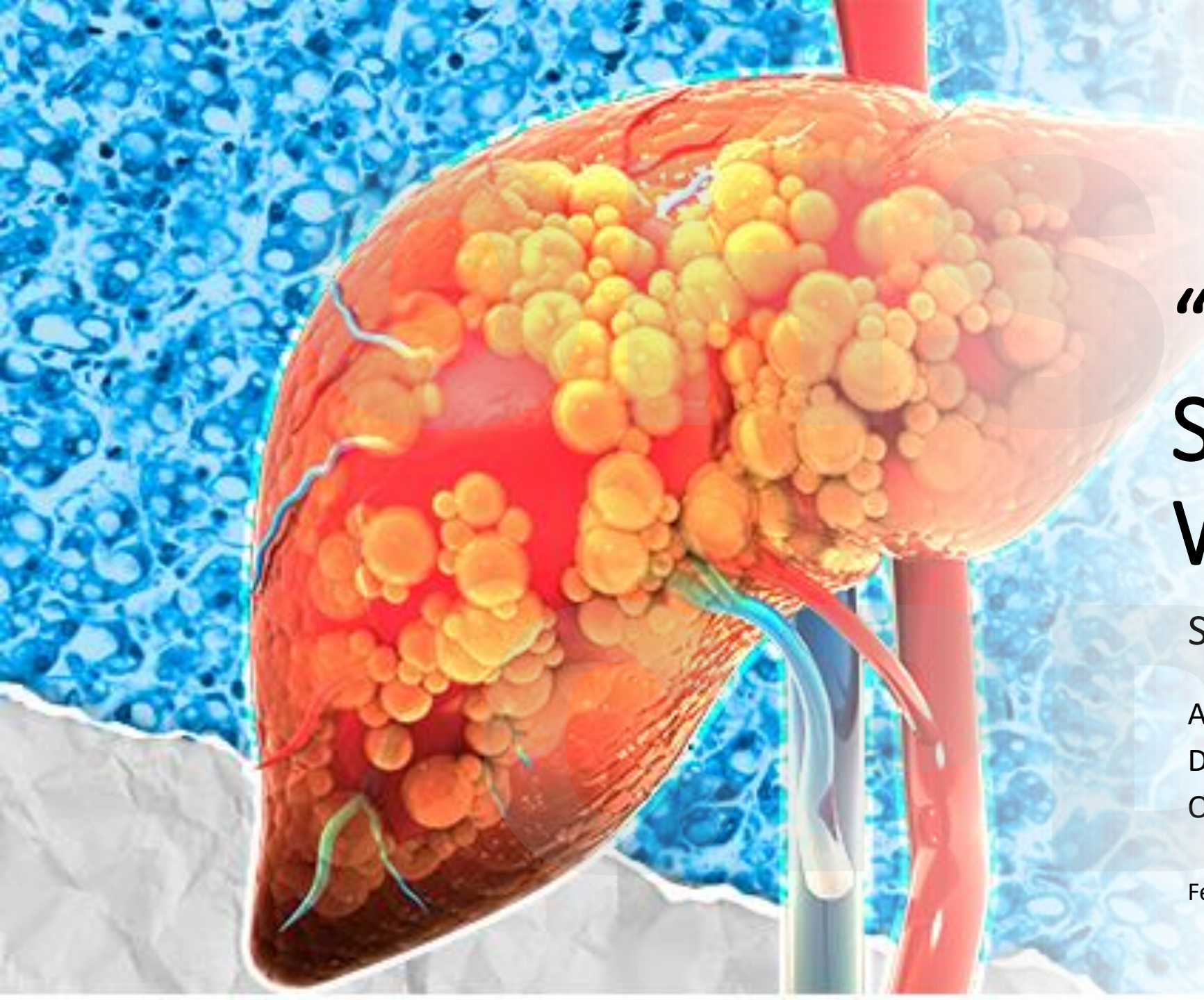


“Hepatic Steatosis”: What do I do?

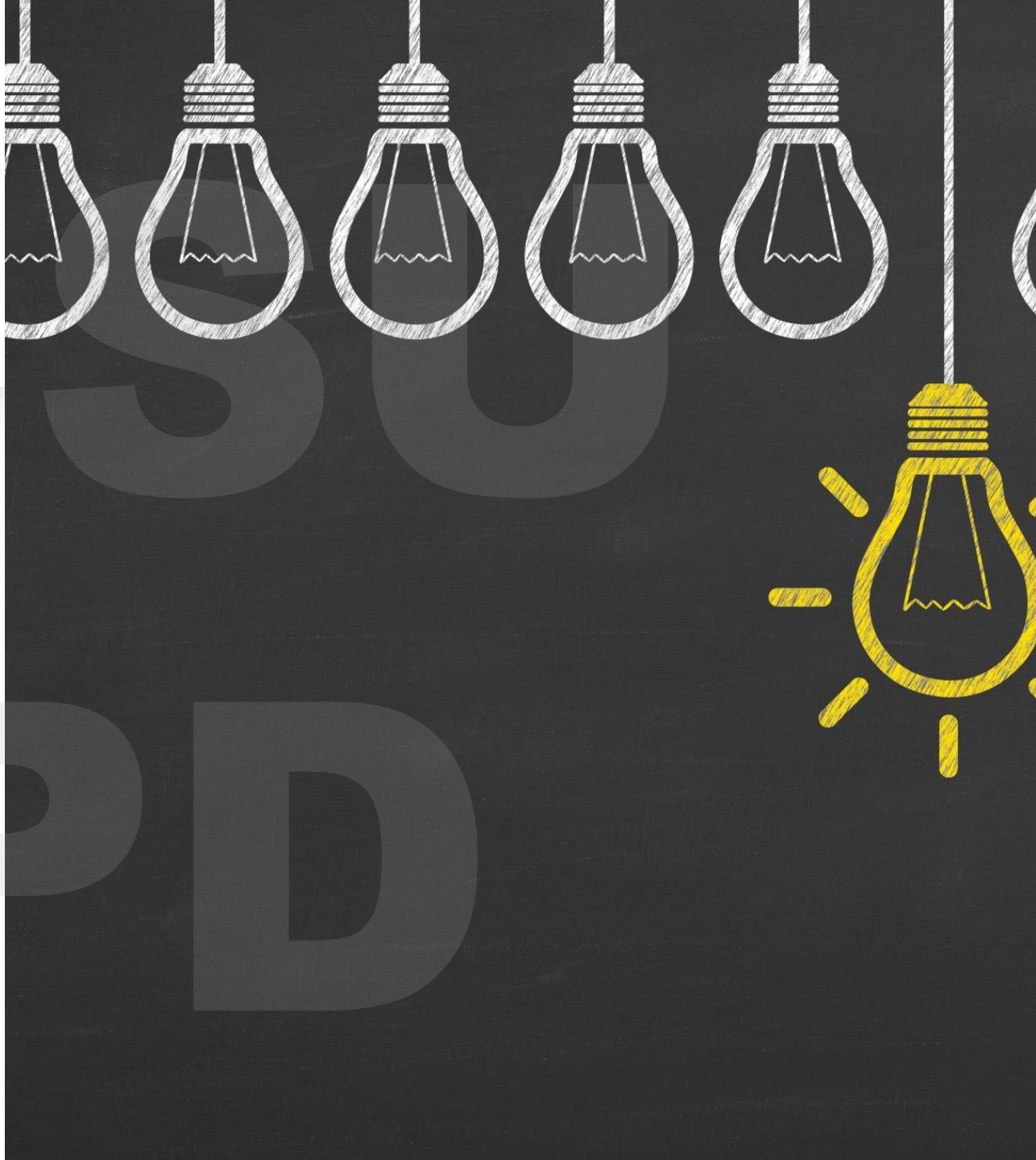
Smriti Ohri MD

Associate Professor
Department of Family Medicine
Oregon Health & Science University

Feb 12, 2025

Objectives

- Define and learn new nomenclature: MASLD (formerly NAFLD) and MASH (formerly NASH)
- Review screening for risk of advanced fibrosis
- Apply risk stratification for fibrosis
- Learn management strategies as a PCP



OHSU

CPD

Case

- 64 y/o F sees you (PCP) for ER follow up where she had reported fatigue and malaise. Labs in ER: Glu= 185, AST= 54, ALT= 46, rest of CMP normal, TG= 254, rest of the lipid profile normal, HbA1C= 7.9, Platelets= 186. ER clinician advised her to follow up with PCP. Has h/o DM2, HTN, dyslipidemia. Meds: metformin 1000 mg BID, glipizide 10 mg, simvastatin 40 mg, lisinopril/HCTZ 20/12.5 mg once daily. Does not smoke or drink alcohol. Vitals: BP= 128/70, HR= 72, RR= 12, BMI= 32. She has truncal obesity and no masses or organomegaly.

