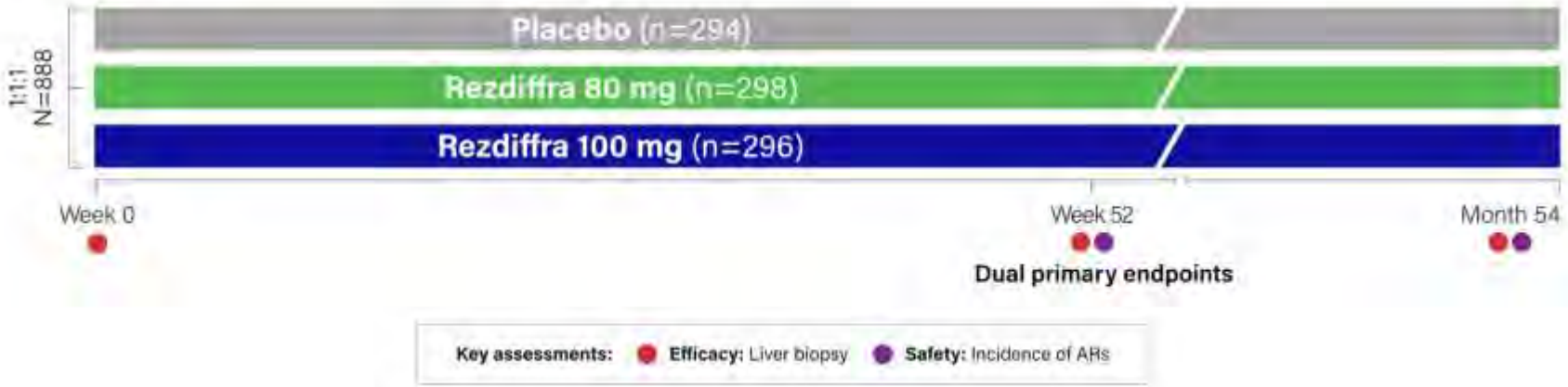
Stimulation of THR-β in the liver reduces intrahepatic triglycerides.

Actions of thyroid hormone outside the liver (including the heart and bones) are largely mediated through THR-α.



Resmetirom- The Maestro Trial

MAESTRO-NASH is an ongoing Phase 3, randomized, double-blind, placebo-controlled trial. Efficacy and safety were evaluated in 888 adults with biopsy-confirmed NASH with liver fibrosis stages F2 and F3 (at eligibility).



Week 52 dual primary endpoints

- **NASH Resolution:** resolution of steatohepatitis (score of 0-1 for inflammation, 0 for ballooning, and any value for steatosis) and no worsening of liver fibrosis.
- **Fibrosis Improvement:** ≥1-stage improvement in fibrosis without worsening of steatohepatitis (defined as no increase in score for ballooning, inflammation, or steatosis). Liver fibrosis was evaluated on the NASH Clinical Research Network (CRN) fibrosis score as 0 to 4.

Safety

- Incidence of adverse reactions

Resmetirom- The Maestro Trial

Stratification

- Patients were stratified by baseline type 2 diabetes status (present/absent) and fibrosis stage (F2 or F3)

Key inclusion and exclusion criteria

Inclusion

- Presence of metabolic risk factors
- NAFLD Activity Score (NAS) ≥4
- Fibrosis stage: F2 or F3

