# NAFLD

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- ***Overall prevalence of NAFLD is 25%,***
- The prevalence of the potentially progressive form of NAFLD or NASH is between 12% and 14%.
- Those with obesity, the prevalence of NASH is between 25% and 30%
- Approximately 30% to 40% of persons with diabetes have NASH.
- 70% of persons with T2D have NAFLD (steatosis), and approximately 15% have clinically significant liver fibrosis (stages >= F2)

- Approximately 20% of persons with NASH could potentially develop significant liver disease including cirrhosis and its complications.
- NASH is now among the top causes of  HCC and the second most common cause of HCC in those on the waiting list for liver transplantation in the United States after hepatitis C.

# To Screen or Not to Screen for NAFLD?

## AASLD Guidance[1]

- **Type 2 diabetes**
  - Have high index of suspicion for NAFLD and NASH; risk stratify with NFS, FIB-4, VCTE
- **Other risk factors for NAFLD**
  - Uncertain long-term benefits, cost-effectiveness of routine screening for NAFLD

## EASL-EASD-EASO Guidelines[2]

- **High CV risk**
  - Screening for NAFLD recommended

1. Chalasani N, et al. Hepatology. 2018;67:328. 2. EASL, EASD, EASO. J Hepatol. 2016;64:1388.

# *Diagnosis of NAFLD is based on the following:*

- ***(1)*** presence of hepatic steatosis, in addition to
- ***(2)*** lack of significant alcohol consumption (defined as ongoing or recent alcohol consumption of >21 standard drinks [1 drink 1⁄4 14 g of pure alcohol]/week for men and >14 standard drinks/week for women),
- {A standard alcoholic drink is defined as a given drink with approximately 14 g of pure alcohol }

- ***(3)*** Exclusion of other liver diseases.

- Initial evaluation in persons with suspected or incidental finding of hepatic steatosis on imaging should include investigations to exclude competing causes for hepatic steatosis and liver disease (eg, hepatitis B and C serology, ANA, ASMA, serum ferritin, alpha 1 antitrypsin, and evaluation for MetS)

# NAFLD

- All disease grades and stages and refers to a population in which ≥5% of hepatocytes display macrovesicular steatosis in the absence of a readily identified alternative cause of steatosis (e.g., medications, starvation, monogenic disorders) in individuals who drink little or no alcohol (defined as less than 20 g/day for women and less than 30 g/day for men). (AASLD2023)

- NAFLD:Term used for the broad spectrum of the disease, ranging from hepatic steatosis only to steatohepatitis (NASH) to cirrhosis, in the absence of ongoing or recent consumption of significant amounts of alcohol or the presence of other secondary causes of fatty liver disease.

- NASH:Presence of 5% hepatic steatosis with inflammation and hepatocyte injury (also known as hepatocyte ballooning), with or without evidence of liver fibrosis.

- NASH Cirrhosis:Cirrhosis with histologic evidence of steatosis or steatohepatitis.

# Liver Enzymes: Inadequate in Assessing NAFLD/NASH

- **ALT can be normal in > 50% of individuals with NASH, 80% of individuals with NAFLD[1,2]**
- ALT can be elevated in > 50% of individuals with NAFLD but without NASH
- In NAFLD, ALT is neither indicative nor predictive of NASH or fibrosis stage[3]:
  - Normal ALT does not preclude NASH/progressive disease
  - Elevated ALT cannot predict NASH or fibrosis
  - **ALT or AST not sensitive for NAFLD/NASH**

**Abnormal ALT may warrant workup for NAFLD,[4]**
**but is not sensitive to confirm, rule out, or characterize NAFLD**

1. Browning. Hepatology. 2004;40:1387. 2. Dyson. Frontline Gastroenterol. 2014;5:211.
3. Mofrad. Hepatology. 2003;37:1286. 4. Younossi. Am J Gastroenterol. 2020;00:1.

- It is important to perform a complete medical history and routine clinical chemistries that allow clinicians to rule out secondary causes of liver steatosis ,

- And elevated plasma aminotransferase levels (Table 5).
- A thorough workup should be performed to rule out competing causes for steatosis, in addition to excluding significant alcohol consumption.

**Table 5**

Additional Causes of Elevated Aminotransferase Levels[22,a]

- Medications, vitamins, and supplements
- Viral hepatitis (A, B, and C)
- Endocrine disorders[a] (hyper- or hypothyroidism, Cushing syndrome, hypogonadism, growth hormone deficiency, Addison's disease, and other)[b]
- Hemochromatosis
- Autoimmune hepatitis
- Primary biliary cholangitis
- Alpha-1 antitrypsin deficiency
- Budd-Chiari syndrome
- Mass lesions

[a] Causes of elevated aminotransferase levels that should be considered in the clinical evaluation of elevated aminotransferase levels in addition to the secondary causes of hepatic steatosis listed in Table 4.

[b] Steatosis in several endocrinopathies linked to associated development of obesity, insulin resistance, and/or type 2 diabetes mellitus.

Causes of Secondary Hepatic Steatosis[101] and Laboratory Evaluation for the Secondary Causes of Liver Disease[22,a]

**Causes**

- Excessive alcohol consumption
- Hepatitis C (genotype 3)
- Lipodystrophy
- Acute weight loss (bariatric surgery and starvation)
- Malnutrition
- Parenteral nutrition
- Abetalipoproteinemia
- Reye syndrome
- Pregnancy associated
  - HELLP syndrome
  - Acute fatty liver of pregnancy
- Medications (eg, corticosteroids, mipomersen, lomitapide, amiodarone, methotrexate, tamoxifen, valproate, and antiretroviral medicines)
- Rare causes: autoimmune hepatitis, A1AT deficiency, Wilson syndrome, and other

**Laboratory evaluation**

- Hepatitis C
  - HCV antibody with reflex testing HCV RNA
- Additional tests to consider:
  - Hepatitis B: HBsAg, HBsAb, and HBcAb[b]
  - ANA
  - AMA
  - ASMA
  - Immunoglobulins
  - Ferritin
  - A1AT

# Recommendations

Non-invasive scores are not recommended for the diagnosis of steatosis in clinical practice (LoE 2; strong recommendation).

- Conventional ultrasound is recommended as a first-line tool for the diagnosis of steatosis in clinical practice, despite its well-known limitations (LoE 1; strong recommendation).
- Conventional ultrasound is the most commonly used imaging method for the diagnosis of steatosis, since it is widely available, innocuous, cheap and well established. (EASL2021)

- In persons with a high pretest probability of NAFLD (such as the 3 at-risk groups identified in the diagnostic algorithm (Algorithm Fig. 1),

It is reasonable to perform a risk stratification (FIB-4) without the need for a liver US for the diagnosis of hepatic steatosis (ie, in the 3 at-risk groups, the chance of having hepatic steatosis is very high(!70%).

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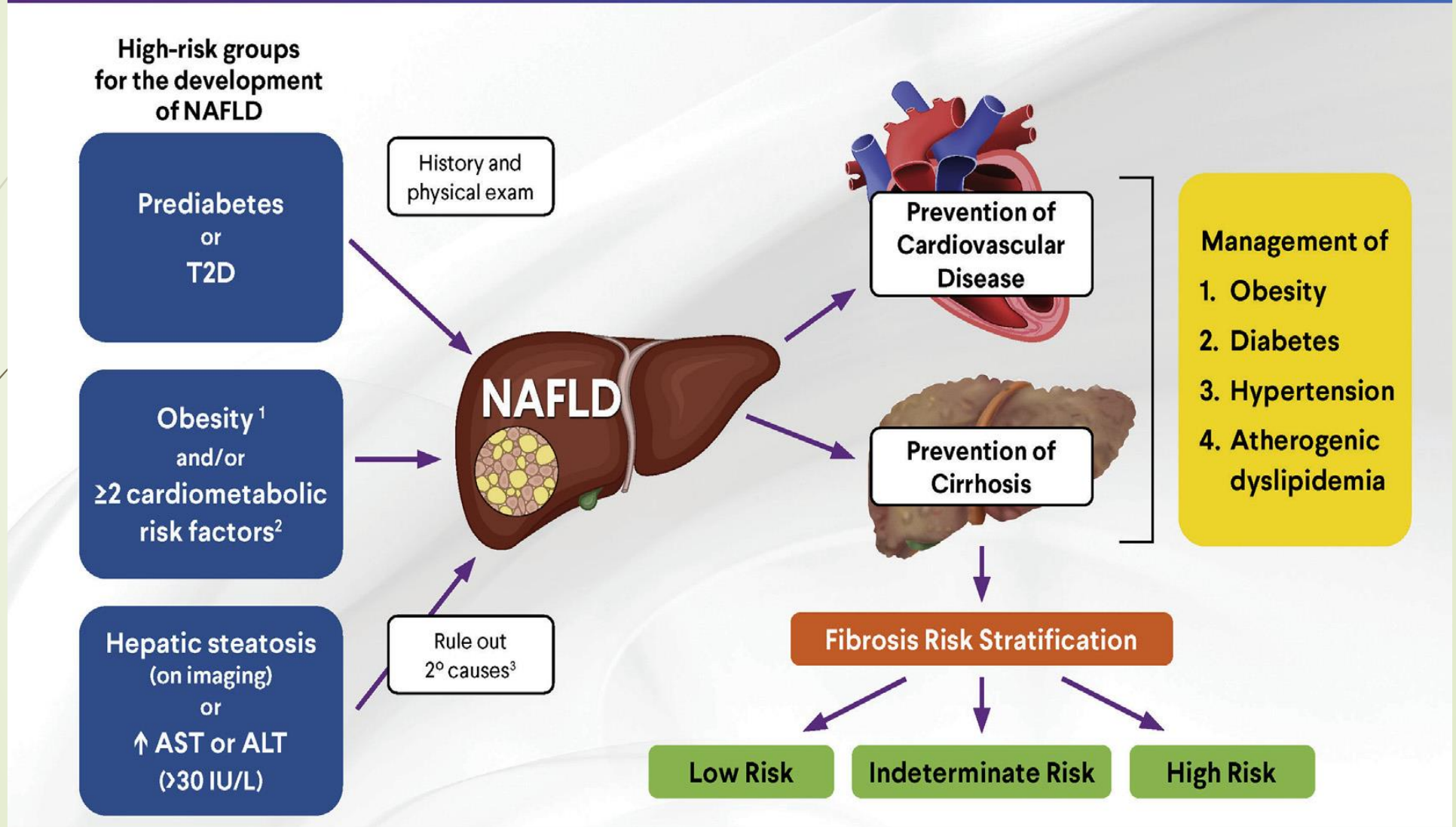
# Screening in high-risk populations