FIB-4= 2.74

What is the next step?

Refer to hepatology

Recommend pioglitazone in place of glipizide to help address DM2 and MASH

Recommend GLP-1 in place of glipizide to help with weight loss, DM2, reduction i…

Referral to a dietitian and comprehensive weight loss program

What is the next step?

Refer to hepatology

0%

Recommend pioglitazone in place of glipizide to help address DM2 and MASH

0%

Recommend GLP-1 in place of glipizide to help with weight loss, DM2, reduction in CV risk and MASH

0%

Referral to a dietitian and comprehensive weight loss program

0%

What is the next step?

Refer to hepatology

0%

Recommend pioglitazone in place of glipizide to help address DM2 and MASH

0%

Recommend GLP-1 in place of glipizide to help with weight loss, DM2, reduction in CV risk and MASH

0%

Referral to a dietitian and comprehensive weight loss program

0%

History

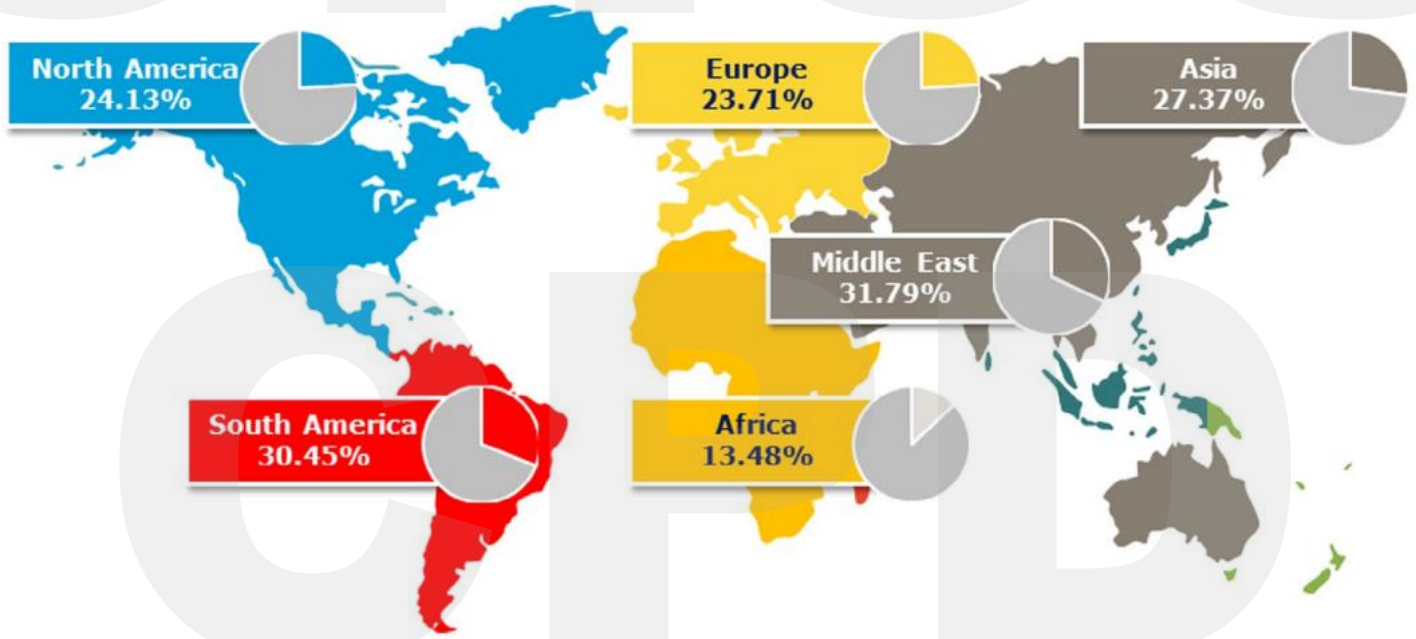
[Nonalcoholic steatohepatitis (NASH)]: term coined to describe changes in liver pathology similar to that seen in [then called] alcoholic hepatitis but in patients not known to be consuming alcohol.

Considerable skepticism that the entity even existed, assuming alcohol use in these patients had not been detected.

[NASH] entity took years to be accepted by the medical community, with only a few publications on NASH/NAFLD per year through 1990 but with a rapid increase to 5388 publications by 2022.

Prevalence

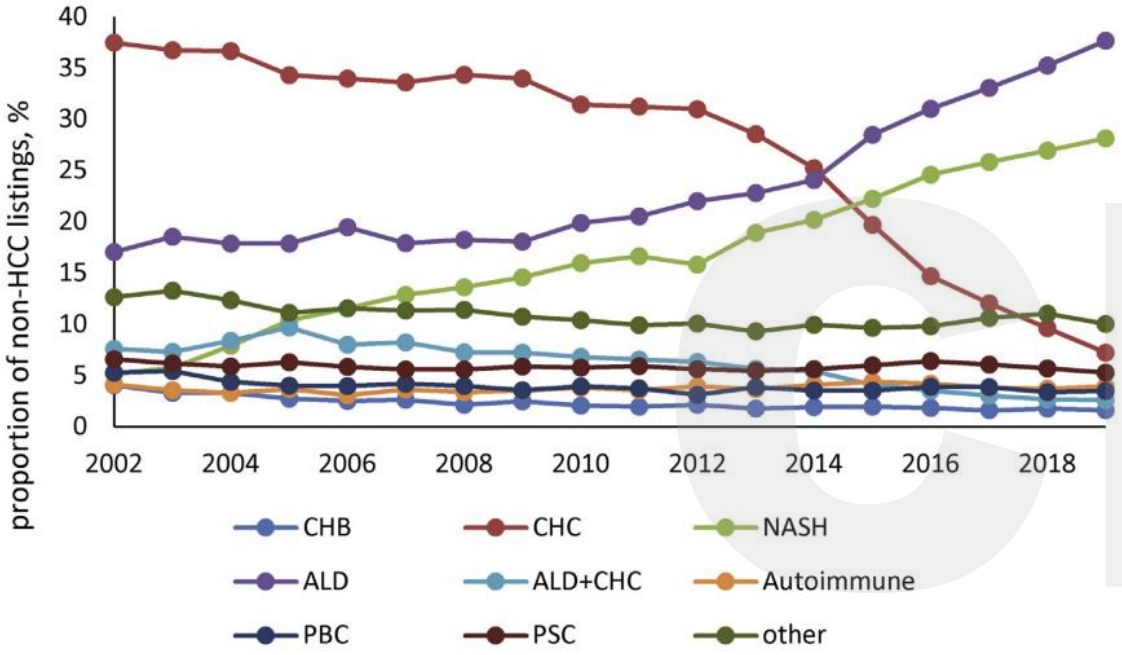
- MASLD: global health problem (2018 data)

