Steatotic Liver Disease: New Nomenclature and Treatment

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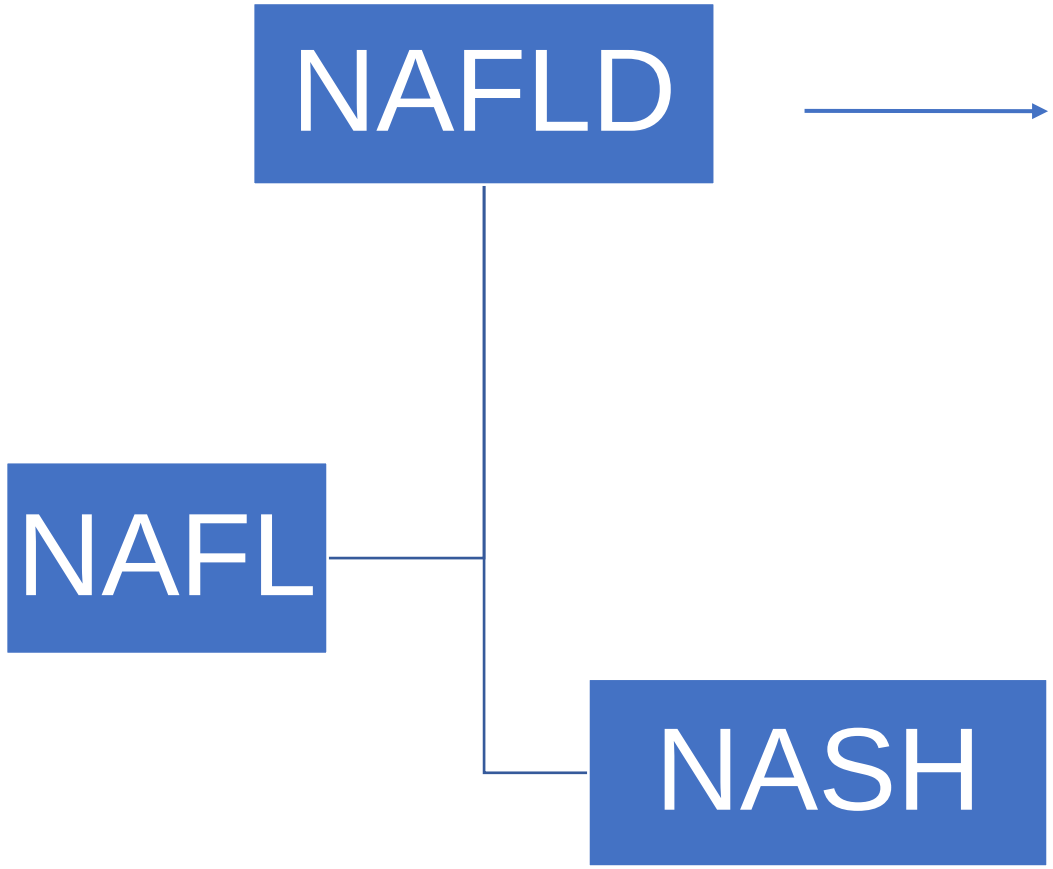
Objectives

- New nomenclature
- Prevalence
- Associations
- Implications
- Treatment

Nothing to disclose

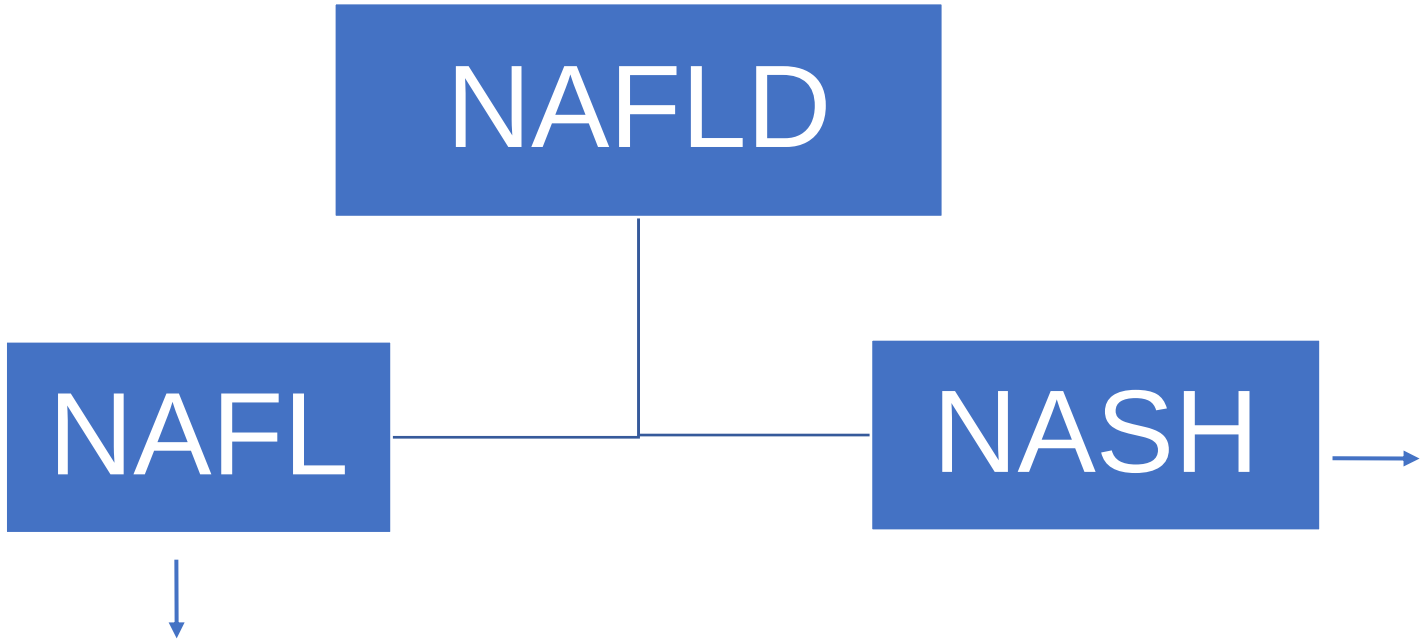
Nonalcoholic Fatty Liver Disease (NAFLD)



- Global term which includes all disease grades and stages
- Refers to a population in which > 5% of hepatocytes display macrovesicular steatosis in the **absence** of readily identified causes
  - Medications
  - Starvations
  - Monogenic diseases
  - Alcohol (<20g/d Women, <30g/d Men)

Rinella, Mary E.1; Neuschwander-Tetri, Brent A.2; Siddiqui, Mohammad Shadab3; Abdelmalek, Manal F.4; Caldwell, Stephen5; Barb, Diana6; Kleiner, David E.7; Loomba, Rohit8. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 77(5):p 1797-1835, May 2023. | DOI: 10.1097/HEP.0000000000000323

Nonalcoholic Fatty Liver Disease (NAFLD)



- Nonalcohoic Fatty Liver (NAFL)
- Hepatic steatosis mild to minimal inflammation

- Nonalcoholic Steatohepatitis (NASH)
- Presence of inflammation and cellular injury (ballooning), with or without fibrosis

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Why the name change in June 2023?

The term non “Nonalcoholic”

- Does not capture the disease etiology

The term “Fatty”considered stigmatizing by some

Individuals with risk factors for NAFLD

- Consume more alcohol than the relatively strict thresholds
- Are not recognized with the existing nomenclature
- Excluded from trials and consideration for treatment

This factors led to growing dissatisfaction

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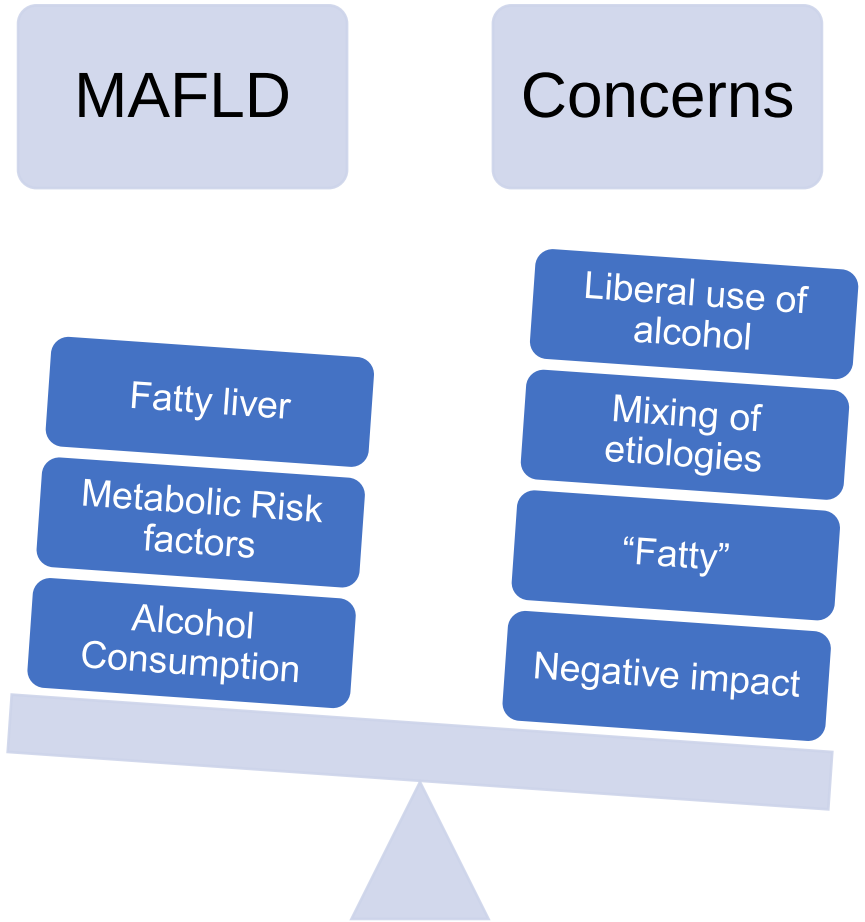
Eslam et al. 2020:
Metabolic dysfunction-associated fatty liver disease (MAFLD)