Exclusion

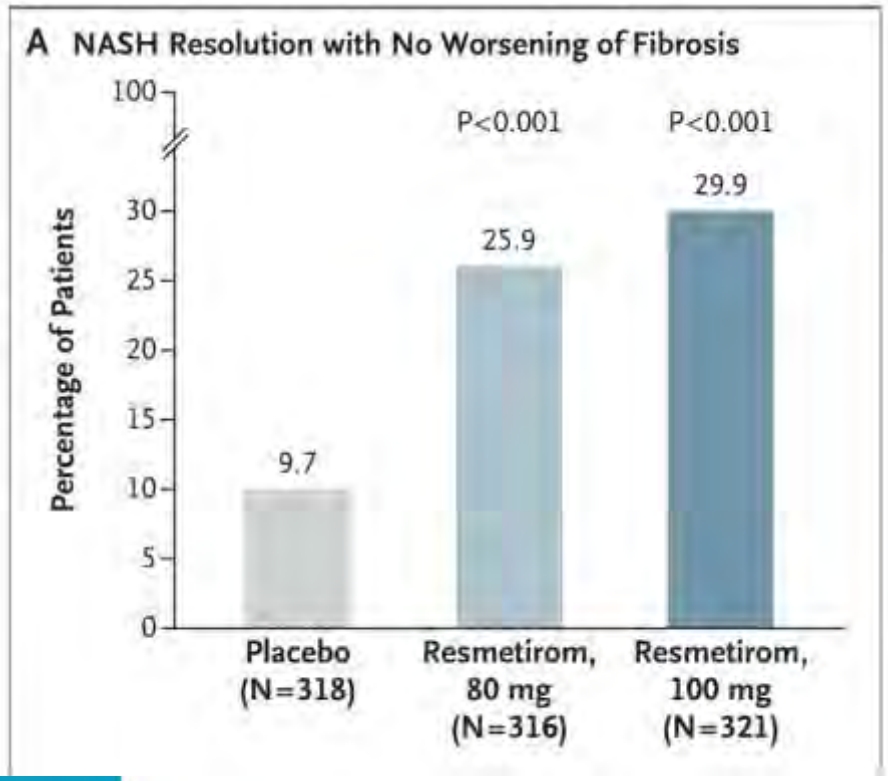
- Moderate to severe hepatic impairment (Child-Pugh B or C)
- Cirrhosis
- Liver decompensation

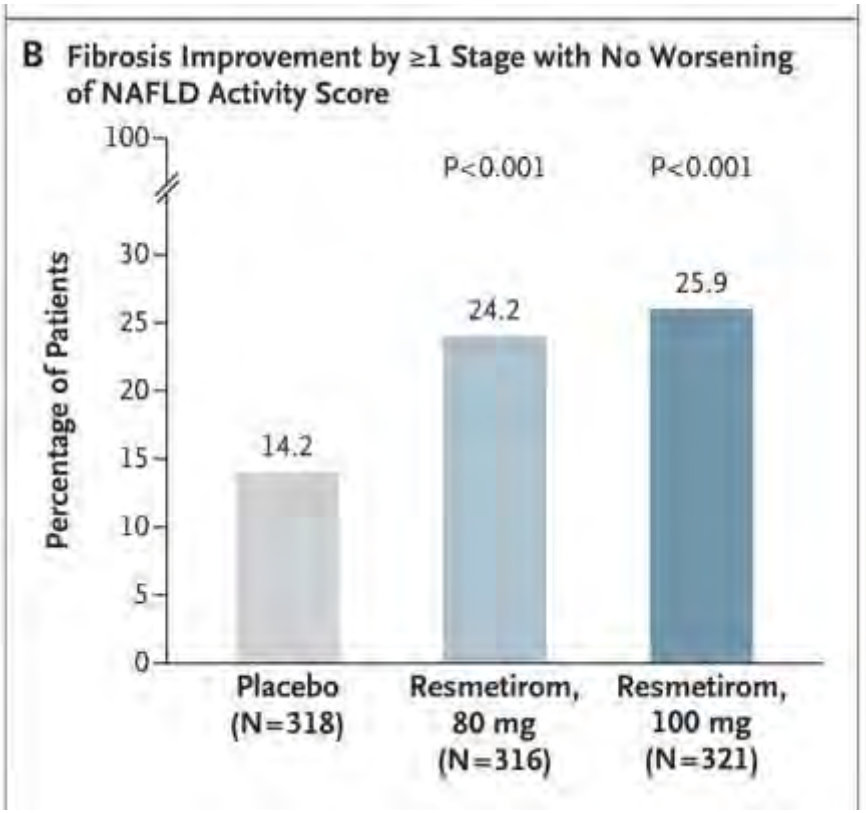
Demographics and comorbidities	Overall (N=888)
Age, years, median (Q1, Q3)	58 (51, 65)
Female, %	56
Hispanic, %	21
White, %	89
Asian, %	3
Black or African American, %	2
BMI, kg/m^2, median (Q1, Q3)	35 (31, 40)
Body weight, kg, median (Q1, Q3)	99 (85, 114)
Type 2 diabetes, n (%)	608 (68)
Hypertension, n (%)	700 (79)
Dyslipidemia, n (%)	633 (71)
Statin use, n (%)	434 (49)
Thyroxine use, n (%)	124 (14)