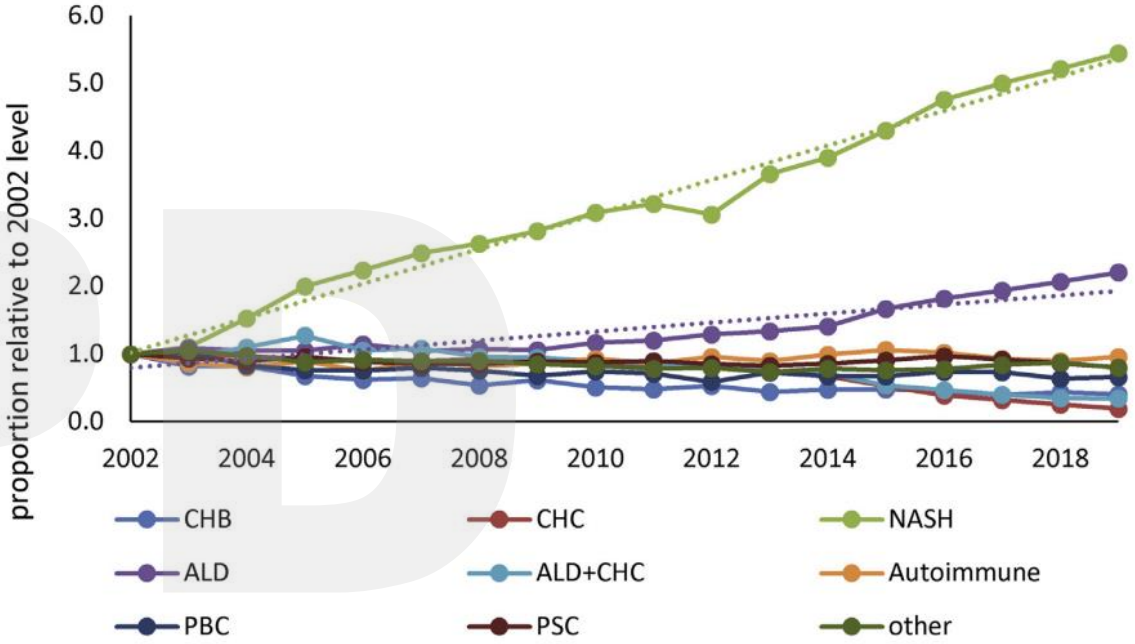


Hepatology . 2019 Jun;69(6):2672-2682.

Prevalence

- US
  - Burden estimated at 75mi
  - One of the most rapidly growing indication for liver transplantation





Clin Gastroenterol Hepatol. 2021 Mar;19(3):580-589.e5.

Nomenclature

No more NAFLD!

No more NASH!

Updated terms as of June 2023

- Fatty Liver Disease: Steatotic Liver Disease (overarching term) **(SLD)**
- NAFLD: Metabolic dysfunction-associated steatotic liver disease **(MASLD)**
- NASH: Metabolic dysfunction-associated steatohepatitis **(MASH)**

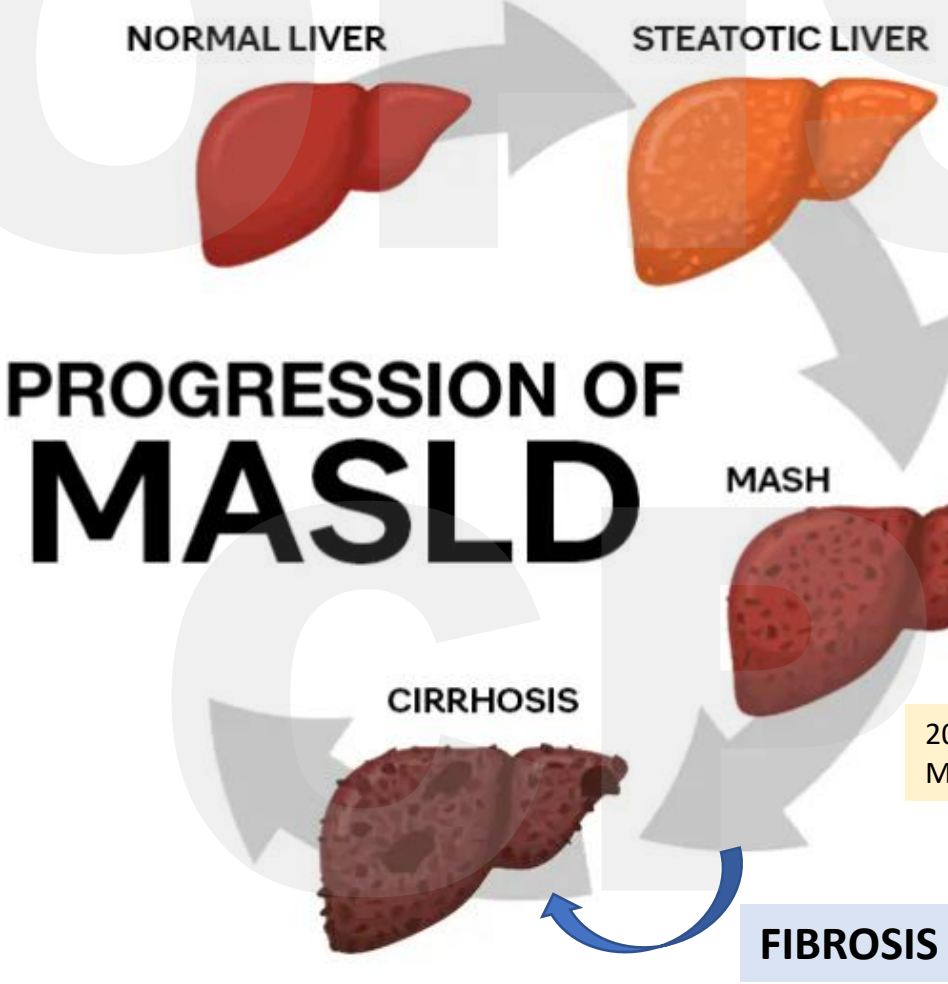
Term steatohepatitis: is retained

Change to non stigmatizing name- remove terms “fatty” and “alcoholic”

Recognize pathogenesis by including terms – “metabolic” and “steatotic”

Move away from the term “non” to describe something that its not!

MASLD Spectrum



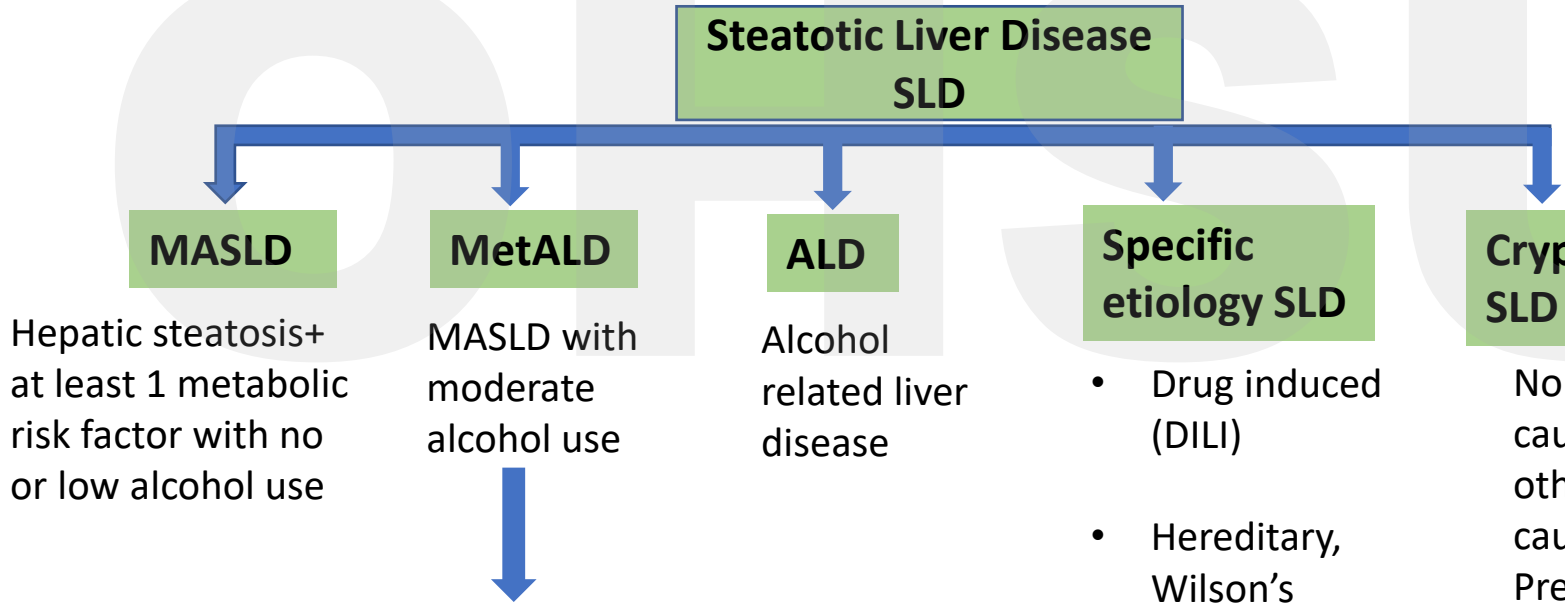
MASL: Hepatic steatosis (triglyceride accumulation in hepatocytes) in the absence of secondary causes (including alcohol).