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This led to the name change

AASLD, EASL, ALEH, Asia-Pacific, MENA, Endocrine

Patient advocacy groups

- Fatty liver foundations
- ALD
- ELPA
- GLI
- ALF

Unified global approach to nomenclature and disease definition

- Disease awareness
- Driving policy change
- Identifying those at risk
- Facilitating diagnosis
- Access to care

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Overarching term: Steatotic Liver Disease (SLD)

Both “non-alcoholic” and “fatty” are perceived to be stigmatizing to some extent

For children/adolescents or parents, the term ”fatty, is perceived to be stigmatizing

Therefore: more neutral, “scientific” term

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What to know about SLD?

Overarching term to encompass the various etiologies of steatosis

The term steatohepatitis was felt to be an important pathophysiological concept that should be retained

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What to know about SLD?

Nonalcoholic fatty liver disease (NAFLD) will now be metabolic dysfunction-associated steatotic liver disease (MASLD)

MASLD encompasses patients who have hepatic steatosis and at least one of five cardiometabolic risk factors

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What to know about SLD?

Metabolic dysfunction-associated Steatohepatitis (MASH) is the replacement term for NASH

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Steatotic Liver Disease

Help categorize other causes of steatosis

Does not alter natural history, clinical trials or biomarkers nor will it impede development

Staging and severity that we use today will stay the same

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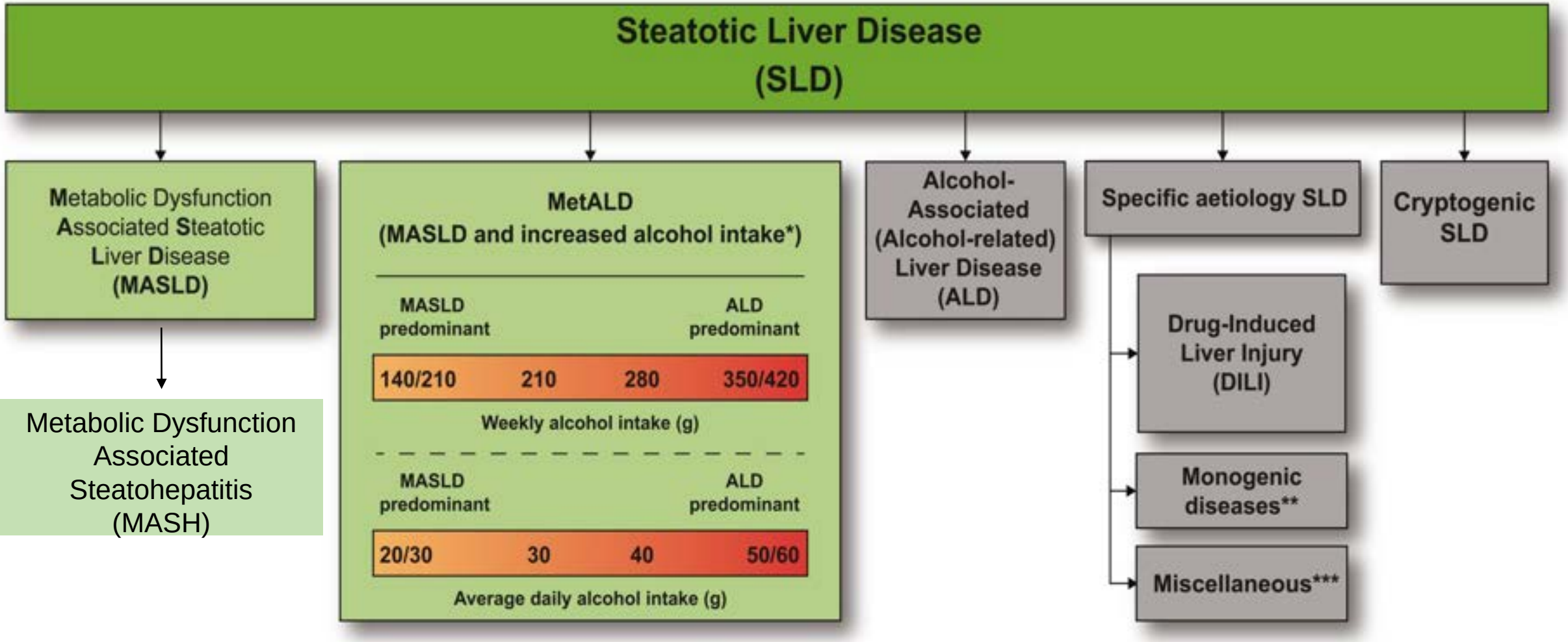

*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease

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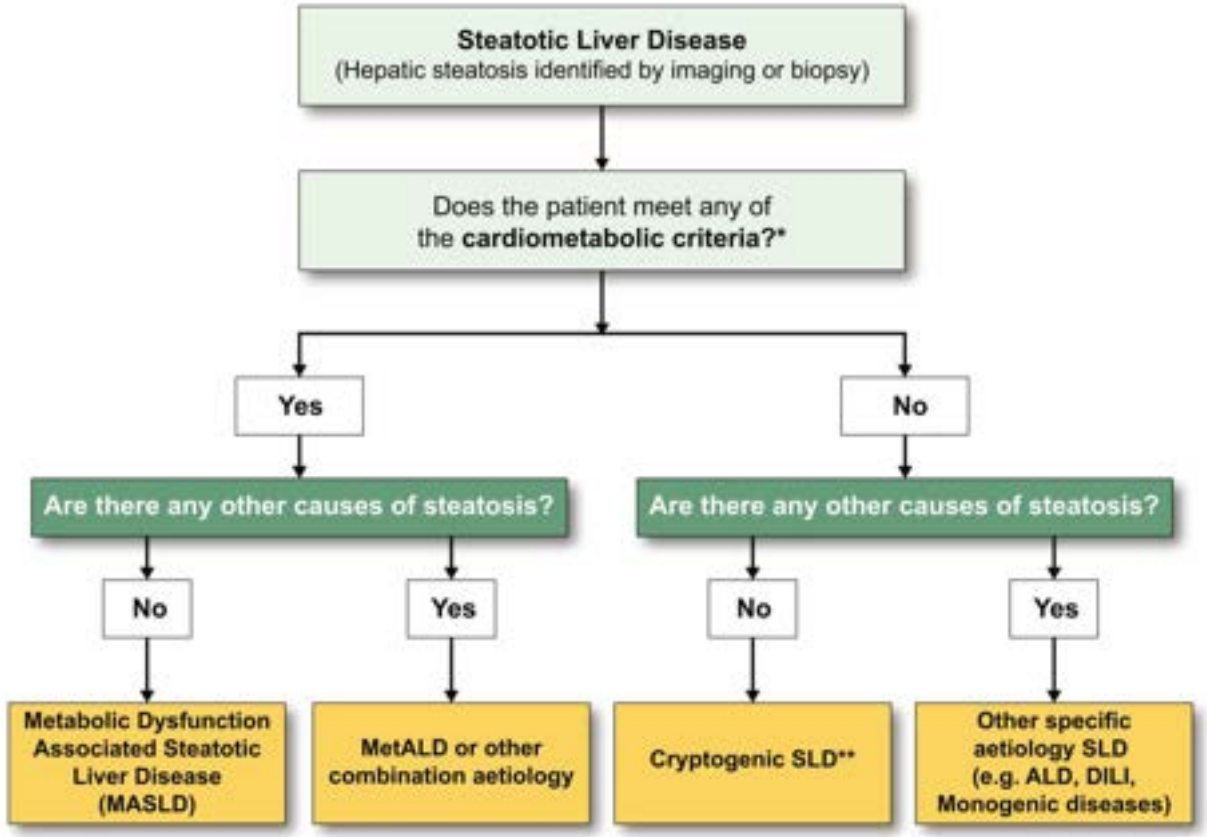
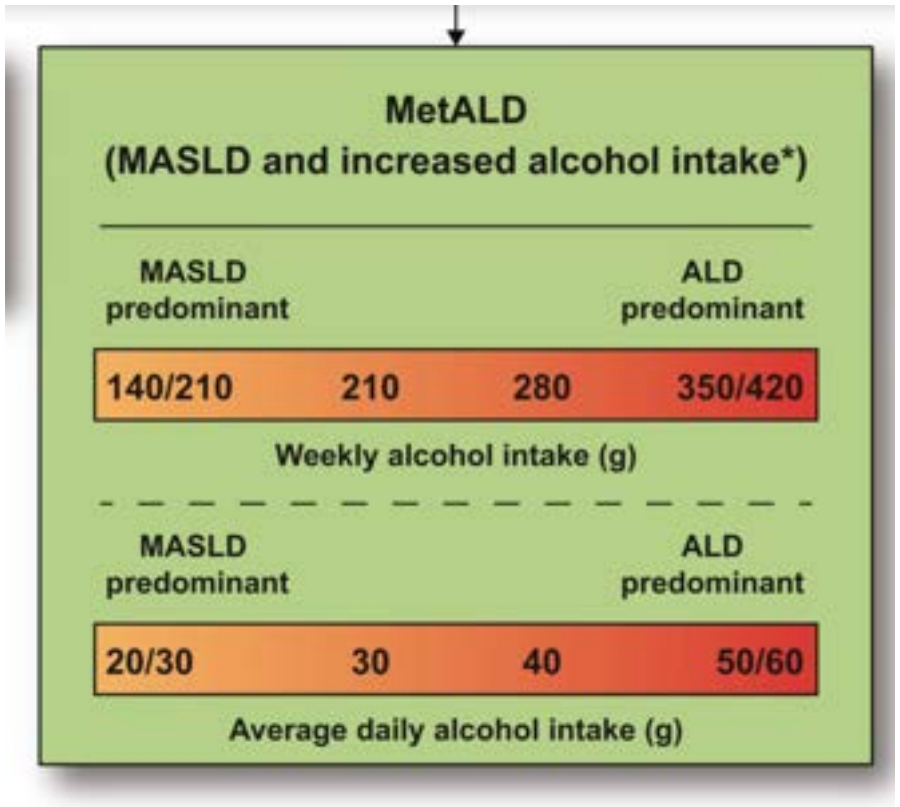