- Those with T2DM
- Obesity with metabolic complications
- A family history of cirrhosis
- Or significant alcohol use

# Management Algorithm for NAFLD – Overview



# Metabolic syndrome

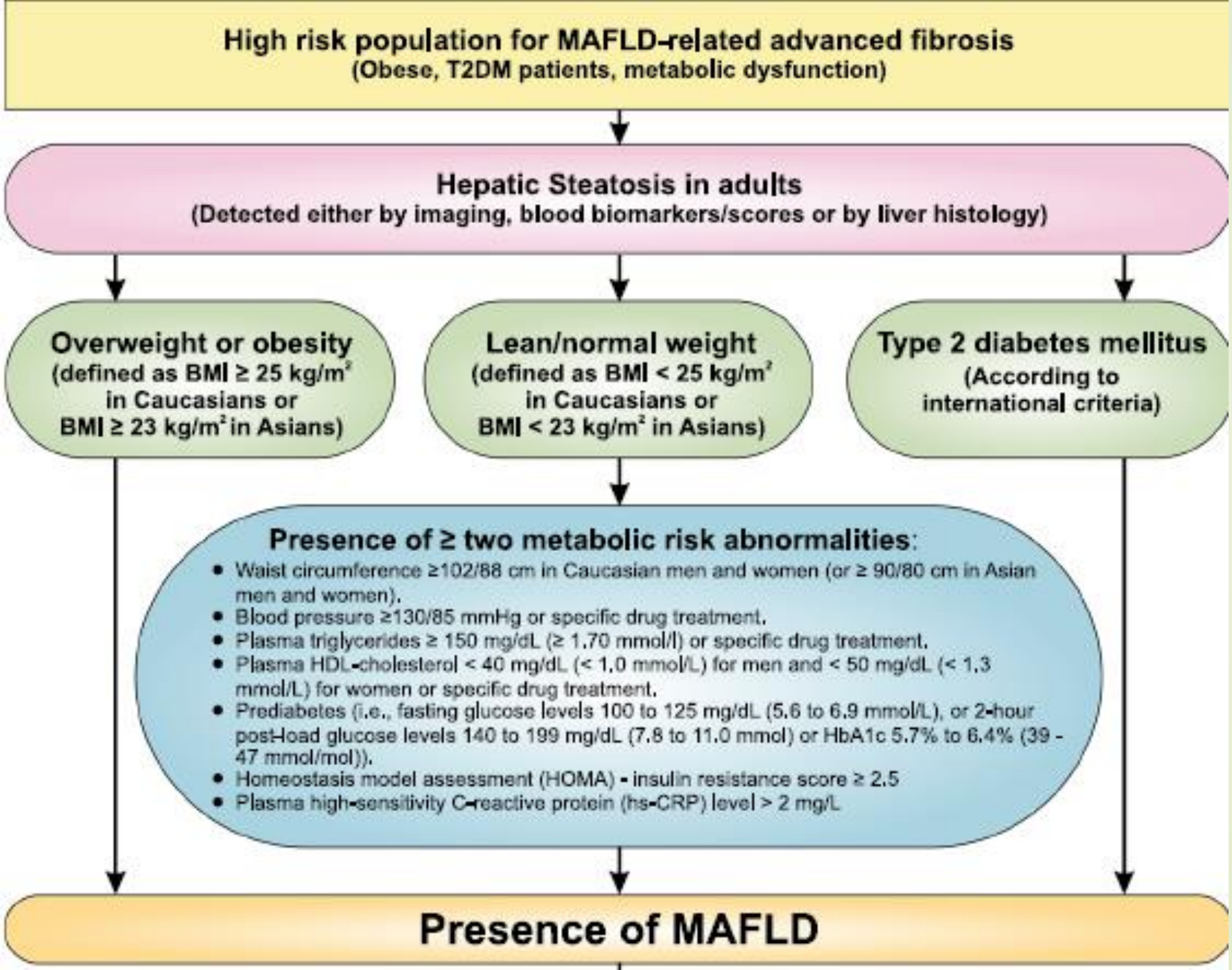
| MetS component | ATP III criteria [19,20] | IDF criteria [21,22] | Modified ATP III criteria [23] |
|---|---|---|---|
| To be identified as Mets | Any three or more of the following five components | Central obesity plus any two other factors | Any three or more of the following five components |
| Waist circumference | | | |
| Men | >102 cm | ≥90 cm for Chinese men | ≥90 cm for Asian men |
| Women | >88 cm | ≥80 cm for Chinese women | ≥80 cm for Asian women |
| TG | ≥1.70 mmol/L (150 mg/dL) | ≥1.70 mmol/L (150 mg/dL) mg/dL or specific treatment for this lipid abnormality | ≥1.70 mmol/L (150 mg/dL) or drug treatment for elevated TG |
| HDL-C | | | |
| Men | <1.03 mmol/L (40 mg/dL) | <1.03 mmol/L (40 mg/dL) in males or specific treatment for this lipid abnormality | <1.03 mmol/L (40 mg/dL) in men or drug treatment for reduced HDL-C |
| Women | <1.30 mmol/L (50 mg/dL) | <1.30 mmol/L (50 mg/dL) in women, or specific treatment for this lipid abnormality | <1.30 mmol/L (50 mg/dL) in women or drug treatment for reduced HDL-C |
| Blood pressure | ≥130/85 mm Hg | SBP ≥130 or DBP ≥85 mm Hg, or treatment of previously diagnosed hypertension | ≥130 mm Hg SBP or ≥85 mm Hg DBP or on antihypertensive drug treatment in a patient with a history of hypertension |
| Fasting glucose | ≥6.1 mmol/L (110 mg/dL) | ≥5.6 mmol/L (100 mg/dL), or previously diagnosed type 2 diabetes | ≥5.6 mmol/L (100 mg/dL) or drug treatment for elevated glucose |

MetS: metabolic syndrome; TG: triglycerides; HDL-C: high-density lipid cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure.
doi:10.1371/journal.pone.0091578.t001

1. Adiposity-based chronic disease (ABCD) is a diagnostic term proposed by AACE to better describe the disease of obesity in a complication-centric manner of abnormal adipose tissue mass, distribution, function and resulting morbidity that can be ameliorated with weight loss.
2. Cardiometabolic risk factors of the metabolic syndrome are waist circumference >40 inches men >35 inches women, triglycerides ≥150 mg/dL, HDL-C <40 mg/dL men, <50 mg/dL women, BP ≥130/≥85 mm Hg, fasting plasma glucose ≥100 mg/dL (NCEP ATP III)
3. Secondary causes of liver steatosis or elevated transaminases (AST or ALT) are excessive alcohol consumption (≥14 drinks/week for women or ≥21 drinks/week for men), hepatitis B, hepatitis C (genotype 3), Wilson's disease, alpha 1 antitrypsin deficiency, lipodystrophy, starvation, parenteral nutrition, abetalipoproteinemia, hemochromatosis, mass lesions, medications and other causes.