MASH: Fat deposition leading to inflammation and cell damage (ballooning)

20- 40% of patients with MASH progress to Fibrosis

Image Source: Mayo Clinic

New nomenclature
Steatotic Liver Disease-overarching term



Hepatic steatosis+ at least 1 metabolic risk factor with no or low alcohol use

MASLD with moderate alcohol use

Alcohol related liver disease

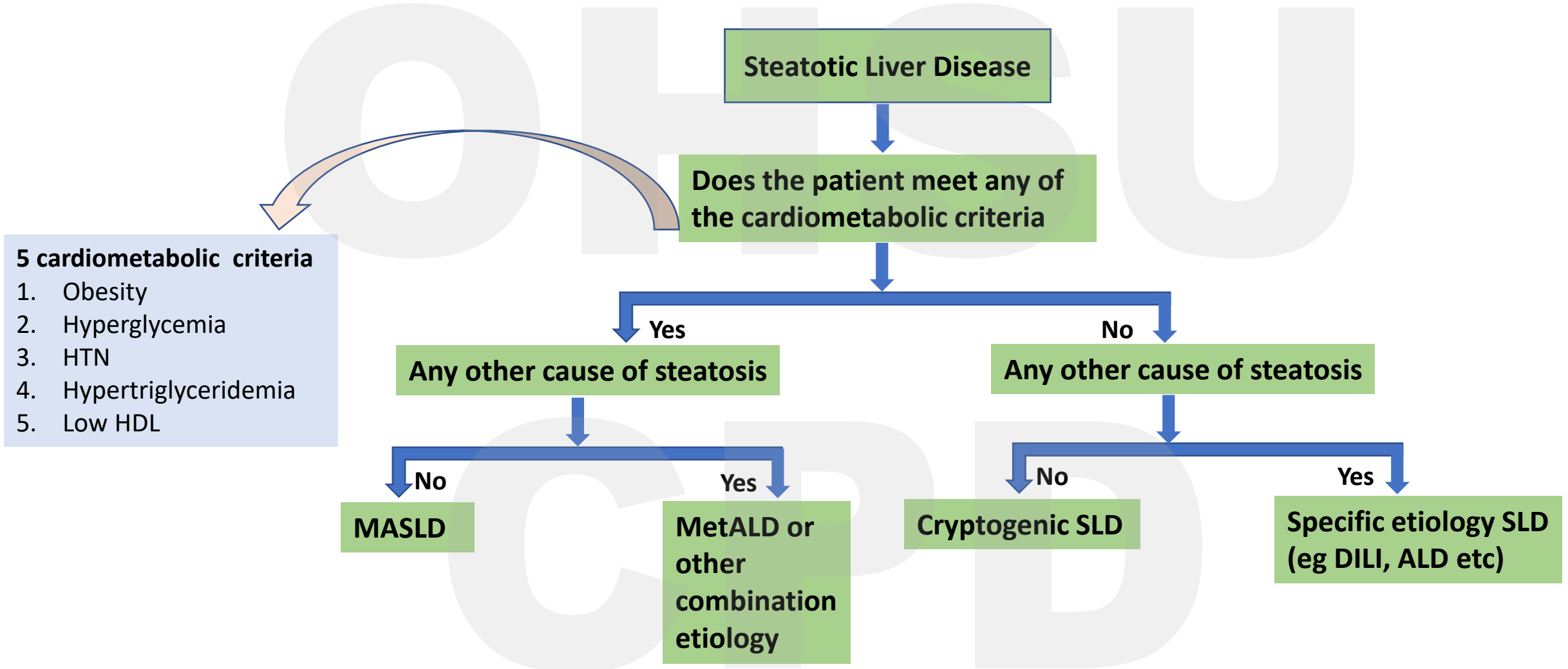
- Drug induced (DILI)
- Hereditary, Wilson's
- Viral hepatitis, Celiac disease, HIV

No metabolic cause and no other identified cause: Previously called "lean NAFLD"

New group-has not been studied but will benefit from being included in clinical trials: recognizing the presence of 2 synergistic driving factors on disease progression

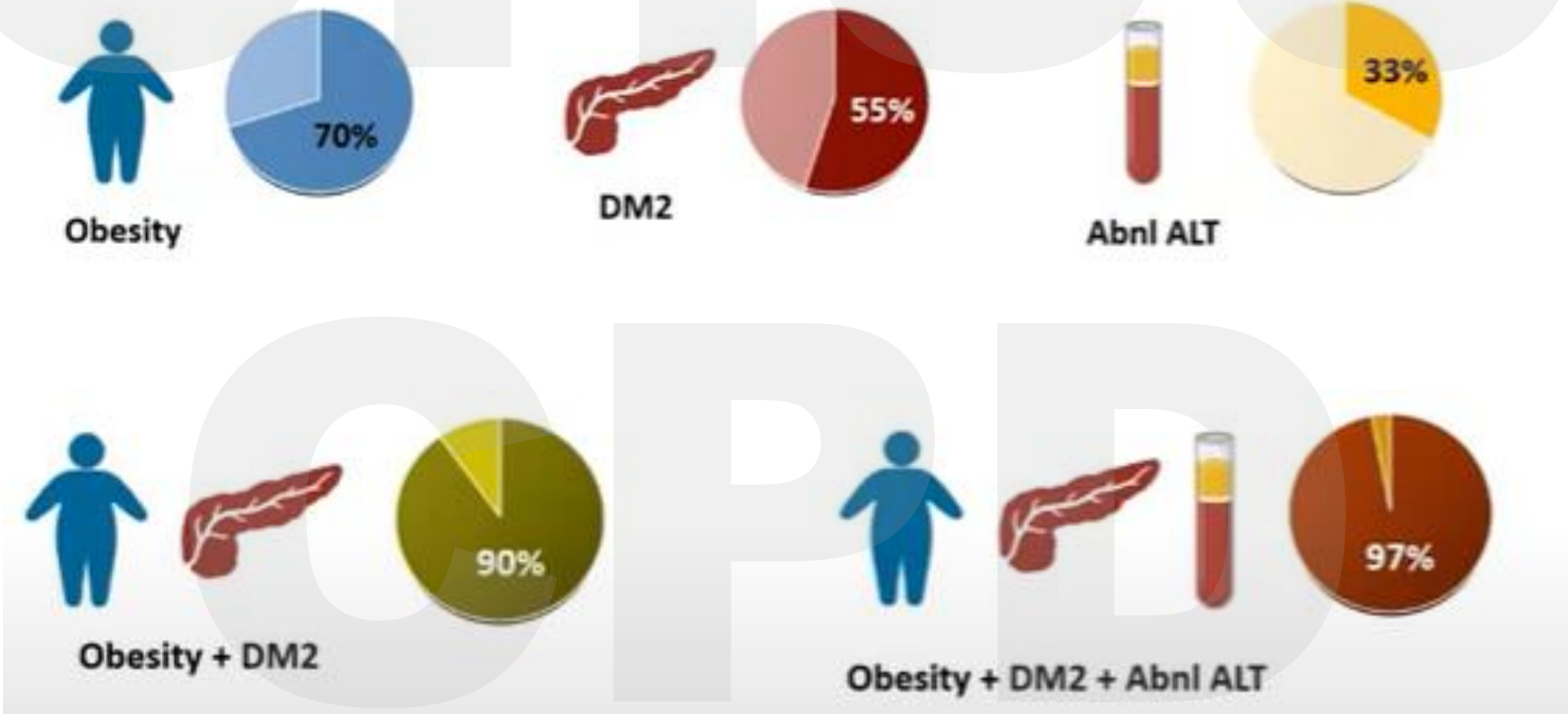
Alcohol use	Women (AFAB) Standard drink/day	Men (AMAB) Standard drink/day
Low	<1	<2
Moderate	2-3	3-4
Significant	>3	>4

Steatotic Liver Disease-Evaluation



Screening

- Pretest probability of MASLD



DM2 and MASLD

- Major risk factor for developing MASLD
- Progression of fibrosis is more in MASLD + DM2 as compared to MASLD without DM2

- Bidirectional relationship between MASLD and DM2 → presence of one increases the risk and severity of the other.
  - MASLD associated with a 2-5 fold risk of incident DM2 → patients with MASLD should be screened for the presence of DM2

- AACE in 2022 and ADA and AASLD in 2023 recommended screening for clinically significant fibrosis in high-risk patients
  - DM2
  - Obesity with cardiometabolic risk factors
  - Hepatic steatosis on imaging
  - Persistently elevated liver enzymes (ALT/AST over 6 months)

What is initial screening strategy for advanced liver fibrosis?