Assessment of baseline disease severity			Overall (N=888)
Liver Biopsy	Fibrosis stage, n (%)	F2	328 (37)
		F3	560 (63)
Other Assessments	VCTE, kPa, median (Q1, Q3)*		12 (10, 15)
	CAP, dB/m, median (Q1, Q3)*		349 (320, 378)
	FIB-4, median (Q1, Q3)*		1.3 (1.0, 1.8)
	ELF, median (Q1, Q3)*		9.7 (9.2, 10.4)

*Less than 5% missingness in these variables is omitted.

- Patients were on stable doses of medications for diabetes, dyslipidemia, and hypertension
- Patients in the study had NAFLD Activity Score (NAS) ≥4 at baseline





The two primary end points at week 52 were resolution of nonalcoholic steatohepatitis (NASH) with no worsening of fibrosis (Panel A), and an improvement (reduction) in fibrosis by at least one stage with no worsening of the nonalcoholic fatty liver disease (NAFLD) activity score (Panel B).

The key secondary end point was the percent change from baseline in the low-density lipoprotein (LDL) cholesterol level at week 24 (Panel C).

Starting at Month 3 and through Month 12, there was a trend of greater reductions from baseline in average ALT and AST in the resmetirom groups as compared to the placebo group.

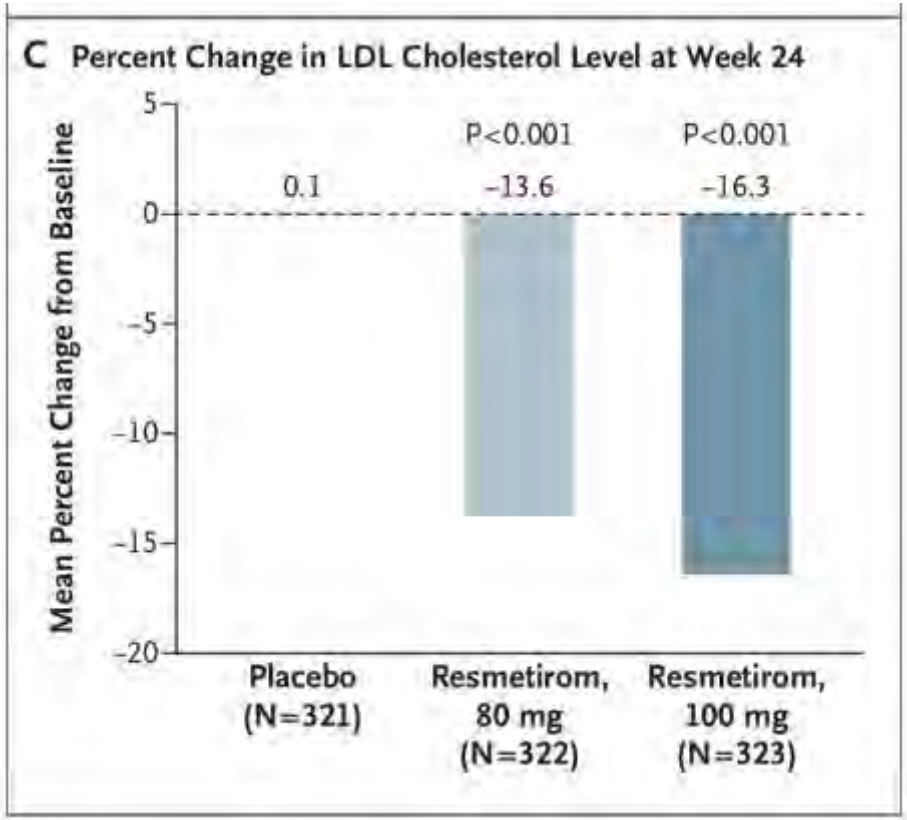


Table 3. Key Secondary and Other Secondary End Points (Primary Population).*

Measurement	Resmetirom, 80 mg (N=322)	Resmetirom, 100 mg (N=323)	Placebo (N=321)	Difference between Resmetirom, 80 mg, and Placebo (95% CI)†	Difference between Resmetirom, 100 mg, and Placebo (95% CI)†
	least-squares mean percent change from baseline			*percentage points*	
LDL cholesterol level at wk 24‡§	−13.6±1.7	−16.3±1.7	0.1±1.7	−13.7 (−17.5 to −10.0)¶	−16.4 (−20.1 to −12.6)¶
Apolipoprotein B level at wk 24§	−16.8±1.3	−19.8±1.3	0.39±1.3	−17.2 (−20.0 to −14.4)	−20.2 (−22.9 to −17.4)
Triglyceride level at wk 24§‖	−22.7±4.0	−21.7±4.3	−2.6±4.1	−20.1 (−28.3 to −11.8)	−19.1 (−27.8 to −10.3)
Lipoprotein(a) level at wk 24§**	−30.4±3.8	−35.9±4.0	−0.84±3.5	−29.5 (−37.6 to −21.5)	−35.1 (−43.5 to −26.6)
MRI-PDFF at wk 52	−35.4±2.8	−46.6±2.8	−8.7±2.7	−26.7 (−32.9 to −20.6)	−37.9 (−44.2 to −31.7)
Alanine aminotransferase level at wk 48††	−26.6±3.7	−33.2±3.9	−6.9±3.8	−19.7 (−27.7 to −11.6)	−26.3 (−34.5 to −18.1)
Aspartate aminotransferase level at wk 48††	−22.1±3.9	−28.3±3.9	−2.9±3.8	−19.3 (−27.2 to −11.3)	−25.4 (−33.5 to −17.4)
γ-Glutamyltransferase level at wk 48††	−25.0±5.5	−31.9±6.3	3.3±5.2	−28.3 (−37.3 to −19.3)	−35.2 (−45.5 to −25.0)

EAIR of Common Adverse Reactions Reported in ≥5% of patients in MAESTRO-NASH*,†,‡