 https://doi.org/10.1016/j.eprac.2022.03.010

Algorithm Figure 1


High risk population for MAFLD-related advanced fibrosis
(Obese, T2DM patients, metabolic dysfunction)
Hepatic Steatosis in adults
(Detected either by imaging, blood biomarkers/scores or by liver histology)
Overweight or obesity
(defined as BMI ≥ 25 kg/m² in Caucasians or BMI ≥ 23 kg/m² in Asians)
Lean/normal weight
(defined as BMI < 25 kg/m² in Caucasians or BMI < 23 kg/m² in Asians)
Type 2 diabetes mellitus
(According to international criteria)
Presence of ≥ two metabolic risk abnormalities:
• Waist circumference ≥102/88 cm in Caucasian men and women (or ≥ 90/80 cm in Asian men and women).
• Blood pressure ≥130/85 mmHg or specific drug treatment.
• Plasma triglycerides ≥ 150 mg/dL (≥ 1.70 mmol/l) or specific drug treatment.
• Plasma HDL-cholesterol < 40 mg/dL (< 1.0 mmol/L) for men and < 50 mg/dL (< 1.3 mmol/L) for women or specific drug treatment.
• Prediabetes (i.e., fasting glucose levels 100 to 125 mg/dL (5.6 to 6.9 mmol/L), or 2-hour post-load glucose levels 140 to 199 mg/dL (7.8 to 11.0 mmol) or HbA1c 5.7% to 6.4% (39 - 47 mmol/mol)).
• Homeostasis model assessment (HOMA) - insulin resistance score ≥ 2.5
• Plasma high-sensitivity C-reactive protein (hs-CRP) level > 2 mg/L
Presence of MAFLD

# Evaluation of fibrosis?

# Noninvasive Tests (NITs) Offer Alternative Ways to Diagnose and Stage Fibrosis

**NITs are reproducible, widely available, and relatively low cost[1-3]**

**Safe, simple way to monitor disease over time[1]**

**May be cost-effective vs biopsy[1]**

**Identify patients with advanced fibrosis while excluding patients with early fibrosis[2]**

**Use of multiple NITs likely to be more predictive[3]**

MONITOR

1. Rockey. Gastroenterol. 2015;110:1298. 2. Lucero. Gasteroenterol Heptaol (N Y). 2018;2:3. 3. Wong. World J Gastroenterol. 2018;24:3361.

# Commonly Used Noninvasive Tests

## Clinical or Laboratory Scores

### Simple

- Fibrosis-4 (FIB-4)[1,2]
- NAFLD fibrosis score[1,2]
- AST/platelet ratio index[1]

### Proprietary

- Enhanced Liver Fibrosis Test[1] (not available in US)
- NIS4
- ADAPT/Pro-C3[3] (not available in US)
- *FibroSure*[1]
- Hepascore

## Imaging

### Elastography

- Transient elastography (eg, *FibroScan*)[1,2]
- 2D shear wave elastography[4]
- Magnetic resonance elastography[1]
- Corrected T1 (*Liver MultiScan*)[5,6]
- MRI-PDFF[7]
- FAST score[8]

1. EASL. J Hepatol. 2015;63:237. 2. Alkhouri. Gastroenterol Hepatol (N Y). 2012:8:661. 3. Daniels. Hepatology. 2019;69:1075.
4. Sigrist. Theranostics 2017;7:1303. 5. Jayaswal. AASLD 2018. Abstr. 1042. 6. Jayaswal. Liver Int. 2020;40:3071.
7. Idilman. Radiology. 2013;267:767. 8. Newsome. Lancet Gastroenterol Hepatol. 2019;[Epub].

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## Imaging

### Elastography

- Transient elastography (eg, *FibroScan*)[1,2]
- 2D shear wave elastography[4]
- Magnetic resonance elastography[1]
- Corrected T1 (*Liver MultiScan*)[5,6]
- MRI-PDFF[7]
- AST score[8]

- Good negative predictive value for **ruling out** fibrosis
- Calculators freely available on the Internet

1. EASL. J Hepatol. 2015;63:237. 2. Alkhouri. Gastroenterol Hepatol (N Y). 2012:8:661. 3. Daniels. Hepatology. 2019;69:1075.
4. Sigrist. Theranostics 2017;7:1303. 5. Jayaswal. AASLD 2018. Abstr. 1042. 6. Jayaswal. Liver Int. 2020;40:3071.
7. Idilman. Radiology. 2013;267:767. 8. Newsome. Lancet Gastroenterol Hepatol. 2019;[Epub].

Slide credit: clinicaloptions.com

- The preferred noninvasive initial test is the fibrosis-4 index (***FIB-4***).

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# Online Calculators Easily Interpret Noninvasive Tests


# NFS: NAFLD fibrosis score

- A liver score commonly used in hepatology clinics,

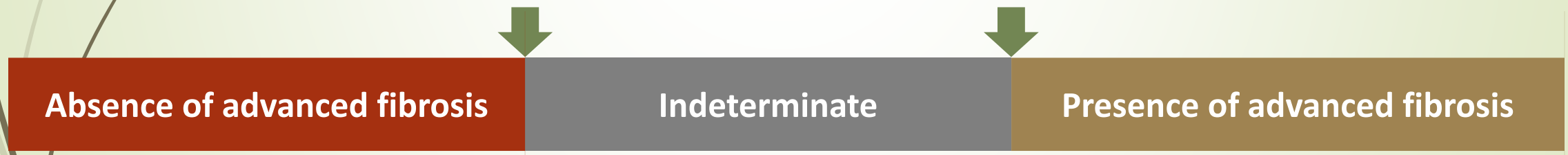
May overestimate in the primary care setting the prevalence of advanced liver fibrosis in persons with obesity, and in particular with T2D

; therefore, it should be avoided in this setting (noninvasive tests and screening tools (AACE2022)

# Noninvasive Tests Exclude or Determine Advanced Hepatic Fibrosis

- FIB-4 recognized by AASLD as useful in identifying patients with a higher likelihood of F3 or F3-F4[1]

**Cutoff Scores for Measurement of Advanced Hepatic Fibrosis[2,3]**




1. Vallet-Pichard. Hepatology. 2007;46:32. 2. Alkhouri. Gastroenterol Hepatol (N Y). 2012:8:661. 3. Shah. Clin Gastroenterol Hepatol. 2009;7:1104.

Slide credit: clinicaloptions.com

# Screening patients with T2DM and suspected NAFLD-related advanced hepatic fibrosis using FIB- 4

- Allow for the prediction of outcomes such as progression to cirrhosis or decompensation,

- Although the performance of NITs may be less robust in patients with diabetes.(AASLD2023)

- Higher cutoffs for the FIB-4, in the range of 1.9 to 2.0 (rather than >1.3), have been suggested with older age (! 65 years) to determine advanced fibrosis.(AACE2022)

# Noninvasive Tests for Diagnosis

| Test | Requirements | Components | Availability |
|---|---|---|---|
| NIS4[1] | Blood test | Alpha-2-macroglobulin, A1C, miR-34a, YKL-40 | Send to lab |
| *FIBROSpect*[2] | Blood test | Alpha-2-macroglobulin, hyaluronic acid, TIMP metallopeptidase inhibitor 1 | Send to lab |
| ADAPT/Pro-C3[3] | Blood test | Age, diabetes, Pro-C3, platelets | Investigational |
| FAST[4,5] | Blood test and imaging | AST, VCTE, CAP | Enter values in app |

1. Hanf. AASLD 2018. Abstr 142. 2. Loomba. Clin Gastroenterol Hepatol. 2019;17:1867. 3. Daniels. Hepatology. 2018;69:1075.
4. [illegible] Abstr 140. 5. Newsome. Lancet Gastroenterol Hepatol. 2019;[Epub].

# Vibration-Controlled Transient Elastography

- Measures 1D velocity of low-frequency shear wave
- Directly related to tissue stiffness (fibrosis)
  - The stiffer the liver, the faster the shear wave propagates
- Quick, bedside test (~ 5 mins)
- Limited by obesity, food intake, operator experience

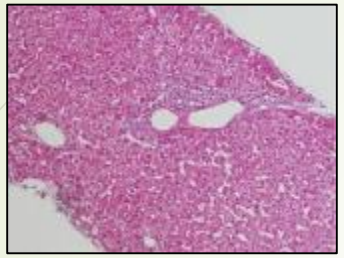

Sigrist. Theranostics 2017;7:1303.