- Elevated liver enzymes
- Liver ultrasound
- Liver MRI
- Non-invasive tests (NITs: eg Fib 4)
- Elastography

What is initial screening strategy for advanced liver fibrosis?

What is initial screening strategy for advanced liver fibrosis?

Non-invasive tests (NITs)

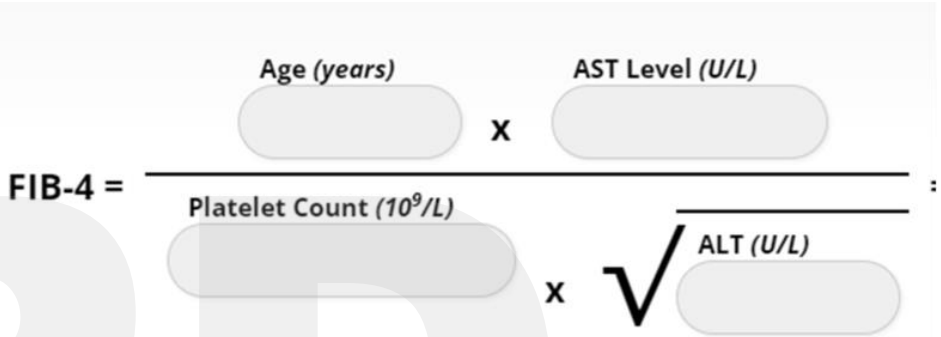
- FIB-4 → Most validated and cost-effective for initial screening in primary care setting
- NAFLD Fibrosis Score (NFS)
- AST Platelet Ratio Index (APRI)

  - Good specificity and negative predictive value → negative result rules out advanced fibrosis
  - Low sensitivity and positive predictive value → positive result requires confirmatory testing
    - Secondary assessment
      - VCTE (Vibration Controlled Transient Elastography)
      - Fibrosis biomarkers- ELF (Enhanced Liver Fibrosis test) *(proprietary)*

Fib-4

- FIB-4 estimates the risk of cirrhosis and predicts changes over time in fibrosis
  - Age
  - Plasma aminotransferases (AST and ALT)
  - Platelets

Fib-4 score	
<1.3	low risk
>2.67	high probability of advanced fibrosis



- Patients with DM2 ≥ 65 y/o → higher cut offs recommended (1.9-2.0 rather than >1.3)
- Not validated for use in patients <35 y/o and is inaccurate in children

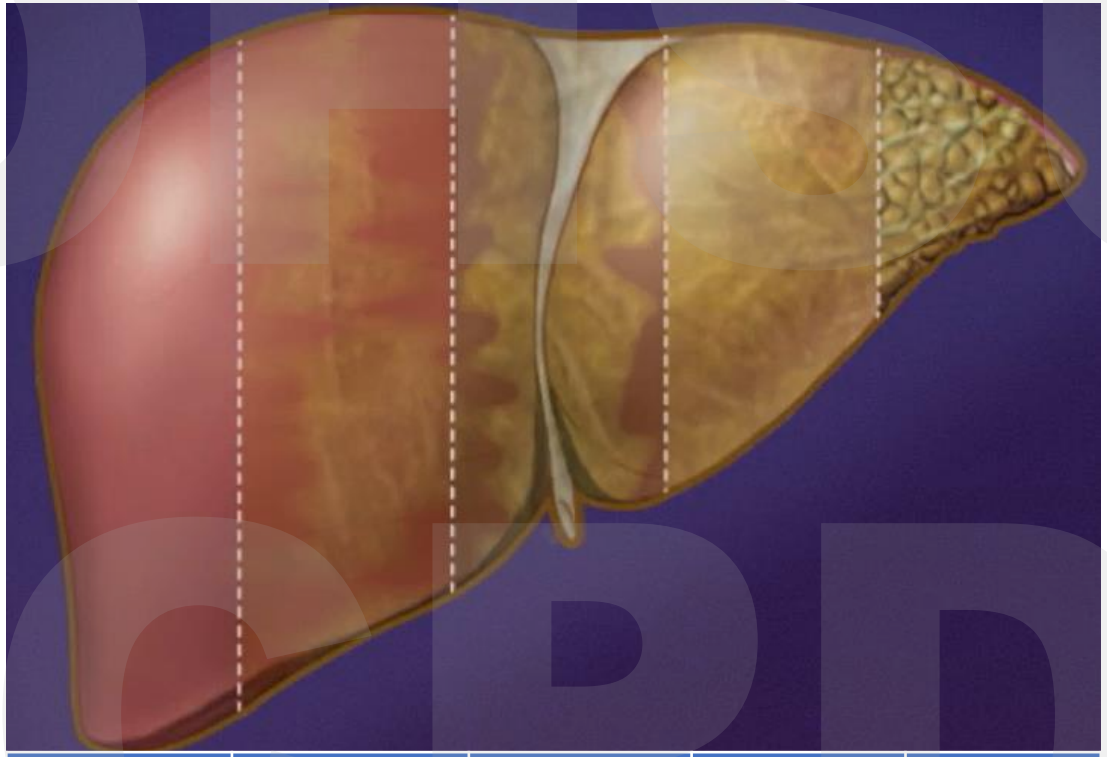
Liver enzymes?

- Screening strategy based on liver enzymes would miss most individuals with MASH, because clinically significant fibrosis (≥F2) is frequently observed with levels below the commonly used cutoff of 40.

- ACG: ULN of ALT =29–33 for males (AMAB) and 19–25 for females (AFAB)
- Easy number to remember= 30

Classification of Fibrosis

Fibrosis: greatest predictor of mortality in MASLD



F0	F1	F2	F3	F4
No fibrosis	Mild	Moderate (Significant)	Severe (Advanced)	Cirrhosis

All cause mortality increases with more fibrosis

Evaluation: Fibrosis Risk Stratification

Incidental steatotic liver on imaging or clinical suspicion based on metabolic risk factors

Rule out other causes: eg: drug induced, viral hepatitis, celiac disease, autoimmune, hereditary, alcohol

- Hepatitis B and C serology
- ANA, AMA, ASMA
- Ferritin
- Alpha-1 antitrypsin

Primary risk assessment: FIB4

FIB4 ≥ 1.3

Low risk — No

- DM2 *or*
- PreDM *or*
- ≥ 2 metabolic risk factors

No → FIB4 q 2-3 years

Yes → FIB4 q 1-2 years

Yes — **Indeterminate risk 1.3- 2.67**

Secondary risk assessment:

Risk level	VCTE	ELF
Low	<8.0	<7.7
Intermediate	8-12	7.7- 9.8
High	>12	>9.8

High risk

FIB4≥ 2.67

Hepatology referral for additional stratification and potential intervention

Eg may consider MRE, liver biopsy in high risk patients

Which one of the following statements is true of MASLD?

Approximately 10% of patients with MASLD develop MASH

It is the leading cause of need for liver transplantation in the US

Its global prevalence in adults is estimated to be >45%

The most common cause of death among patients with MASLD is CVD.

Which one of the following statements is true of MASLD?

Approximately 10% of patients with MASLD develop MASH

0%

It is the leading cause of need for liver transplantation in the US

0%

Its global prevalence in adults is estimated to be >45%

0%

The most common cause of death among patients with MASLD is CVD.

0%

Which one of the following statements is true of MASLD?