***Cardiometabolic criteria**

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

MetALD

- Continue to limit alcohol intake (as previously limited for NAFLD) in the context of steatosis
- Separate category outside of pure MASLD, namely MetALD, with alcohol intake greater than that allowed for NAFLD/MASLD



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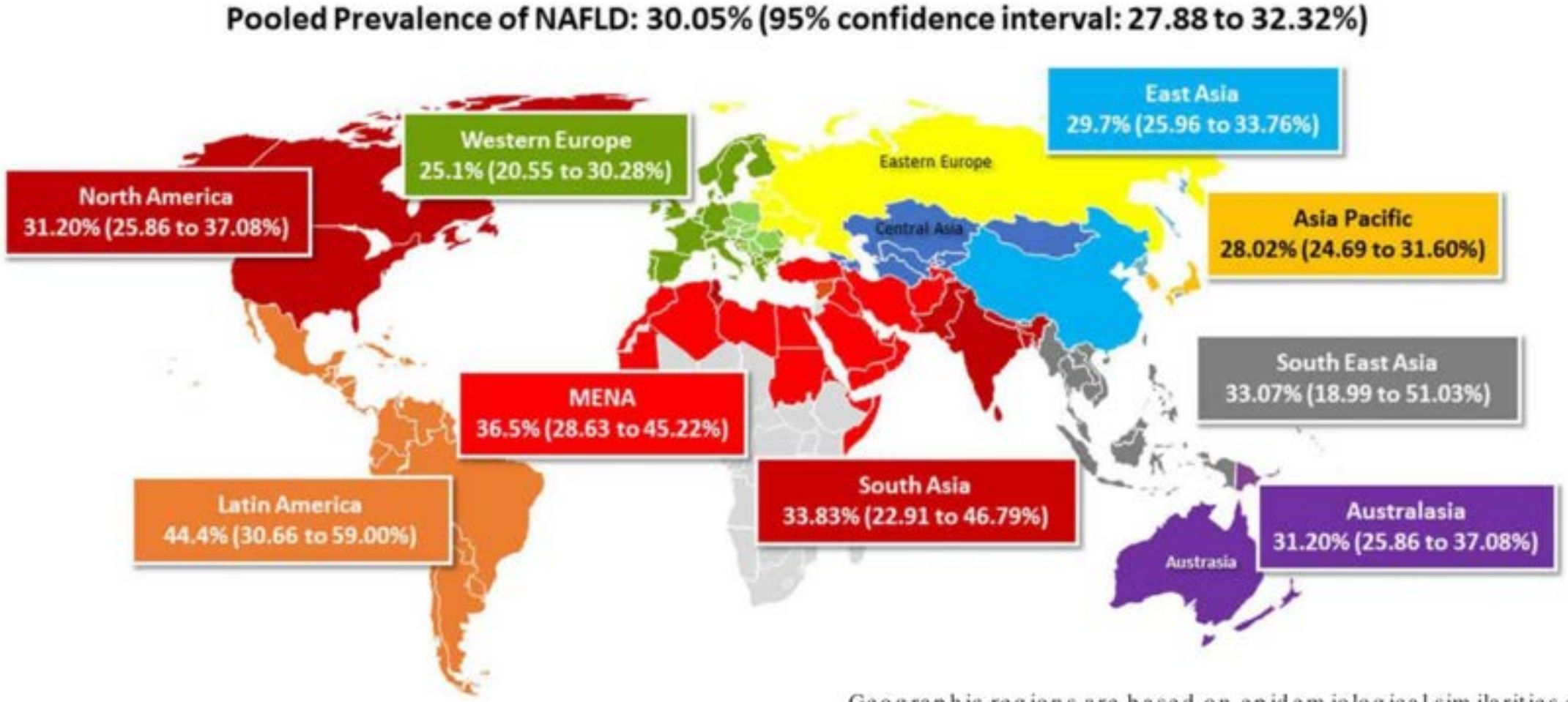
Review

- SLD and the more specific term MASLD provide an affirmative non-stigmatizing description of the condition
- Proposed nomenclature is not intended to be static, but rather allows the flexibility for refinement as new evidence emerges about underlying pathophysiology and risk factors

Why is learning from MASLD important?

- Most common chronic liver disease around the world
- Affects more than 30% of the global population

Prevalance



Younossi et al., Hepatology. 2023 Apr; 77(4): 1335–1347

Geographic regions are based on epidemiological similarities and geographical proximity from the Global Burden of Diseases study

Epidemiology

Incidence of hepatic decompensation, HCC and death

- Related to MASH cirrhosis -> 2-3x fold by 2030

MASH-related cirrhosis **leading** indication for liver transplant

- Women
- > 65 years of age
- Expected to increase further!!

Is on par with alcohol as the leading indication overall

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Natural Disease History

Fibrosis and presence of steatohepatitis

- Primary predictors of disease progression

Fibrosis progression is influenced by many factors

- Co-morbid disease
- Genomic profile
- Environmental factors

The diagnosis of cirrhosis is important because it changes clinical management

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Co-morbid Conditions Associated with MASLD

- Obesity
- Type 2 Diabetes Mellitus
- Hypertension
- Dyslipidemia
- Obstructive Spleen Apnea
- CVD
- Chronic Kidney Disease
- Hypothyroidism (Controversial)
- GH deficiency
- Hypogonadism
- PCOS

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Co-morbid Conditions Associated with MASLD

Most common causes of death in patients with MASLD	• **Cardiovascular Disease** and **Non-Hepatic Malignancy**
Death from liver disease complications predominates	• **Patients with advanced fibrosis**
Linked to and often precedes development of metabolic abnormalities	• Insulin resistance, dyslipidemia, central obesity and hypertension • Having several metabolic abnormalities confers greater risk of histological progression and all cause mortality
T2DM is the most impactful risk factor for development of MASLD, fibrosis progression and HCC	

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Drugs with potential mechanistic links to macrovesicular steatosis or steatohepatitis

Drug	Histological pattern
Amiodarone	Hepatic steatosis and steatohepatitis, phospholipidosis, cirrhosis
5-FU	Hepatic steatosis
Irinotecan	Steatohepatitis
Tamoxifen	Steatosis and steatohepatitis
Methotrexate	Steatosis, steatohepatitis, cirrhosis
Corticosteroids	Steatosis

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Less common causes of hepatic steatosis

Condition	Clinical scenario	Diagnostic test	Treatment
Hypobetalipoproteinemia	Low LDL, low triglycerides, fat malabsorption	ApoB level, genetic testing (MTTP, PCSK-9)	Low-fat diet, fat-soluble vitamin supplementation
LAL deficiency	Markedly elevated LDL-C and low HDL-C, elevated triglycerides, xanthelasma, hypersplenism, advanced fibrosis in young age, predominately microvesicular steatosis on liver biopsy	Enzyme assay, genetic testing	LAL replacement
Nutrient deficiency (eg, carnitine, choline)	Anorexia, short bowel, bypass surgeries	Nutrient levels	Supplementation
Wilson disease	Younger age, neuropsychiatric symptoms, low alkaline phosphatase, low ceruloplasmin	24-h urine copper; quantitative copper on liver biopsy	Chelation
Celiac disease	Iron deficiency, abdominal pain, bloating, vitamin D deficiency, bone loss, diarrhea, dermatitis herpetiformis	Tissue transglutaminase IgA, duodenal biopsy	Gluten-free diet

Abbreviations: ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; IgA, immunoglobulin A; LAL, lysosomal acid lipase; LDL-C, LDL cholesterol.