Slide credit: clinicaloptions.com

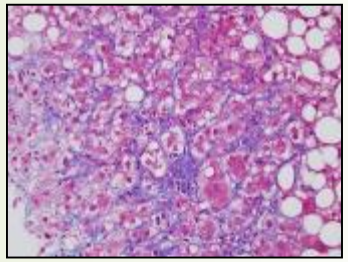
# VCTE for NASH Fibrosis

**Fibrosis Stage**

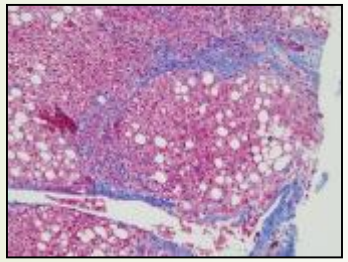
**F0**: Normal



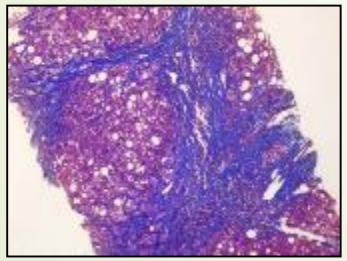
**F1/2:** Perisinusoidal ± Portal



**F3:** Bridging Fibrosis



**F4:** Cirrhosis



***FibroScan* Liver Stiffness (kPa)[1,2]**

**Increasing liver stiffness**

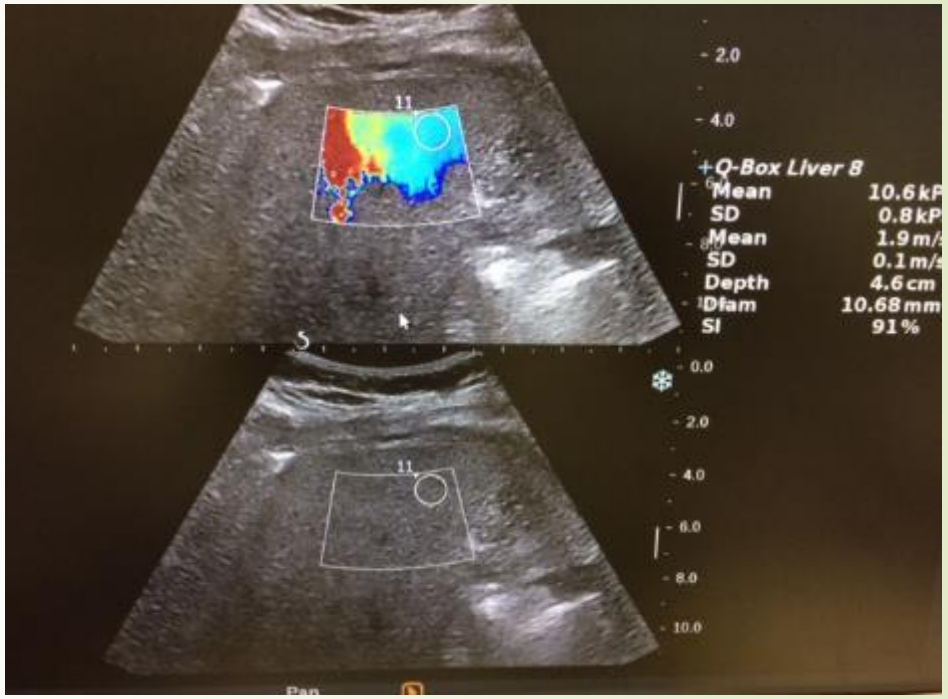
- Most reliable in **ruling out advanced hepatic fibrosis (NPV > PPV)**[2]
  - Fibrosis unlikely with low value (< 6 kPa)
- Higher values increase likelihood of more severe fibrosis, predicts risk of decompensation and complications[3]
- **Overestimation of fibrosis can occur** in cases of hepatitis, cholestasis, liver congestion, obesity, and if mass lesions are present in the liver[1,3]
- Correlates well with portal pressure (20+ kPa)[4]

1. Vuppalanchi. Hepatology. 2018;67:134. 2. Hashemi. Caspian J Intern Med. 2016;7:242.
3. Kemp. Australian Family Physician. 2013;42:468. 4. Robic. J Hepatol. 2011;55:1017.

Slide credit: clinicaloptions.com

# 2D Shear Wave Elastography

- Ultrasound system, using real-time SWE map of liver elasticity to determine liver stiffness[1]
  - 2D SWE color-coded map superimposed on B-mode image confirms readings are in liver, not in nearby vessels or kidneys[1]
- May require radiologist/sonographer[1]
- Liver elasticity measurements can be obtained in challenging cases of obesity[1]



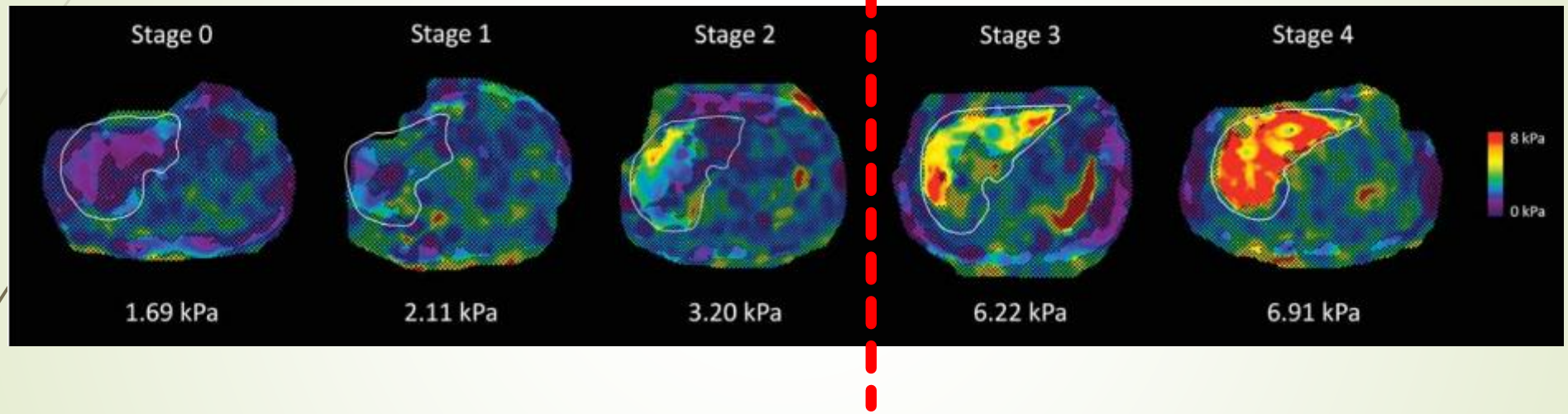

| Cutoff for Detecting Advanced Hepatic Fibrosis ≥ F3 in HCV[2] | Sensitivity | Specificity | AUROC |
|---|---|---|---|
| 2D-SWE stiffness > 8.7 kPa | .973 | .951 | .98 |

1. Sigrist. Theranostics 2017;7:1303. 2. Ferraiolo. Hepatology 2012;56:2125.

Slide credit: clinicaloptions.com

# MRE: Detecting Advanced Hepatic Fibrosis in NAFLD

- Prospective, cross-sectional analysis of 2D MRE in N = 117 patients with biopsy-proven NAFLD




| Cutoff for Detecting Advanced Hepatic Fibrosis ≥ F3 | Sensitivity | Specificity | AUROC |
|---|---|---|---|
| MRE stiffness > 3.63 kPa | .86 | .91 | .924 |

Loomba. Hepatology. 2014;60:1920.

Slide credit: clinicaloptions.com

# Common Imaging Tests for Hepatic Fibrosis: Summary

| Imaging | Comments |
|---|---|
| ***Vibration-controlled transient elastography – FibroScan*** | ▪ Can be point of care<br>▪ **Most reliable in ruling out advanced hepatic fibrosis (great NPV)** |
| ***MR elastography/MR spectroscopy/ Liver MultiScan*** | ▪ Requires radiology referral<br>▪ Most accurate of the imaging modalities |
| ***2D shear wave elastography*** | ▪ May require radiology referral but can be point of care with minimal training |

These imaging tests measure liver stiffness, which is an indirect measure of hepatic fibrosis and not hepatic fat content

Slide credit: clinicaloptions.com

# The CAP score

- It shows how much of your liver is affected by fat buildup

- CAP is a promising point-of-care technique for rapid and standardized detection of steatosis. However, given its limited availability and lack of head-to-head studies compared to ultrasound, CAP cannot yet be recommended as a first-line technique (LoE 2).

- Although there are no consensual cut-offs, values above 275 dB/m might be used to diagnose steatosis, since they showed over 90% sensitivity to detect steatosis (LoE 2).

EASL2021

- CAP as a point-of-care technique may be used to identify steatosis.(AASLD cuttoff:288db/min)

- MRI-PDFF can additionally quantify steatosis.

- To stage the risk of fibrosis in persons with NAFLD,

clinicians should prefer the use of ***VCTE*** as best validated to identify advanced disease and predict liver-related outcomes.

- Alternative imaging approaches may be considered, including shear wave elastography (SWE) (less well validated) and/or MRE (most accurate but with a high cost and limited availability; best if ordered by a liver specialist for selected cases).(AACE2022)