Approximately 10% of patients with MASLD develop MASH

0%

It is the leading cause of need for liver transplantation in the US

0%

Its global prevalence in adults is estimated to be >45%

0%

The most common cause of death among patients with MASLD is CVD.

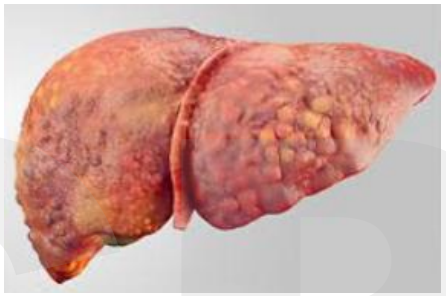
0%

MASLD management

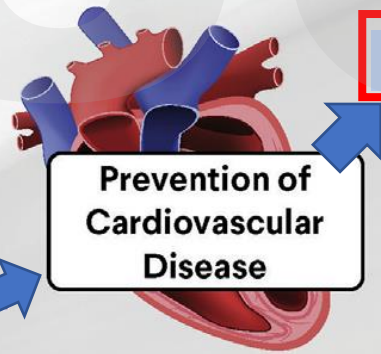
High risk groups

- Obesity
- Hyperglycemia
- HTN
- Hypertriglyceridemia
- Low LDL
- Hepatic Steatosis (on imaging)
- Increased AST or ALT

Rule out 2° causes

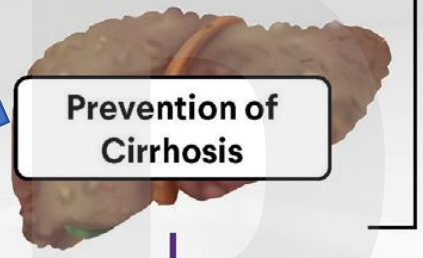


MASLD



Prevention of Cardiovascular Disease

Leading cause of mortality



Prevention of Cirrhosis

Management of

1. **Obesity**
2. **Diabetes**
3. **Hypertension**
4. **Atherogenic dyslipidemia**

Fibrosis Risk Stratification

AACE: Endocrine Practice 28 (2022) 528-562

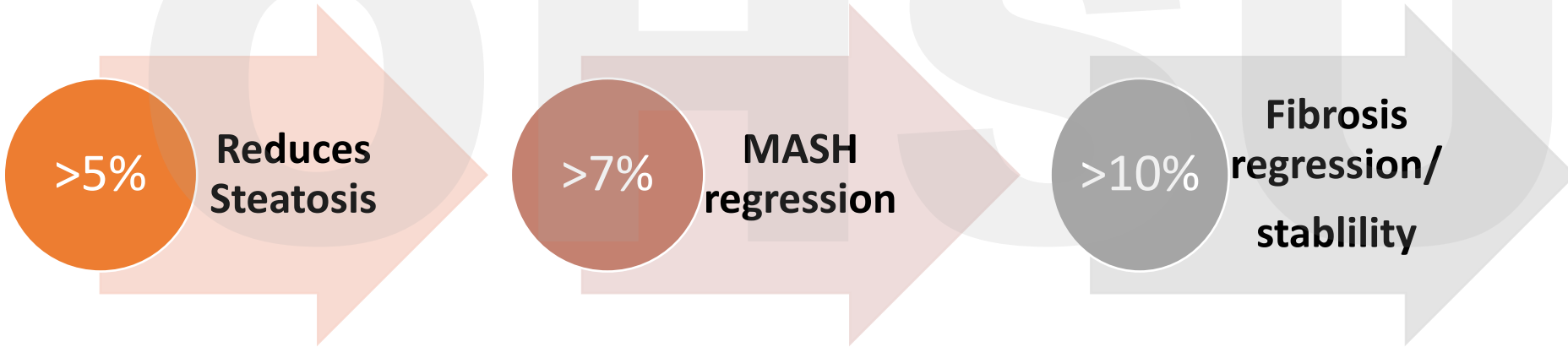
Nonpharmacological management

Lifestyle modification

- Diet recommendations: foods rich in antioxidants, limited carbohydrates and saturated fat and enriched with high fiber and unsaturated fats (eg, Mediterranean diet -best evidence) or Dietary Approaches to Stop Hypertension
- Avoid excessive alcohol intake
- Increased physical activity decreases plasma aminotransferases and steatosis, even in the absence of significant weight loss. Recommend individualized prescriptive exercise program.

Weight management

Weight management



Hepatology. 2010;51(1):121e129. *Gastroenterology. 2015;149(2):367e378* *Metabolism. 2021;115:154455.*

- Lifestyle modification
- Medications
- Bariatric surgery

Bariatric surgery

- MASLD/MASH without cirrhosis: indicated in patients meeting criteria for metabolic weight loss surgery for resolution of MASLD/MASH
- MASH with compensated cirrhosis: safety and efficacy not well established
- MASH with decompensated cirrhosis: absolute contraindication unless performed in conjunction with liver transplantation

Nonpharmacological management

- Coffee consumption, independent of caffeine content, *may* be beneficial.

- Drinking ≥3cups/day could be recommended in the absence of contraindications based on the reduced risk for MASLD and liver fibrosis demonstrated in epidemiological studies and meta-analyses.
  - Filtered ONLY, not unfiltered coffee
  - Not espresso – has added sucrose.
    - Sucrose composed of glucose and fructose and fructose has been associated with increased severity of hepatic fibrosis in MASH.

REVIEW ARTICLE

Impact of coffee on liver diseases: a systematic review

Liver Int. 2014: 34: 495–504

Conclusion:

- Coffee consumption associated with improved serum GGT, AST, ALT in a dose dependent manner in individuals at risk for liver disease.
- Chronic liver disease patients who consume coffee, a decreased risk of progression to cirrhosis, a lowered mortality rate in cirrhosis patients, and a lowered rate of HCC development were observed.
- In chronic hepatitis C patients, coffee was associated with improved virologic responses to antiviral therapy.
- Coffee consumption was inversely related to the severity of steatohepatitis in patients with MASLD

Coffee consumption and risk of nonalcoholic fatty liver disease: a systematic review and meta-analysis

Eur J Gastroenterol Hepatol. 2017;29:e8–12

Significantly decreased risk of MASLD among coffee drinkers and significantly decreased risk of liver fibrosis among patients with MASLD who drank coffee on a regular basis.

Meta-analyses

A systematic review and a dose–response meta-analysis of coffee dose and nonalcoholic fatty liver disease

Clin Nutr. 2019;38:2552–7.

Coffee intake level >3 cups was observed with lower risk of MASLD than <2cups/day.

Which one of the following medications has been shown to increase the resolution of MASLD?

- Glyburide
- Metformin
- Pioglitazone
- Repaglinide
- Vitamin D

Which one of the following medications has been shown to increase the resolution of MASLD?

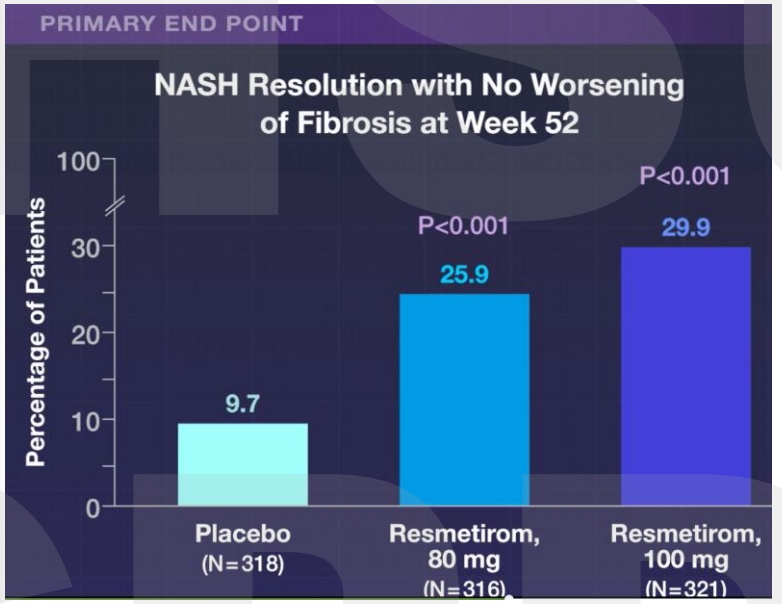
Which one of the following medications has been shown to increase the resolution of MASLD?