Adverse Reaction	Placebo (n=294) n (EAIR§)	Rezdiffra 80 mg (n=298) n (EAIR§)	Rezdiffra 100 mg (n=296) n (EAIR§)
Diarrhea	52 (14)	78 (23)	98 (33)
Nausea	36 (9)	65 (18)	51 (15)
Pruritus	18 (4)	24 (6)	36 (10)
Vomiting	15 (4)	27 (7)	30 (8)
Constipation	18 (4)	20 (5)	28 (8)
Abdominal pain	18 (4)	22 (5)	27 (7)
Dizziness	6 (1)	17 (4)	17 (4)

*Population includes adult patients with noncirrhotic NASH with liver fibrosis (stages F2 and F3 at eligibility).

†Median exposure duration was 68 weeks for placebo, 74 weeks for Rezdiffra 80 mg once daily, and 66 weeks for Rezdiffra 100 mg once daily.

‡EAIRs are per 100 PY where total PYs were 435, 435, and 407 for placebo, 80 mg once daily, and 100 mg once daily arms, respectively.

§The EAIR per 100 PY can be interpreted as an estimated number of first occurrences of the adverse reaction of interest if 100 patients are treated for 1 year.

Increases in mean ALT and AST levels were observed in the first 4 weeks after initiating treatment with resmetirom. Mean elevation in ALT and AST values was <1.5x baseline at 4 weeks after treatment initiation and returned to baseline around 8 weeks.

EAIR Exposure Adjusted Incidence Rate

WARNINGS AND PRECAUTIONS

Hepatotoxicity

Hepatotoxicity has been observed in one patient. *Please see full Prescribing Information for more details on this specific case of Hepatotoxicity [see Warnings and Precautions (5.1)].*

Monitor patients during treatment for elevations in liver tests and for the development of liver-related adverse reactions. Monitor for symptoms and signs of hepatotoxicity (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash, and/or eosinophilia [>5%]). If hepatotoxicity is suspected, discontinue Rezdiffra and continue to monitor the patient. If laboratory values return to baseline, weigh the potential risks against the benefits of restarting Rezdiffra. If laboratory values do not return to baseline, consider DI-ALH or autoimmune liver disease in the evaluation of elevations in liver tests.

Gallbladder-Related Adverse Reactions

In clinical trials, cholelithiasis, acute cholecystitis, and obstructive pancreatitis (gallstone) were observed more often in Rezdiffra-treated patients than in placebo-treated patients. If cholelithiasis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated. If an acute gallbladder event is suspected, interrupt Rezdiffra treatment until the event is resolved.