Relevant Definitions in NAFLD

| | | |
|---|---|---|
| NAFLD[a] | Nonalcoholic fatty liver disease | Term used for the broad spectrum of the disease, ranging from hepatic steatosis only to steatohepatitis (NASH) to cirrhosis, in the absence of ongoing or recent consumption of significant amounts of alcohol or the presence of other secondary causes of fatty liver disease. |
| NASH[a] | Nonalcoholic steatohepatitis | Presence of $\geq$5% hepatic steatosis with inflammation and hepatocyte injury (also known as hepatocyte ballooning), with or without evidence of liver fibrosis. |
| NASH cirrhosis[a] | | Cirrhosis with histologic evidence of steatosis or steatohepatitis. |
| NAS[a] | NAFLD activity score | An unweighted composite of steatosis, lobular inflammation, and ballooning scores. |
| Significant alcohol consumption[a,b] | … | Defined as ingestion of >21 standard drinks per week in men and >14 standard drinks per week in women over a 2-year period preceding baseline liver histology. |
| FIB-4 | Fibrosis-4 index | An index to estimate the risk of hepatic cirrhosis calculated from the computation of age, plasma aminotransferases (AST and ALT), and platelet count. This noninvasive estimate of liver scarring is used to assess the need for biopsy. The score is calculated using a person's age, AST level, platelet count (PLT), and ALT level. FIB-4 score = age (years) $\times$ AST (U/L)/[PLT ($10^9$/L) $\times$ ALT ½ (U/L). |
| ELF | Enhanced liver fibrosis test | This blood test measures the levels of tissue inhibitor of metalloproteinases 1, amino-terminal propeptide of type III procollagen, and hyaluronic acid and is used to estimate the rate of liver extracellular matrix metabolism reflecting the severity of liver fibrosis. |
| NFS | NAFLD fibrosis score | $-1.675 + 0.037 \times$ age (years) $+ 0.094 \times$ BMI (kg/m$^2$) $+ 1.13 \times$ (impaired fasting glucose or DM) $+ 0.99 \times$ (AST/ALT) $- 0.013 \times$ platelet ($\times 10^9$/L) $= 0.66 \times$ albumin (g/dL) (where impaired fasting glucose/DM had a value of 1 if the participants had impaired fasting glucose and 0 if they did not) |
| APRI | AST-to-platelet ratio index | [AST level (IU/L)/AST (upper limit of normal AST range (IU/L) $\times$ 100] divided by platelet count ($10^9$/L) |
| $^1$H-MRS | Proton magnetic resonance spectroscopy | A technique for quantifying hepatic steatosis |
| MRI-PDFF | Magnetic resonance imaging-proton density fat fraction | A technique for quantifying hepatic steatosis |
| VCTE | Vibration-controlled transient elastography | A technique for liver stiffness measurement that is correlated with the severity of liver fibrosis on histology. |
| MRE | Magnetic resonance elastography | Technology that combines MRI with low-frequency vibrations to assess liver stiffness. |

# Pragmatic First Steps in Suspected NAFLD

## 1. Risk Identification

- Metabolic syndrome or other high prevalence group, such as:
  - T2D
  - Metabolic risk factors (eg, BMI > 25, lipids, PCOS, OSA)
  - First-degree relative with NAFLD cirrhosis or HCC

## 2. History

- Alcohol intake (< 14/21 drinks/wk)
- No known preexisting liver disease

## 3. Tests

- Liver biochemistry (ALT, AST, etc)
- Exclude/identify other liver diseases:
  - Negative HBV and HCV serology
  - Negative autoantibodies (ANA, AMA, SMA, LKM1, ANCA)
  - Negative celiac serology
  - Normal immunoglobulins, ferritin, A1AT, Cu2+, etc
- Liver ultrasound: increased echogenicity (steatosis)

Chalasani. Hepatology. 2018;67:328.

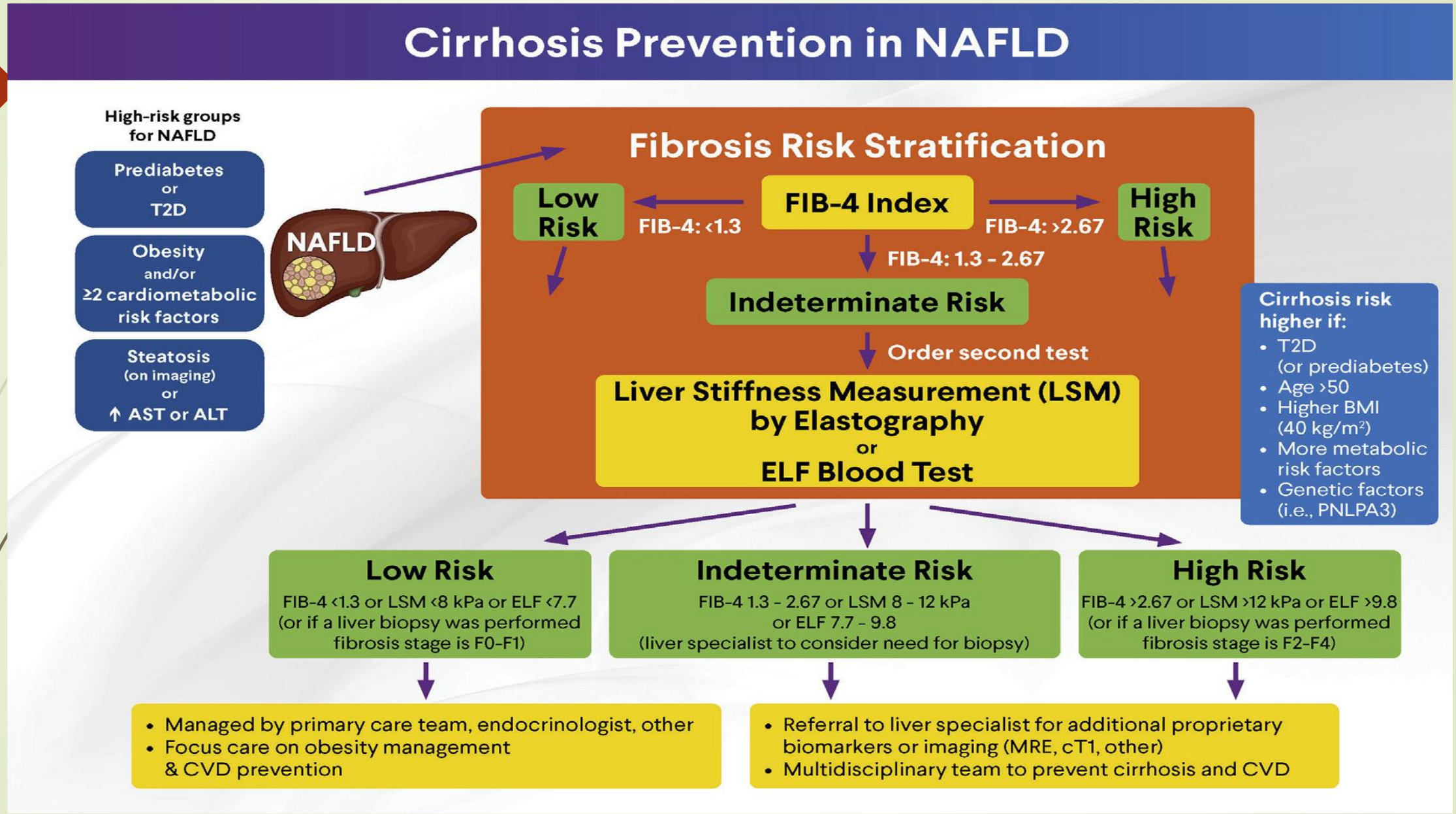
Slide credit: clinicaloptions.com

# Q2.1 Which adults with NAFLD should be considered at “high risk” of clinically significant fibrosis (stages F2-F4) and at risk of cirrhosis?

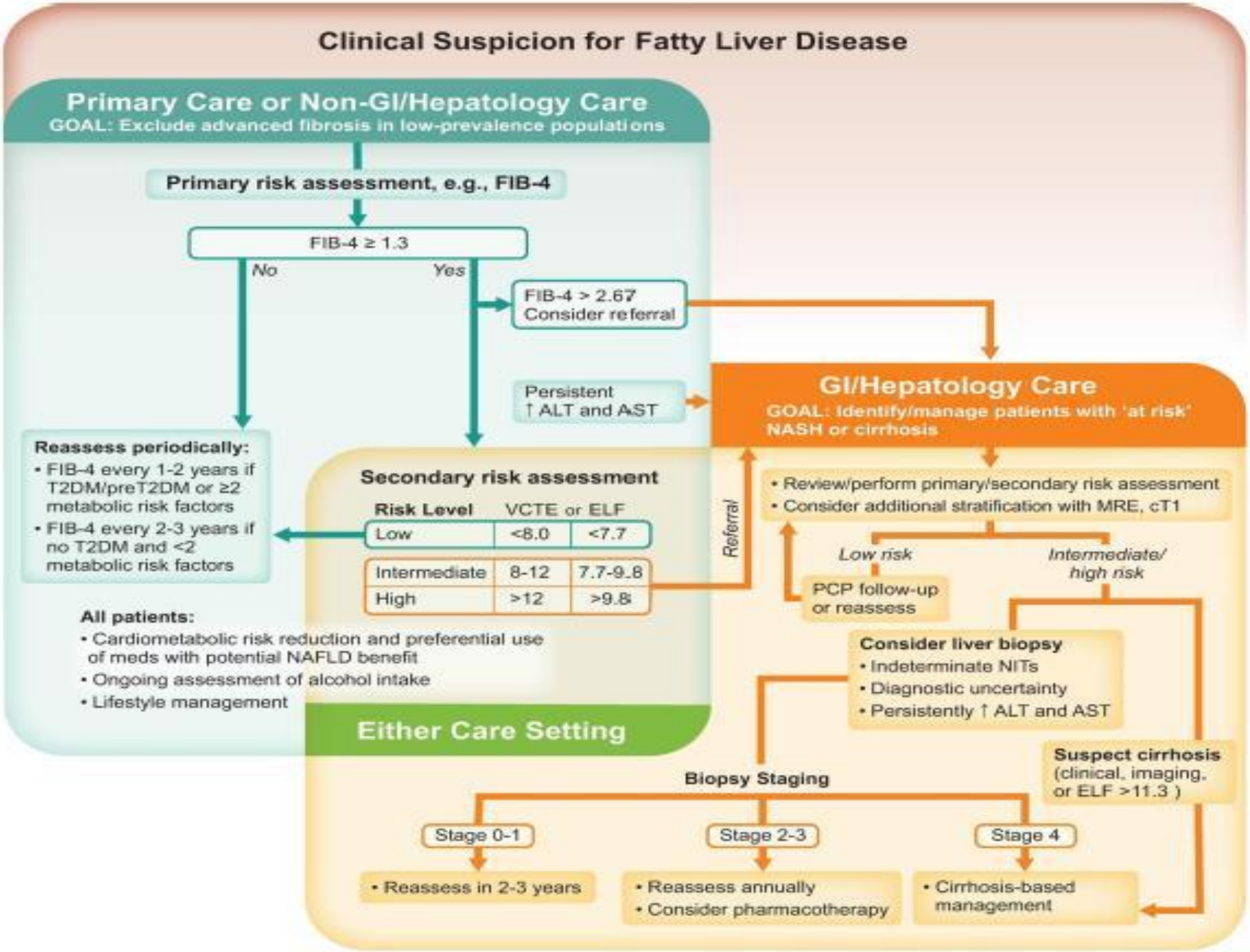
- ✓ Clinicians should consider persons with obesity and/or features of metabolic syndrome, those with prediabetes or T2D, and those with hepatic steatosis on any imaging study and/or persistently elevated plasma aminotransferase levels (over 6 months) to be “high risk” and screen for NAFLD and advanced fibrosis.