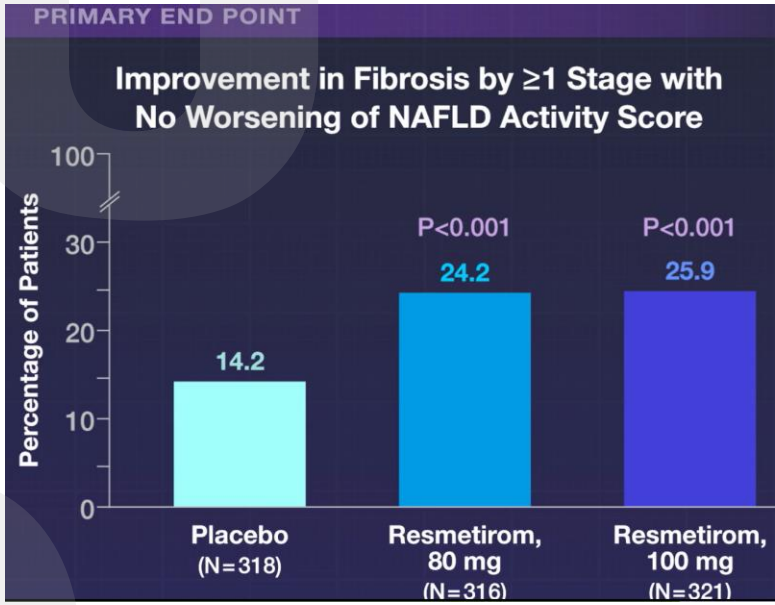
MAESTRO-NASH Trial

- Adults with biopsy confirmed NASH with F2-F3 fibrosis, n= 966
- 1:1:1 ratio, in addition to standard care for NASH (counseling for healthy diet and exercise)

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

For Immediate Release: March 14, 2024





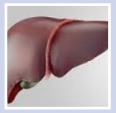
- Adverse effects: diarrhea, nausea, drug-induced liver toxicity, gall bladder related side effects.
- Avoid in patients with decompensated cirrhosis
- Significant drug interactions: STATIN!

N Engl J Med 2024;390:497-509

Resmetirom

Rezdiffra: noncirrhotic MASH with moderate to severe fibrosis (F2-F3), to be used along with diet and exercise.

Mechanism: targets thyroid hormone receptor beta (THR-β)-helps maintain liver homeostasis. THR-β agonists have been shown to improve lipid metabolism

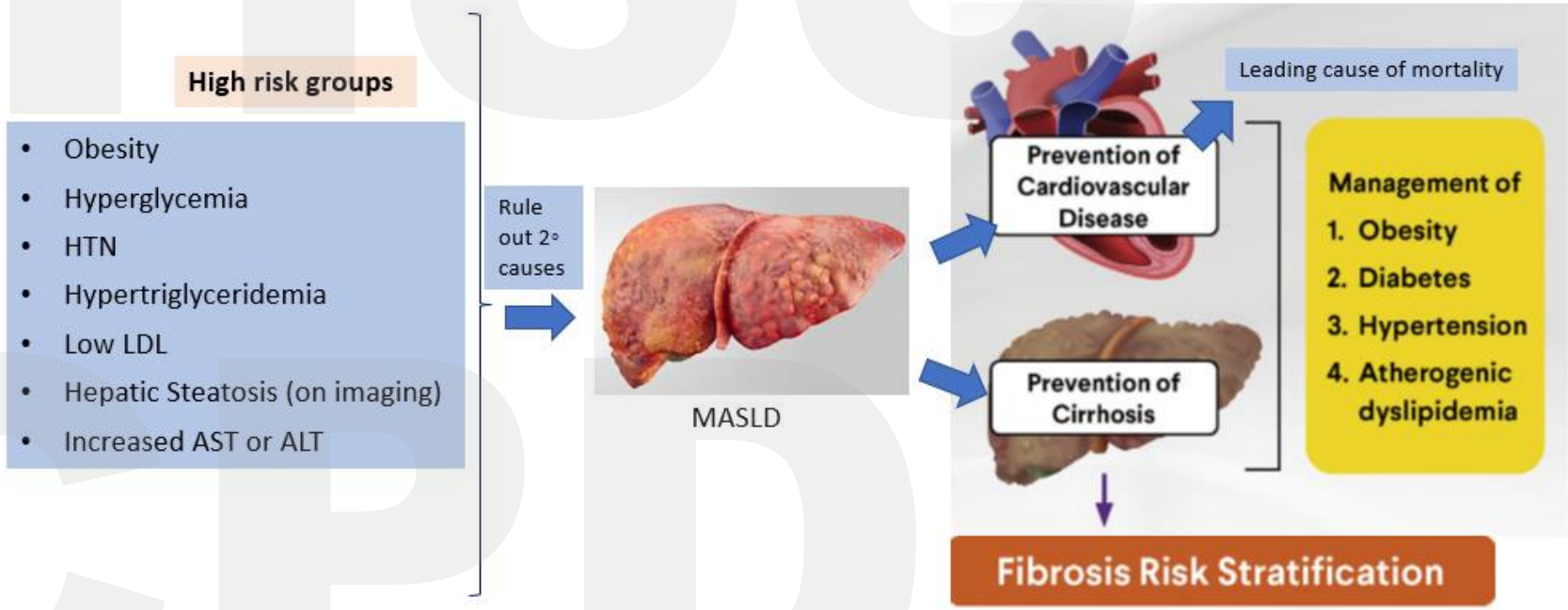


Safety and efficacy: based on surrogate endpoint (liver inflammation and scarring) at month 12 in a 54-month RCT – still ongoing, will be completed

Approved under the accelerated approval pathway, final approval contingent on results

Pharmacological management

- Medications approved for comorbidities have shown potential benefits in clinical trials



MASLD with Obesity

- Meds currently FDA approved for chronic weight management:
  - Orlistat
  - Phentermine/Topiramate
  - Naltrexone/Bupropion
  - Liraglutide
  - Semaglutide
  - Tirzepatide

In addition to significant weight loss, role in improving MASH

GLP1 RA

Liraglutide (Victoza)

Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study

Lancet 2016; 387: 679–90

- Improved steatosis
- Some improvement in MASH

Semaglutide (Ozempic)

A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

N Engl J Med 2021;384:1113-24.

- Resolved MASH
- Delayed progression of fibrosis although no significant improvement in fibrosis stage

ESSENCE Trial: Effect of Semaglutide in Subjects with Non-cirrhotic Non-alcoholic Steatohepatitis:
Ongoing, predicted to be published in 2025

Dual GLP1RA/GIP

Tirzepatide (Mounjaro)

Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial

Lancet Diabetes Endocrinol. 2022;10:393–406

- Significant reduction in steatosis in patients with DM2
- Effect on MASH unknown

Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis

N Engl J Med 2024;391:299-310

- Resolution of MASH

Pioglitazone

A Placebo-Controlled Trial of Pioglitazone in Subjects with Nonalcoholic Steatohepatitis

N Engl J Med 2006;355:2297-307

Improves glucose and cholesterol and reverses steatohepatitis in preDM and DM2

Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus

A Randomized Trial

Ann Intern Med.2016;165:305-315

Thiazolidinediones and Advanced Liver Fibrosis in Nonalcoholic Steatohepatitis

A Meta-analysis

JAMA Intern Med. 2017;177(5):633-640

Improves advanced fibrosis, even in patients without DM (decrease in the mean fibrosis stage, although does not reach the endpoint of one-stage fibrosis regression)

Randomized, Placebo-Controlled Trial of Pioglitazone in Nondiabetic Subjects With Nonalcoholic Steatohepatitis

Gastroenterology 2008;135:1176–1184

Improves metabolic and histologic parameters in MASH even without DM

Side Effects:

- Weight gain – dose dependent
- Osteoporosis in postmenopausal women
- Risk of HF exacerbation
- Increase risk of bladder cancer (controversial)

Vit E

Vitamin E has a beneficial effect on nonalcoholic fatty liver disease: A meta-analysis of randomized controlled trials

Nutrition. 2015;31:923–30.