DRUG INTERACTIONS

Clinically Significant Interactions Affecting Rezdiffra

- **Strong or Moderate CYP2C8 Inhibitors:** Resmetirom is a CYP2C8 substrate. Concomitant use with strong CYP2C8 inhibitors (e.g., gemfibrozil) is not recommended. Reduce dosage if used concomitantly with a moderate CYP2C8 inhibitor (e.g., clopidogrel).
- **Organic Anion-Transporting Polypeptides (OATP) 1B1 and OATP1B3 Inhibitors:** Resmetirom is an OATP1B1 and OATP1B3 substrate. Concomitant use with OATP1B1 or OATP1B3 inhibitors (e.g., cyclosporine) is not recommended.

Clinically Significant Interactions Affecting Other Drugs

- **Statins**
  - Limit daily rosuvastatin and simvastatin dosage to 20 mg
  - Limit daily pravastatin and atorvastatin dosage to 40 mg
- **CYP2C8 Substrates:** Resmetirom is a weak CYP2C8 inhibitor. Monitor patients more frequently for substrate-related adverse reactions if Rezdiffra is co-administered with CYP2C8 substrates where minimal concentration changes may lead to serious adverse reactions.

Recommended dosage and administration

Dosage	Rezdiffra 80 mg	Rezdiffra 100 mg
	One tablet QD	One tablet QD
Weight	<100 kg (220 lbs)	≥100 kg (220 lbs)

In The Pipeline

TABLE 1 - Current planned phase 3 MASH studies

Name	Mechanism of action/route	Estimated participants for subpart H	Primary endpoint	NITs included
Resmetirom MASTRO-NASH study NCT03900429	Liver-directed, β-selective THR agonist/oral	2000	MASH resolution or fibrosis improvement	FIB-4, Pro-C3, ELF, VCTE, MRI-PDFF-MRE
Lanifibranor NATiV3 study NCT04849728	Pan-PPAR agonist/oral	1000	MASH resolution and fibrosis improvement (SAF was used for entry criteria)	FIB-4, VCTE
Semaglutide ESSENCE study NCT04822181	GLP-1 receptor agonist/subcutaneous	1200	MASH resolution or fibrosis improvement	FIB-4, ELF, VCTE
Starting soon/details pending				
Efruxifermin	Sustained Fc-FGF21 fusion protein/subcutaneous	TBD	MASH resolution or fibrosis improvement	TBD
Pegozafermin	Glycopegylated FGF21 fusion protein/subcutaneous	TBD	MASH resolution or fibrosis improvement	TBD
Cirrhosis studies in parallel to pre-cirrhosis MASH trials				
Resmetirom NCT05500222	Liver-directed, β-selective THR agonist/oral	700	Major adverse liver-related outcomes and all-cause mortality	ELF, VCTE, MRI-PDFF, MRE

Abbreviations: ELF, Enhanced Liver Fibrosis; GLP-1, glucagon-like peptide 1; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging, proton density fat fraction; NIT, noninvasive test; PPAR, peroxisome proliferator-activated receptor; TBD, to be determined; THR-B, thyroid hormone receptor-B; VCTE, vibration controlled transient elastography.

Noureddin et al, Hepatology, March 2024

Take Home Messages

- General population-based screening for MASLD is not advised.
- All patients with hepatic steatosis or clinically suspected MASLD, notably 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 (FIB-4).
- In high-risk individuals, FIB-4 should be repeated every 1–2 years.
- If FIB-4 ≥1.3, VCTE, MRE, or ELF may be used to exclude advanced fibrosis.
- In the non- gastroenterology/hepatology setting, patients with suspected advanced fibrosis or discordant NITs should be referred to a specialist.

Take Home Messages

- Aminotransferase levels should not be used in isolation to exclude the presence of clinically significant fibrosis.
- Normative values for ALT reported by most laboratories exceed what is considered a true normal. Generally, ALT >30 U/L should be considered abnormal.
- Diet, exercise, weight loss and control of MASLD risk factors are the cornerstone of treatment.
- Resmetiron: first FDA approved drug for MASLD with F2 – F3 fibrosis. More data is needed, and more medications are in the pipeline.
- Histological response may be tracked using non-invasive testing.

Thank You

Questions?

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