Grade B; Intermediate/High Strength of Evidence; BEL 2

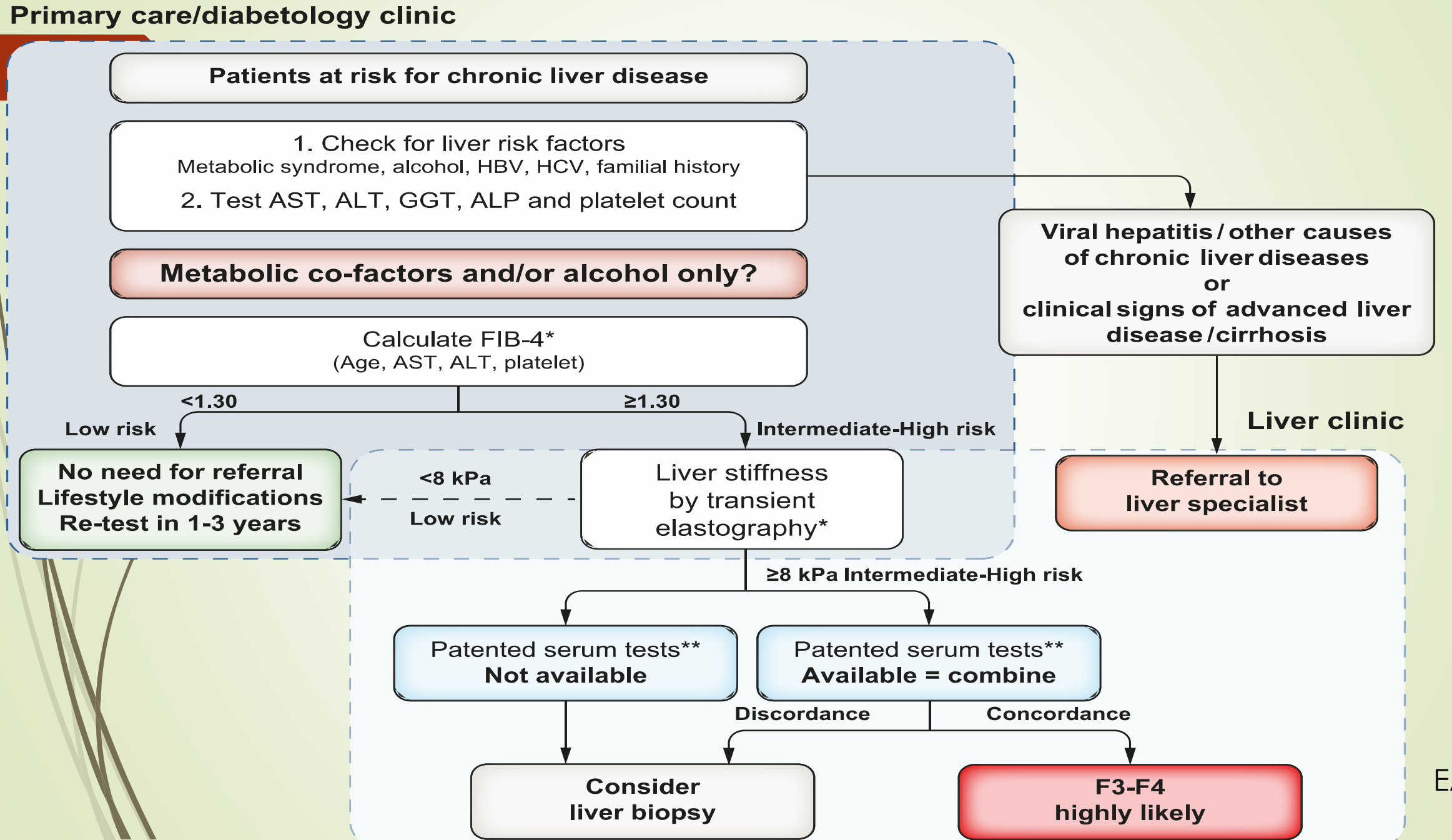
# Cirrhosis Prevention in NAFLD




AACE2022


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

AASLD2023


Primary care/diabetology clinic
Patients at risk for chronic liver disease
1. Check for liver risk factors
Metabolic syndrome, alcohol, HBV, HCV, familial history
2. Test AST, ALT, GGT, ALP and platelet count
Metabolic co-factors and/or alcohol only?
Calculate FIB-4*
(Age, AST, ALT, platelet)
<1.30
Low risk
≥1.30
Intermediate-High risk
No need for referral
Lifestyle modifications
Re-test in 1-3 years
<8 kPa
Low risk
Liver stiffness
by transient
elastography*
≥8 kPa Intermediate-High risk
Patented serum tests**
Not available
Patented serum tests**
Available = combine
Discordance
Concordance
Consider
liver biopsy
F3-F4
highly likely
Viral hepatitis / other causes
of chronic liver diseases
or
clinical signs of advanced liver
disease / cirrhosis
Liver clinic
Referral to
liver specialist

EASL2021

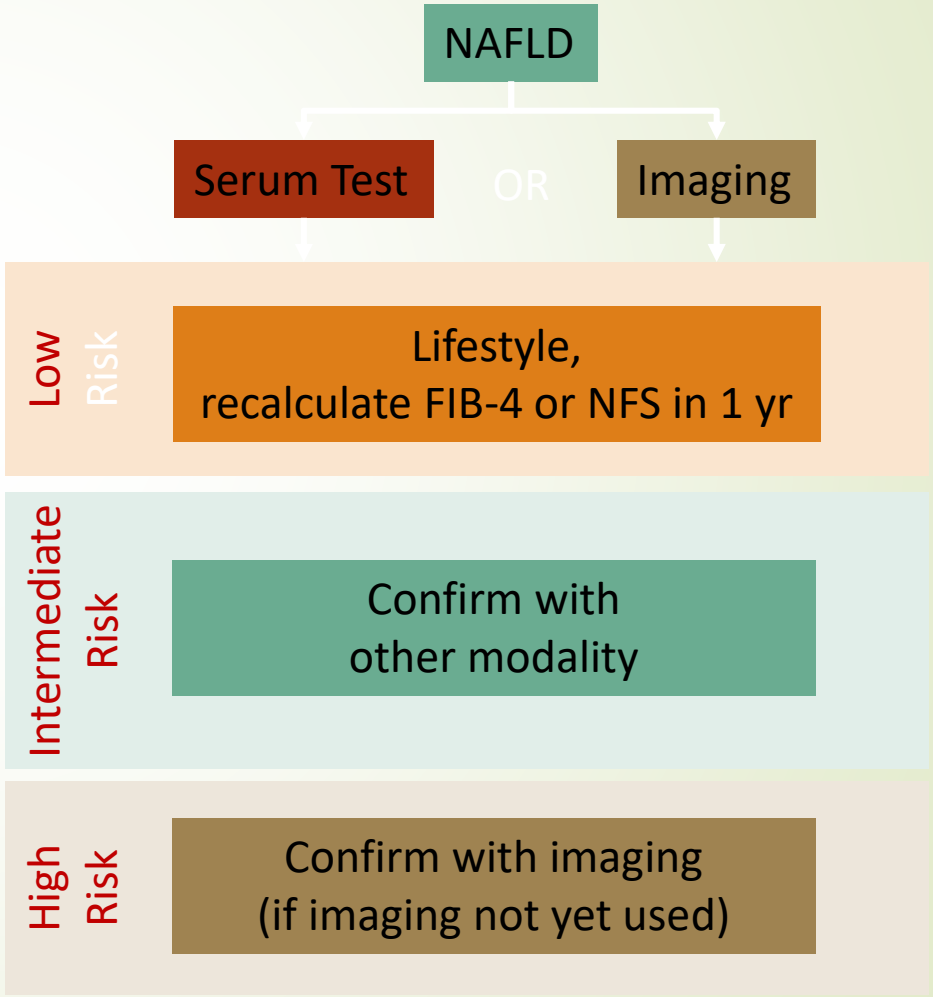
## Recommendations

### In patients with NAFLD:

- The following NITs are recommended to rule-out advanced fibrosis in clinical practice **(LoE 1, strong recommendation):**
  - LSM by TE <8 kPa
  - Patented tests: ELF™ <9.8 or FibroMeter™ <0.45 or FibroTest® <0.48
  - Non-patented tests: FIB-4 <1.3 or NFS <-1.455
- Upon referral of a patient with FIB-4 over 1.3, the use of TE and/or patented serum tests should be used to rule-out/in advanced fibrosis (see Fig. 1) **(LoE 2, strong recommendation).**
- MRE is the most accurate non-invasive method for staging liver fibrosis. However, it is only marginally better than other NITs for F3–F4 fibrosis and it is not recommended as a first-line NIT given its cost and limited availability **(LoE 2; strong recommendation).** Therefore, it is more suited to clinical trials.