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Who should we screen and what screening method can be used?

AASLD Practice Guidance on the Clinical Assessment and Management of Nonalcoholic Fatty Liver Disease (May 2023)

- Screening for advanced fibrosis in high risks populations
- Noninvasive diagnosis of “at risk” NASH/MASH, advanced fibrosis and cirrhosis
- Off-label use of available medications
- Optimal care model

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Screening for advance fibrosis in high-risk populations

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

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Screening for Advanced Fibrosis and Risk Stratification

General population-based screening for NAFLD is not advised

All patients with hepatic steatosis should be screened for T2DM and OSA

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Evaluate for Fibrosis via Non-Invasive Tests

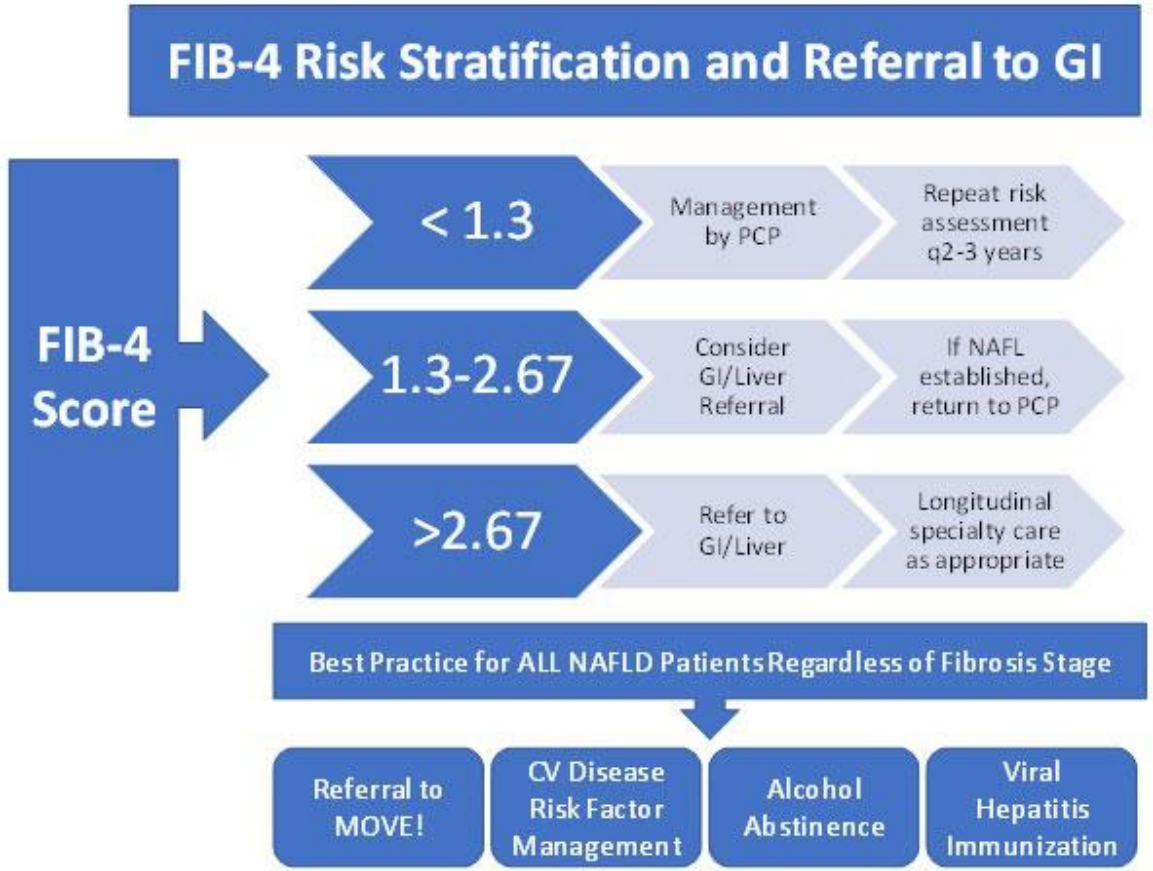
FIB-4

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		years
AST Aspartate aminotransferase	Norm: 15 - 41	U/L
Platelet count	Norm: 150 - 350	× 10⁹/L
ALT Alanine aminotransferase	Norm: 1 - 35	U/L