Vitamin E significantly improved liver function and histologic changes in patients with MASLD.

NASH CRN Trial

N Engl J Med 2010;362:1675-85

Pioglitazone vs Vit E vs Placebo in MASH **without** DM

Benefits seen with both Vit E and Pioglitazone as compared to Placebo

- Decrease in AST/ALT
- Reduction in hepatic steatosis

- **No reduction in fibrosis**
- **Potential Side Effects:**
  - Hemorrhagic stroke
  - Increased risk of prostate cancer (conflicting data)

Vit E can be considered for treatment of MASH without DM2

Future landscape

ENLIGHTEN-Fibrosis study: Pegozafermin- aims to prolong the biological activity of fibroblast growth factor 21 (FGF21), for non-cirrhotic with Fibrosis stage F2-F3

ENLIGHTEN-Cirrhosis: Pegozafermin in patients with compensated cirrhosis (F4)

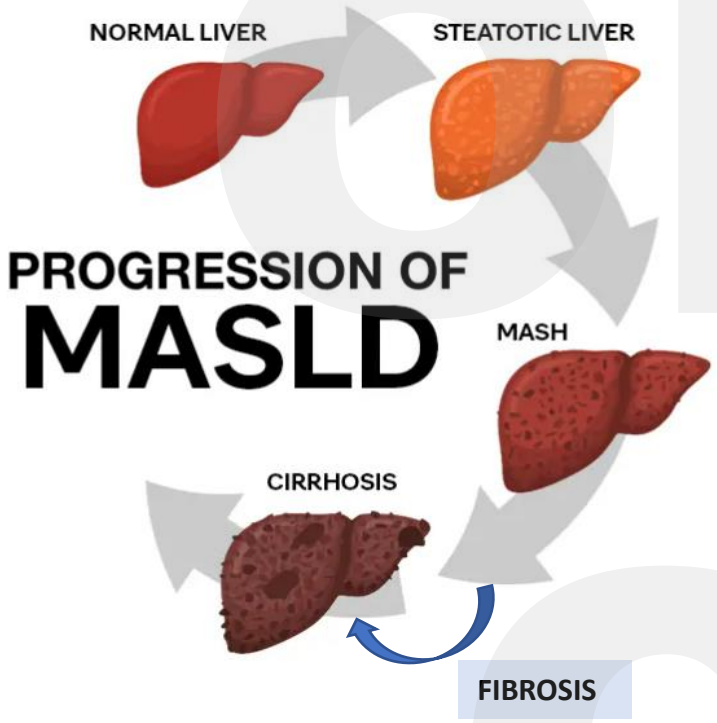
NATiV3 study: Lanifibranor in patients with MASH with Fibrosis stage F2-F3

At least 23 —of the 105 obesity treatments in development or on the market are also being investigated for MASH

“Triple G” drug: targeting GLP1, GIP, glucagon – Ozempic 3.0?

Take Home

MASLD spectrum



Screen: clinically significant fibrosis

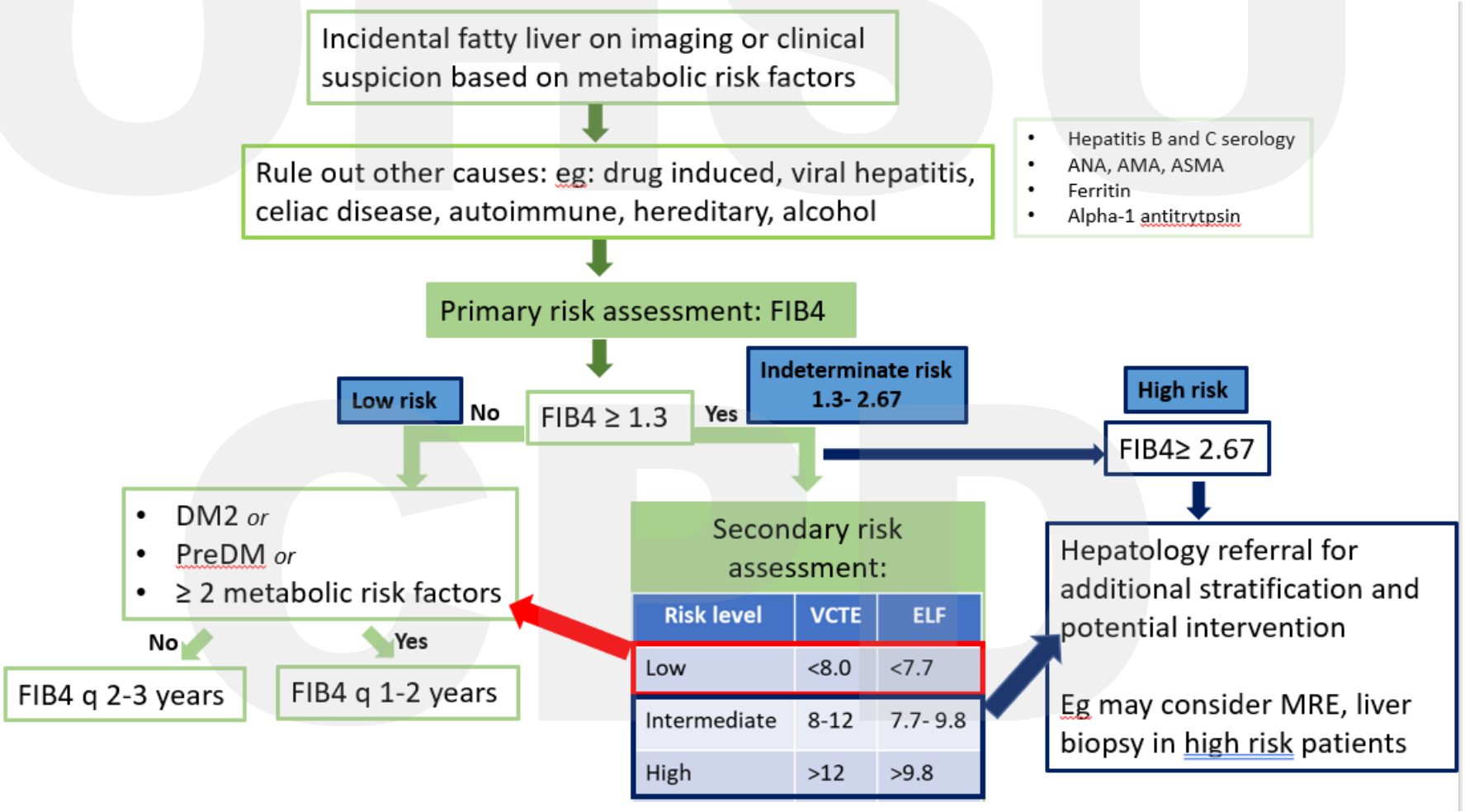
HIGH RISK GROUP

- Obesity
- Hyperglycemia
- HTN
- Hypertriglyceridemia
- Low LDL
- Hepatic Steatosis (on imaging)
- Increased AST or ALT

FIB-4

Most validated and cost-effective

Take home- Fibrosis risk stratification



References

1. Metabolic dysfunction–associated steatotic liver disease: Update and impact of new nomenclature on the American Association for the Study of Liver Diseases practice guidance on nonalcoholic fatty liver disease
   Hepatology. 2023 Nov 9.
2. AASLD Practice Guidance of the clinical assessment and management of NAFLD
   Hepatology. 2023;77:1797–1835
3. Nonalcoholic fatty liver disease from a primary care perspective
   Diabetes Obes Metab.2023;25:1421–1433.
4. AACE Clinical Practice Guidelines for the Diagnosis and Management of NAFLD in Primary Care and Endocrinology Clinical Settings
   Endocrine Practice 28 (2022) 528-562
5. Nonalcoholic Fatty Liver Disease: Review of Management for Primary Care Providers
   Mayo Clin Proc. 2022;97(9):1700-1716
6. Clinical Care Pathway for the Risk Stratification and Management of Patients with Nonalcoholic Fatty Liver Disease
   Gastroenterology 2021;161:1657–1669
7. ADA: Standards of Care in Diabetes, 2025
8. Therapeutic management of metabolic dysfunction associated steatotic liver disease
   United European Gastroenterol J. 2024;12:177–186.