# Example of a Proposed Sequence of Testing in NAFLD

- If NAFLD, rule out low risk with either:
  - **Serum biomarker/algorithm** (FIB-4, NFS, ELF) or
  - **Imaging** (VCTE, MRE, or shear wave elastography)
- If low risk not ruled out, use the other modality to confirm intermediate or high risk




Younossi. Am J Gastroenterol. 2020;00:1.

Slide credit: clinicaloptions.com

- R2.1.2 Persons undergoing bariatric surgery should be evaluated for the presence and severity of NASH, and a liver biopsy should be considered at the time of bariatric surgery.

- Liver biopsy should be recommended if presurgical stratification suggests indeterminate or high risk of liver fibrosis.

Grade B; Intermediate Strength of Evidence; BEL 2

# Should all persons with diabetes mellitus be screened for clinically significant fibrosis (stages F2-F4) associated with NAFLD?

R2.4.1 In persons with T2D, clinicians should consider screening for clinically significant fibrosis (stages F2-F4) using the FIB-4, even if they have normal liver enzyme levels.

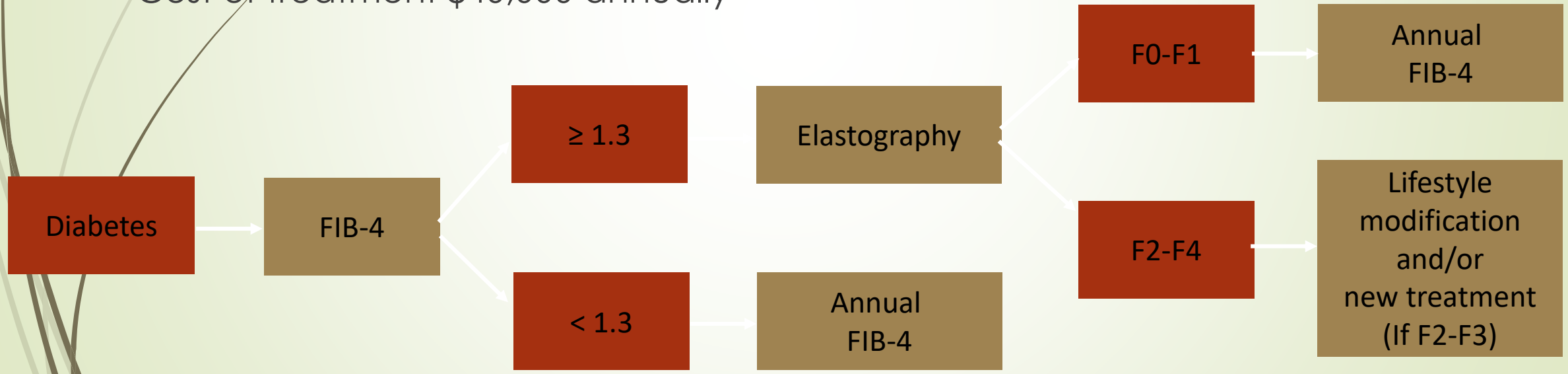
Grade B; High/Intermediate Strength of Evidence; BEL 2

R2.4.2 In persons with T1D, clinicians may consider screening for NAFLD with clinically significant fibrosis (stages F2-F4) using the FIB-4, only if there are risk factors such as obesity, features of metabolic syndrome, elevated plasma aminotransferase levels (>30 U/L), or hepatic steatosis on imaging.

Grade C; Intermediate/Weak Strength of Evidence; BEL 2;

# Screening for NAFLD in People With Diabetes: Modeling Analysis

- Model developed to assess impact of screening for liver fibrosis using routine variables and elastography in people with diabetes
- Assumptions regarding hypothetical new treatment for people 50 yrs of age with F2-F3 disease
  - Reduces annual progression rate by 15%, increases regression rate by 15%
  - Cost of treatment $40,000 annually



R2.4.3 Clinicians should further risk stratify persons with T2D, or T1D with cardiometabolic risk factors and/or elevated plasma aminotransferase levels (>30 U/L) using the FIB-4, elastography, and/or ELF test.

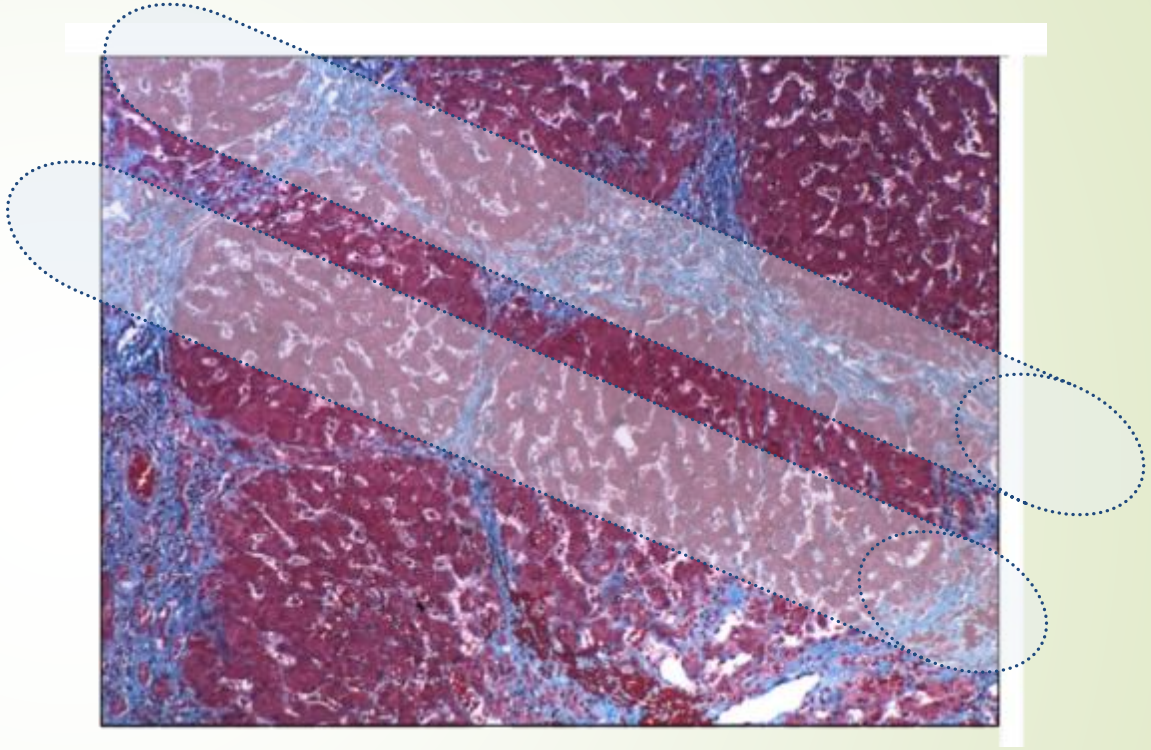
Grade B; High/Intermediate Strength of Evidence; BEL 2

# Is a Liver Biopsy Always Necessary in NAFLD?

- Not always required but remains necessary and useful in many cases
  - Confirm diagnosis and exclude alternative/secondary pathology
  - Stage disease
  - Stratify progression risk
- Use of biopsy should be tailored to the individual patient
  - Marked biochemical abnormalities on LFTs
  - Diagnostic doubt
  - Noninvasive scores that are high or indeterminate risk
  - Patient choice

# Liver Biopsy: The Imperfect Gold Standard

- **Limitations**
  - Invasive
  - Painful
  - Expensive
  - Morbidity/mortality
  - Sampling variability
  - Observer variability
  - Expertise to perform
  - Impractical for population screening



**Sampling variability:**
Same biopsy may give
2 different grades of liver fibrosis

# Key Points

- Noninvasive tests needed to identify which patients with NAFLD require follow-up
  - ALT or AST are not sensitive for NAFLD
  - Alone, AST, FIB-4, NFS, VCTE lack sufficient PPV to predict NASH and fibrosis
- Many noninvasive tests, alone or in combination, being studied for:
  - Diagnosis of NASH patients with NAS ≥ 4 and fibrosis ≥ F2
  - Assessment of therapeutic response
  - Assessment of long-term patient outcomes

## 3. Management of NAFLD in adults

### Q3.1 How should cardiometabolic risk and other extrahepatic complications be managed in the setting of NAFLD?

**R3.1** Clinicians must manage persons with NAFLD for obesity, metabolic syndrome, prediabetes, diabetes mellitus, dyslipidemia, hypertension, and CVD based on the current standards of care.