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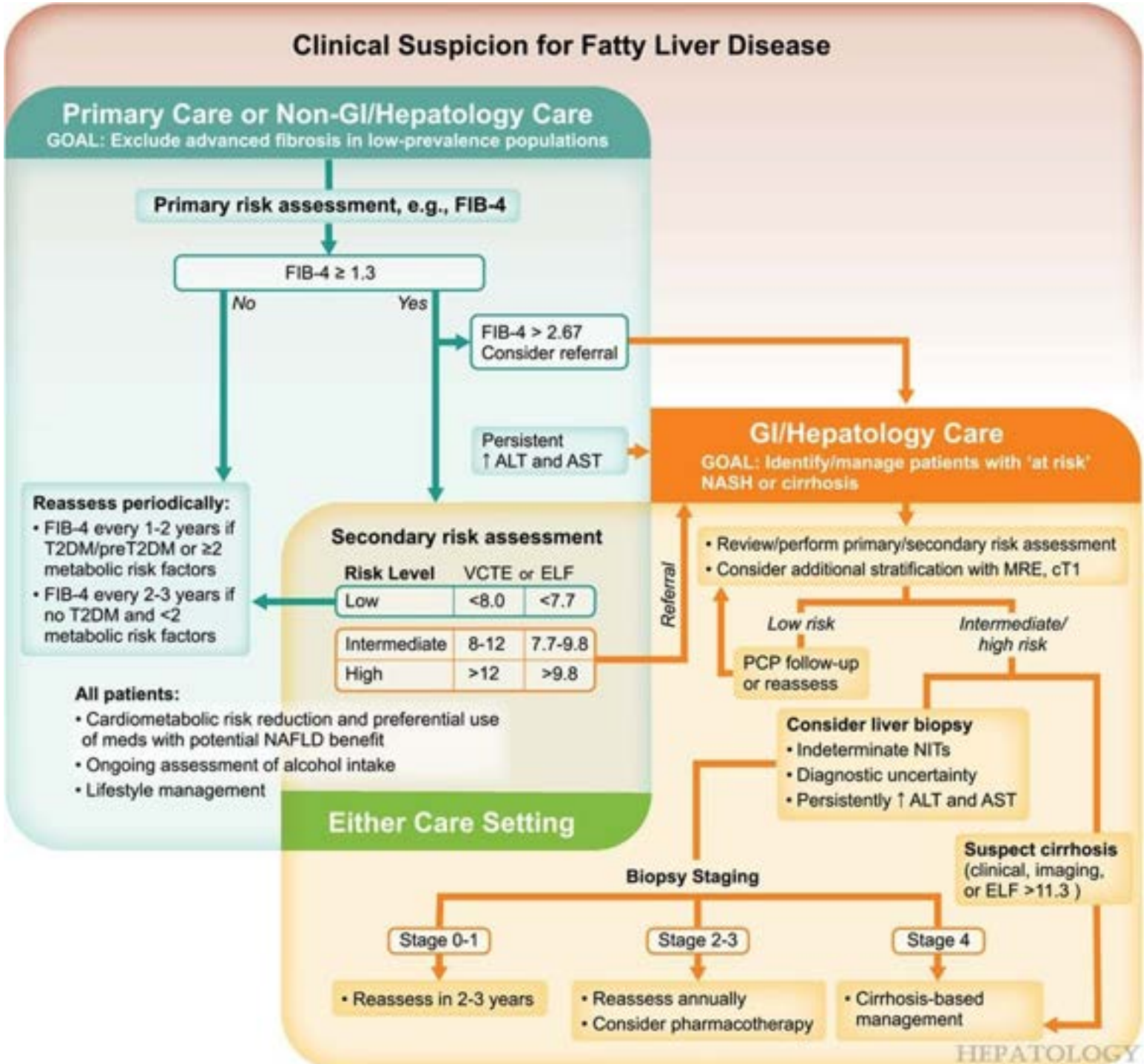
Clinical Suspicion for Fatty Liver Disease
Primary Care or Non-GI/Hepatology Care
GOAL: Exclude advanced fibrosis in low-prevalence populations
Primary risk assessment, e.g., FIB-4
FIB-4 ≥ 1.3
No
Yes
FIB-4 > 2.67
Consider referral
Persistent
↑ ALT and AST
GI/Hepatology Care
GOAL: Identify/manage patients with 'at risk' NASH or cirrhosis
Reassess periodically:
• FIB-4 every 1-2 years if T2DM/preT2DM or ≥2 metabolic risk factors
• FIB-4 every 2-3 years if no T2DM and <2 metabolic risk factors
Secondary risk assessment
Risk Level VCTE or ELF
Low <8.0 <7.7
Intermediate 8-12 7.7-9.8
High >12 >9.8
Referral
• Review/perform primary/secondary risk assessment
• Consider additional stratification with MRE, cT1
Low risk
Intermediate/ high risk
PCP follow-up or reassess
Consider liver biopsy
• Indeterminate NITs
• Diagnostic uncertainty
• Persistently ↑ ALT and AST
All patients:
• Cardiometabolic risk reduction and preferential use of meds with potential NAFLD benefit
• Ongoing assessment of alcohol intake
• Lifestyle management
Either Care Setting
Suspect cirrhosis
(clinical, imaging, or ELF >11.3)
Biopsy Staging
Stage 0-1
Stage 2-3
Stage 4
• Reassess in 2-3 years
• Reassess annually
• Consider pharmacotherapy
• Cirrhosis-based management
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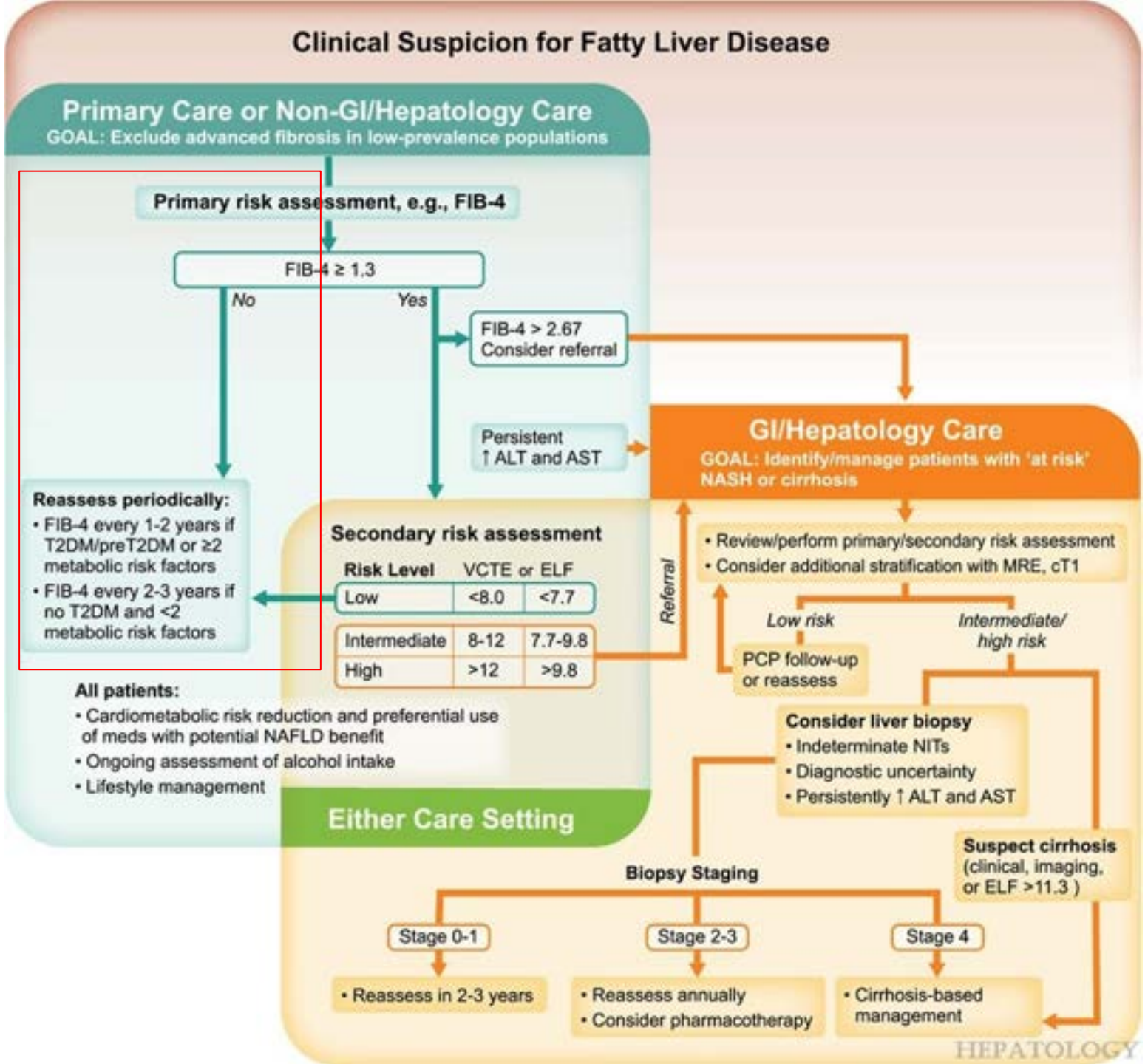
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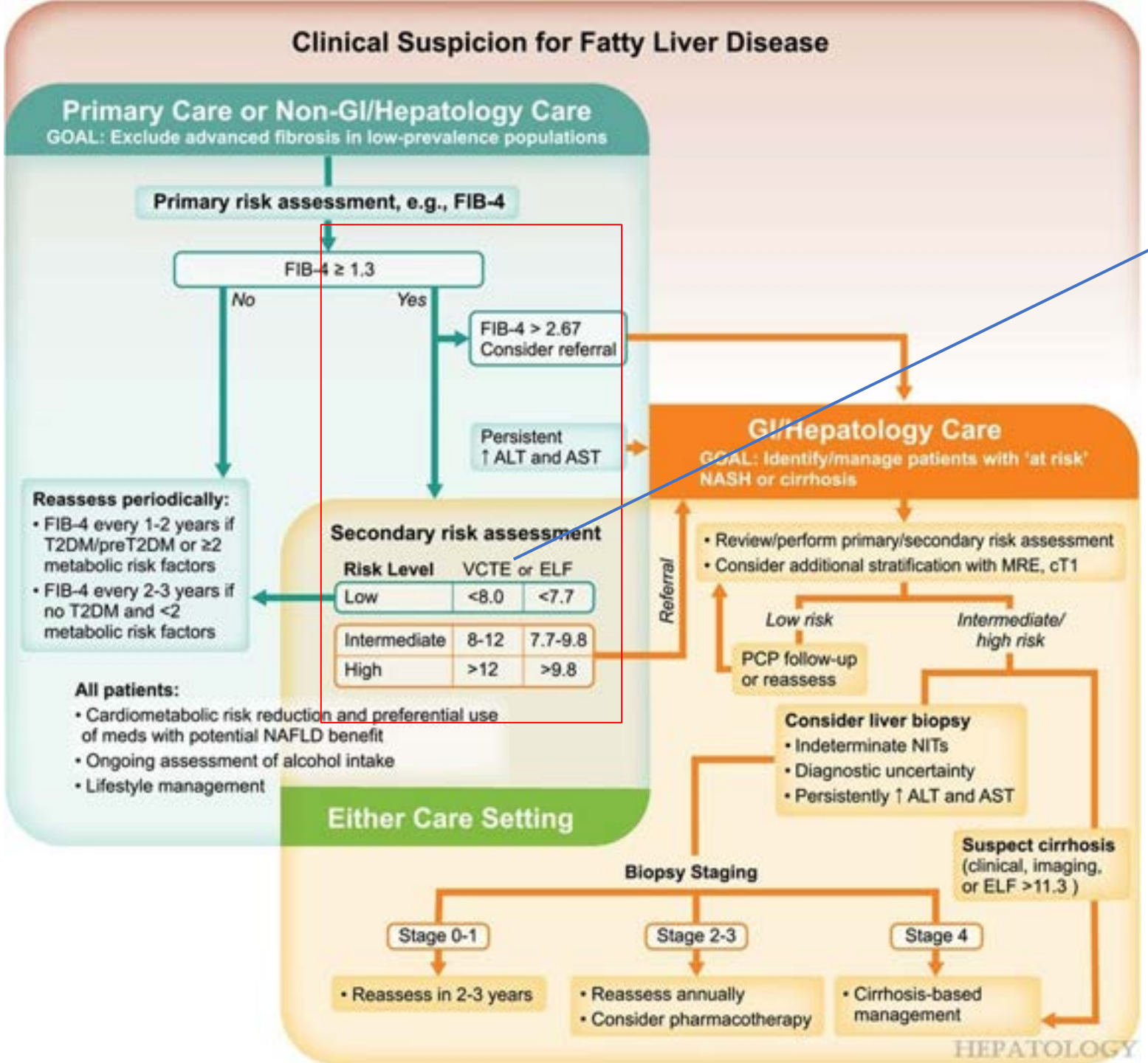
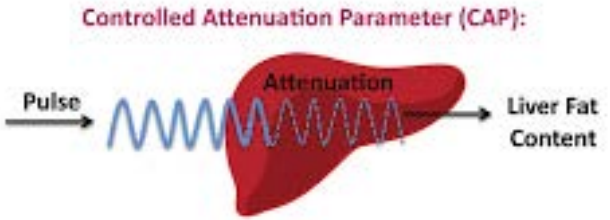
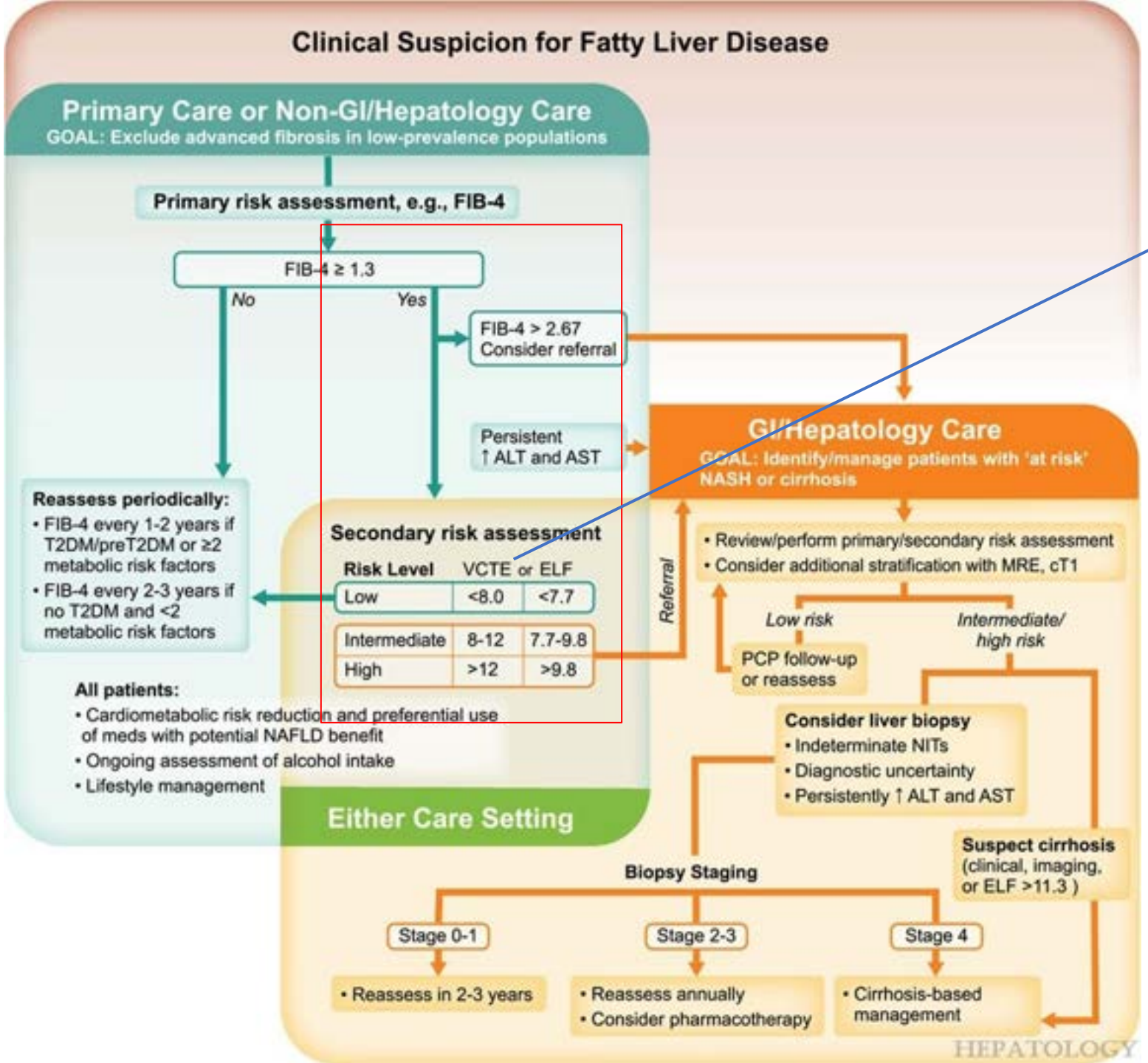


Vibration Controlled Transient Elastrography (VCTE)

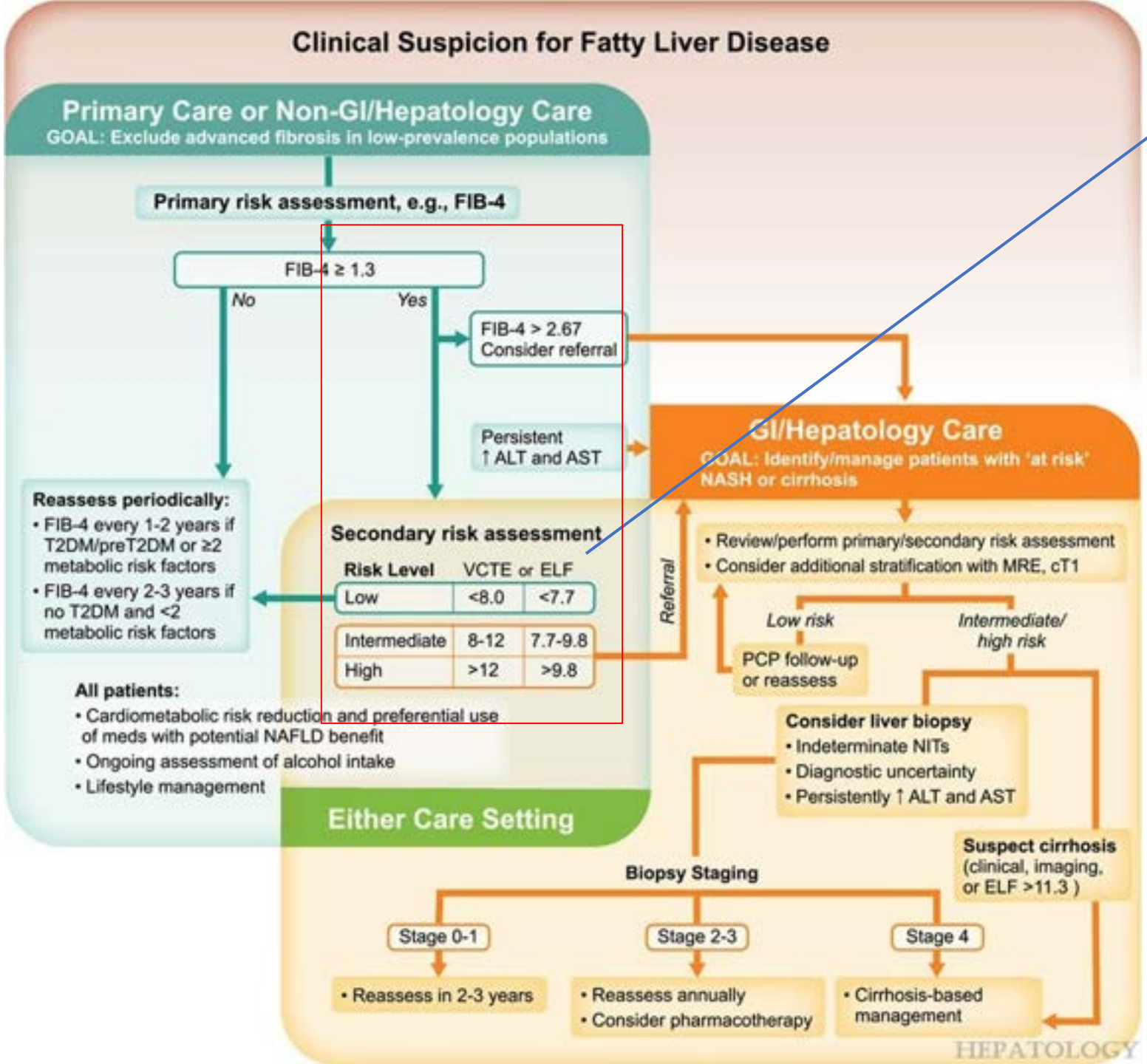
- Point of care tool for noninvasive assessment of liver fibrosis
- Performed at bedside in outpatient clinics with immediate results and good reproducibility
- Measurements in kPA
- CAP: Controlled attenuation parameter: % of fatty change in the liver





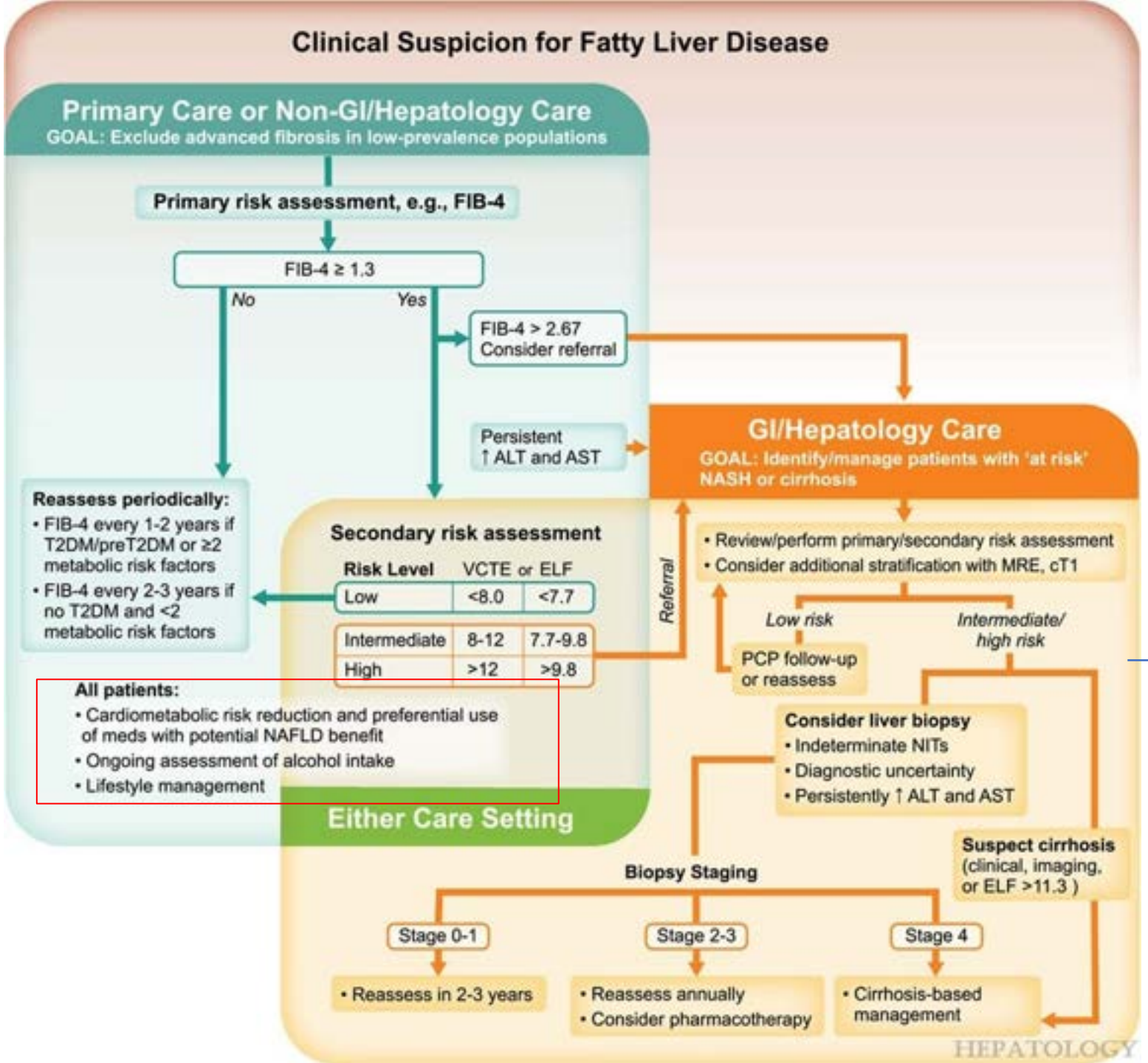
Vibration Controlled Transient Elastrography (VCTE)

- Avoid in CHF patients
- Fasting of at least 4 hours
- Obesity
- Ascites
- Acute liver injury (>5x ULN)



Enhance liver fibrosis (ELF)

- Serum blood test
- Identify patient at increase risk of progression to cirrhosis or related clinical events
- Prognostic biomarker



At “Risk F2” Cirrhosis

Pearls for the Assessment MASLD

Aminotransferase levels are frequently normal in patients with advanced liver disease due to NASH/MASH

- **Should not** be used in isolation to exclude the presence of NASH/MASH

Ultrasound can detect hepatic steatosis

It is **not recommended** as a tool to identify hepatic steatosis due to low sensitivity across the NAFLD spectrum

Patient with suspected advance NASH/MASH or discordant NITs should be referred to a specialist

Patient with clinically significant hepatic fibrosis **(F2+) should abstain from alcohol use completely**

Improvement in ALT or reduction in liver fat content by imaging in response to an intervention may indicate histological improvement in disease activity

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Role of Alcohol Consumption

- Co-factor for liver disease progression and intake should be assessed on a regular basis
- Classified
  - Mild : 20g women and 30 g daily for men
    Moderate: 21-39 g women and 31-59 g men per day
  - Heavy: > 40 g women and 60 g men per day
- Substantial variability in individual susceptibility to alcohol-induced injury

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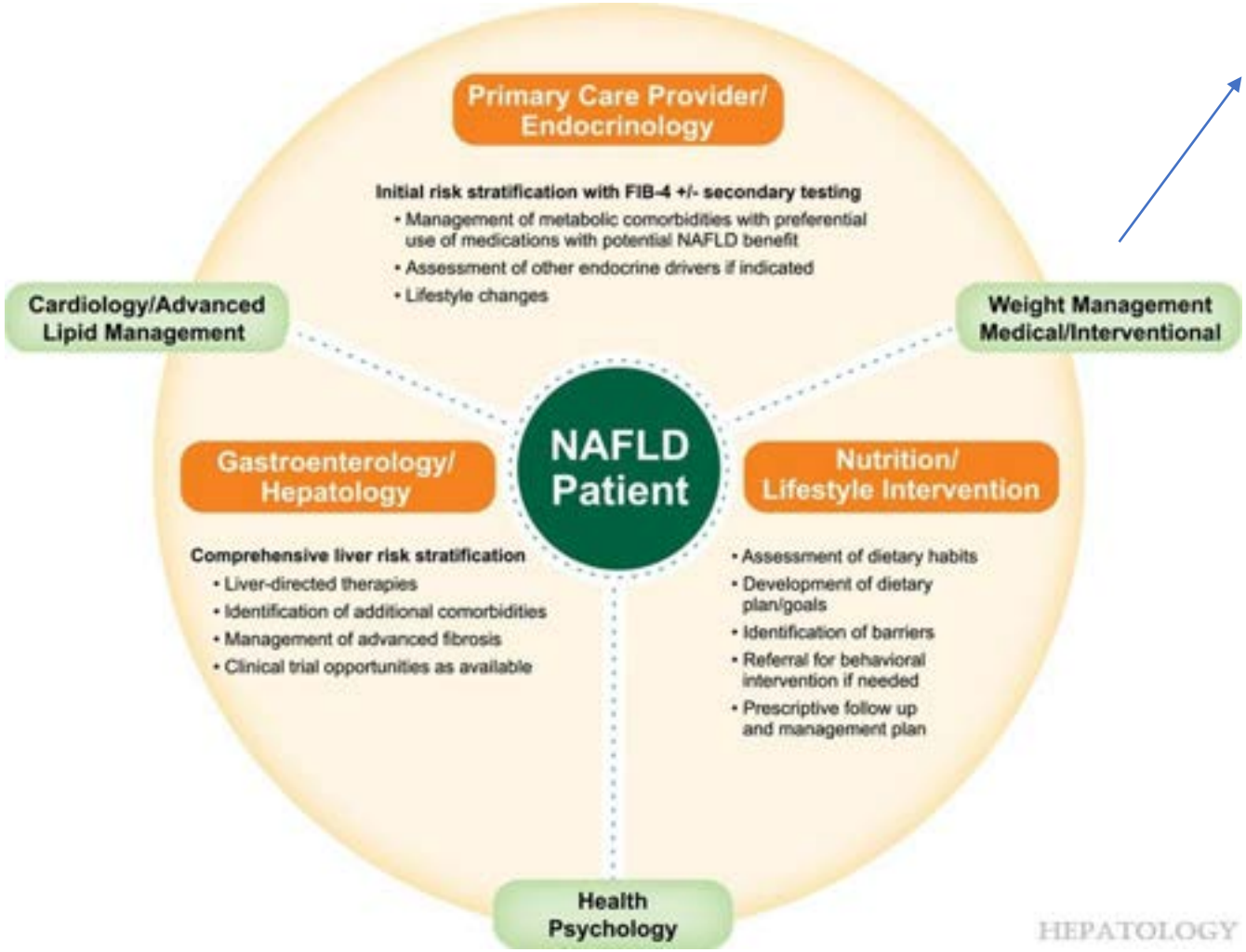
There are currently ***NO*** FDA-approved drugs for the treatment of NASH at any disease stage

Treatment Approach



Weight Loss (WL)

- 3-5% improves steatosis
- > 10% improves NASH/MASH and Fibrosis
- (<10%) achieve effective WL despite structured intervention in one 1 year
  - Fewer than half of these maintain the weight loss 5 years after intervention
- Multidisciplinary approach-> lifestyle changes
  - Patients support systems and family engagement
  - Behavioral medicine specialist
  - Dietitians
  - Nutritionist

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Treatment: Role of Macronutrients

- Avoid diet containing excess calories
  - Excess saturated fats
  - Refined carbohydrates
  - Sugar-sweetened beverages
  - Fructose
- Mediterranean diet improvement in CV Health + reduction in liver fat
- Coffee consumption: may reduce NAFLD/MASLD and liver fibrosis
  - Independent of caffeine content
  - 3 or more cups, in the absence of contraindications

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Treatment: Impact of Exercise

- Has hepatic and cardio metabolic benefit
  - Routinely recommended and tailored to the patient’s preference and physical abilities
- Prevent and/or improve NAFLD
  - Regular moderate exercise at least 5 times per week
    - 150 minutes per week
  - Increase in activity by more than 60 minutes per week
  - Some studies suggest more vigorous exercise is needed to improve NASH histology with higher intensity to reduce fibrosis

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Treatment: Bariatric Surgery (BS)

- Current criteria for BS
  - BMI > 40 kg/m2 irrespective of metabolic co-morbid disease
  - BMI> 35 with co-morbidities (DMT2, Pre-DM, U-HTN, OA of hip or knee)
- MASLD/MASH
  - Increasingly accepted as a co-morbid condition that could benefit
- Can resolve MASH, improve hepatic fibrosis, induced sustained weight loss of up to 30%, cure diabetes and decrease all-cause morbidity and mortality
- (BRAVES): a multi-center, open-label, randomized trial
  - Publish in The Lancet 04/21/2023

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Verrastro O, Panunzi S, Castagneto-Gissey L, De Gaetano A, Lembo E, Capristo E, Guidone C, Angelini G, Pennestrì F, Sessa L, Vecchio FM, Riccardi L, Zocco MA, Boskoski I, Casella-Mariolo JR, Marini P, Pompili M, Casella G, Fiori E, Rubino F, Bornstein SR, Raffaelli M, Mingrone G. Bariatric-metabolic surgery versus lifestyle intervention plus best medical care in non-alcoholic steatohepatitis (BRAVES): a multicentre, open-label, randomised trial. Lancet. 2023 May 27;401(10390):1786-1797. doi: 10.1016/S0140-6736(23)00634-7. Epub 2023 Apr 21. PMID: 37088093.

Treatment: Available medications

Medication	FDA indication	Patient population	Clinical benefits	Potential side effects	Cardiac benefit
Vitamin E (rrr-alpha) 800 IU daily	NA	NASH without T2DM or cirrhosis	Liver related: improves steatosis, NASH resolution? No proven benefit on fibrosis	Hemorrhagic stroke, risk of prostate cancer?	No

- Multi-center, (RCT), Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with NASH (PIVENS), Treatment with rrr α-tocopherol (the natural form of vitamin E) 800 IU daily for 96 weeks improved histology (≥2-point reduction in NAS) compared with placebo
- Findings were supported by a meta-analysis showing that vitamin E improved serum aminotransferases in addition to steatosis, inflammation, and cellular ballooning on biopsy
- Reduction in serum ALT to ≤40 U/L and by ≥30% of baseline value after initiation of vitamin E is associated with improvement in histological parameters
- **No study has demonstrated that vitamin E meaning fully reduces fibrosis**
- A retrospective study of 236 patients with NASH and advanced fibrosis showed that vitamin E use was associated with lower rates of hepatic decompensation and higher transplant free survival

Tonascia, James (2023). The Nonalcoholic Steatohepatitis Research Network (NASH CRN) Pioglitazone vs Vitamin E vs Placebo for Treatment of Non-Diabetic Patients With Nonalcoholic Steatohepatitis (V3) [Dataset]. NIDDK Central Repository. https://doi.org/10.58020/bhat-mx96

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Treatment: Available medications

Medication	FDA indication	Patient population	Clinical benefits	Potential side effects	Cardiac benefit
Pioglitazone 30–45 mg po daily	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, bladder cancer?	Yes

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Treatment: Available Medication

Medication	FDA indication	Patient population	Clinical benefits	Potential side effects	Cardiac benefit
Liraglutide[a] 1.8 mg s.c. daily (T2DM) 0.6–3 mg s.c. daily (obesity)	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	T2DM, obesity	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

[a]Study with small sample size and underpowered to determine key histological outcomes (ie, fibrosis). [b]Phase 3 trial to determine efficacy currently enrolling.

Treatment

Medication	FDA indication	Patient population	Clinical benefits	Potential side effects	Cardiac benefit
SGLT-2i	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

- Induce 2%–3% weight loss and have cardio renal protective benefits
- Role of SGLT-2i in the treatment of NAFLD/NASH are limited by relatively small sample sizes and lack of histological outcome
- Within these limitations, available data suggest SGLT-2i improve hepatic steatosis; however, the therapeutic impact of SGLT-2i on liver histology needs to be better defined

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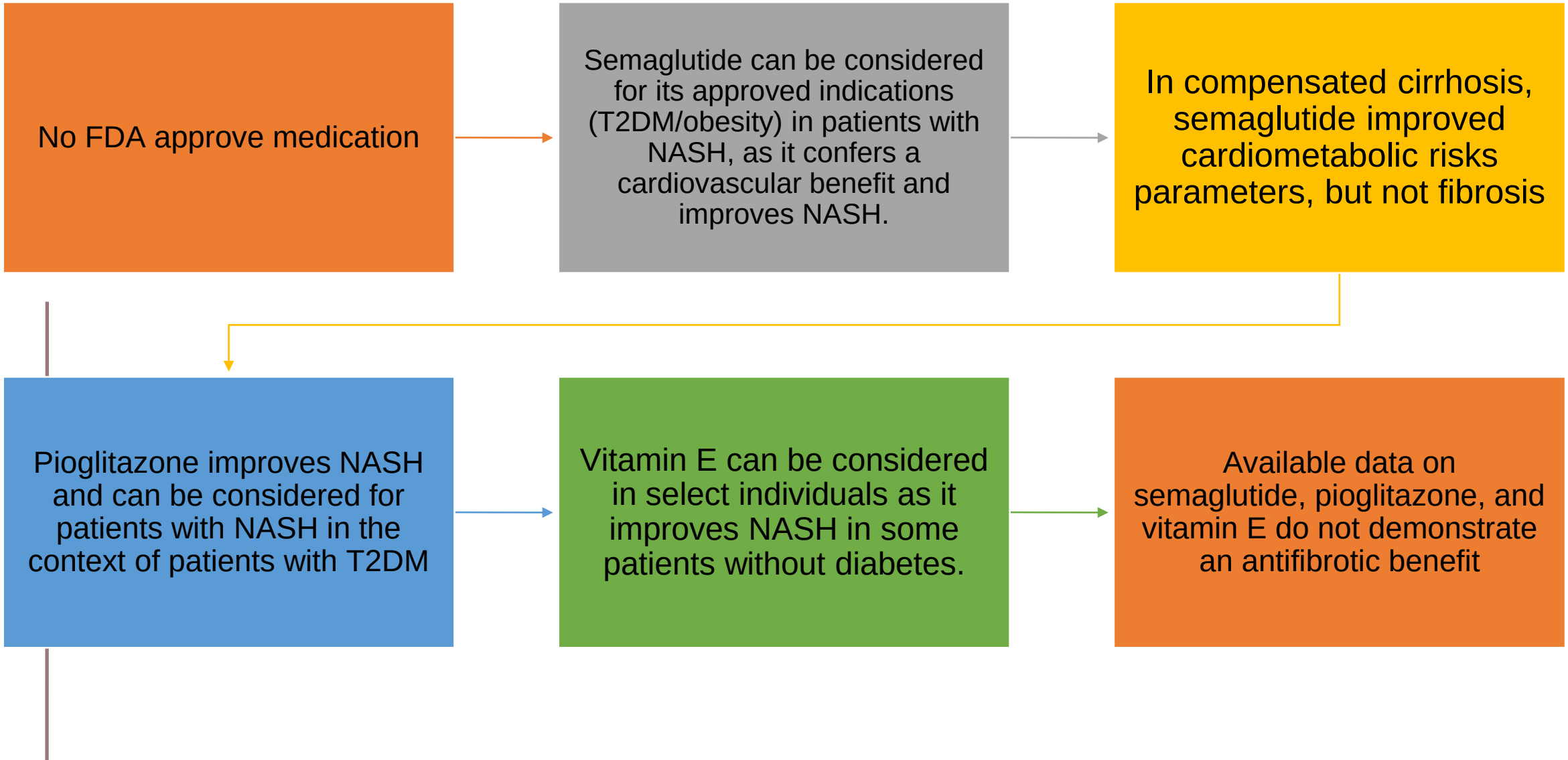
Medications Key Points



Summary

SLD is the new overarching term	MASLD is the new NAFLD	MASH is the new NASH	Met-ALD (mixed), more studies
Risk stratify for advanced fibrosis with FIB-4	Standard liver US not recommended	Screen for T2DM in all patients with hepatic steatosis	Risk stratify for advanced fibrosis in all patients with T2DM
No alcohol in F2 or higher	General population screening not indicated	Excessive fructose consumption increases risk of MASLD/MASH and advanced fibrosis	Treatment • Consider semaglutide/ tirzepatide or bariatric surgery in those with indications • Treat metabolic co-morbidities


Questions?