**Grade A; High/Intermediate Strength of Evidence; BEL 1**

### Q3.2 What lifestyle modifications (dietary intervention and exercise) should be recommended in adults with NAFLD?

**R3.2.1** Clinicians should recommend lifestyle changes in persons with excess adiposity and NAFLD with a goal of at least 5%, preferably ≥10%, weight loss, as more weight loss is often associated with greater liver histologic and cardiometabolic benefit, depending on individualized risk assessments. Clinicians must recommend participation in a structured weight loss program, when possible, tailored to the individual's lifestyle and personal preferences.

**Grade B; Intermediate/High Strength of Evidence; BEL 1; downgraded due to small sample sizes, large heterogeneity of interventions, short duration, and few studies with liver biopsy**

**R3.2.2** Clinicians must recommend dietary modification in persons with NAFLD, including a reduction of macronutrient content to induce an energy deficit (with restriction of saturated fat, starch, and added sugar) and adoption of healthier eating patterns, such as the Mediterranean diet.

**Grade A; Intermediate Strength of Evidence; BEL 1**

**R3.2.3** In persons with NAFLD, clinicians must recommend physical activity that improves body composition and cardiometabolic health. Participation in a structured exercise program should be recommended, when possible, tailored to the individual's lifestyle and personal preferences.

**Grade A; Intermediate Strength of Evidence; BEL 1**

# Diet

# Topics for Today: Which Diets Are Advisable in NAFLD?

- Low dietary sugar?
- Nonnutritive sweeteners?
- Low-caloric, low-fat, or low-carbohydrate diet?
- Popular diets (eg, very low–carbohydrate ketogenic diets)?
- Vitamin supplementation?

Slide credit: clinicaloptions.com

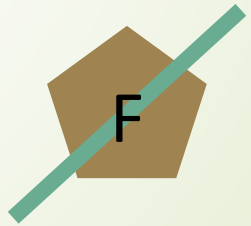
# Should Dietary Sugar Be Limited in Patients With NAFLD?

## AASLD Guidelines

- No specific recommendation for restricting sugar

## My Opinion

- Excellent theoretical reasons to limit sugar in patients with NAFLD
  - Limiting hepatic exposure to fructose and insulin will likely prove beneficial




Chalasani. Hepatology. 2018;67:328.

Slide credit: clinicaloptions.com

# Which Diets Are Advisable in NAFLD?

- Low dietary sugar?
- Nonnutritive sweeteners?
- Low-caloric, low-fat, or low-carbohydrate diet?
- Popular diets?
- Vitamin supplementation?

- Theoretical reasons to limit sugar (esp fructose)
- Theoretical reasons to avoid; practical reasons to use in moderation to limit sugar
- No diet has consistent superiority: Provided **simple sugars** and **total calories** are reduced, key is **weight loss**
  - **Individualize** to patient preference
- Vitamin E recommended for nondiabetic adults with NASH, but consider risks

Slide credit: clinicaloptions.com

# Potential Mechanisms of NNS-Induced Metabolic Dysfunction

- Activation of sweet taste receptors at both oral and extraoral sites (intestinal cells, pancreatic β cells)
  - Change in taste preference?
  - Increased insulin secretion?
  - Increased appetite?
- Alterations to microbiome
- Specific effects of particular sweeteners (ie, aspartame vs sucralose)
- Particular populations (ie, greater appetite increases in obese people?)
- Findings from human and animal studies are inconsistent

Rother. Trends Endocrinol Metab. 2018;29:455.

Slide credit: clinicaloptions.com

# Popular Diets in NAFLD

**Mediterranean diet good choice for a balanced diet with strong evidence for benefit**

**More restrictive diets can work in the short term, but adherence is difficult and long-term data are lacking**

**None has evidence of consistent superiority**
**Key is likely to be patient preference and adherence**

Slide credit: clinicaloptions.com

# Vitamins and NAFLD?

## Vitamin levels

- The liver is involved in transport and storage of many micronutrients
- In general, patients with NAFLD have lower blood levels of **zinc, copper, vitamin A, vitamin D, vitamin E**
  - Low levels of these micronutrients associated with NAFLD severity, although the mechanisms remain unclear

## Vitamin supplementation

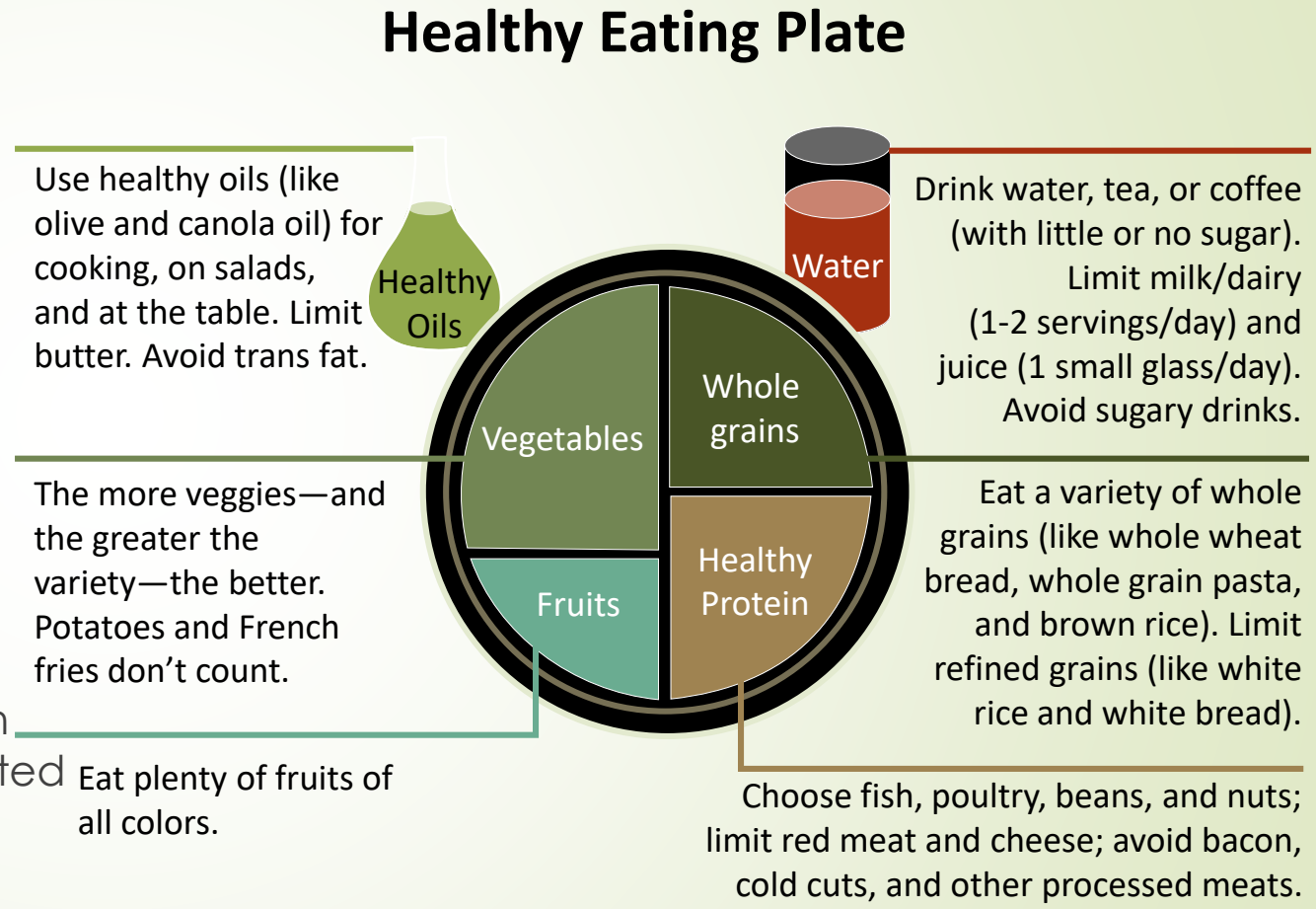
- Vitamin supplementation in NAFLD is **hypothesized** to have antioxidant, antifibrotic, immune, and lipoprotective benefits
- **Except for vitamin E, no vitamins are approved to treat NAFLD**

Pickett-Blakely. CMGH 2018;6:451.

Slide credit: clinicaloptions.com

# Dietary Habits: My Approach

- "Healthy eating" (instead of "dieting")
- Mediterranean diet
- Harvard Healthy Eating Plate
- Eliminate sugar-sweetened beverages (get history from every patient—it's shocking)
- Use healthy oils (olive, canola)
- Portion control
- Minimize restaurants or split portions
- Avoid fast food
  - Calorie dense (1300 cal and more fat than a stick of butter in some commonly marketed burgers)
- Avoid eating at night




https://www.hsph.harvard.edu/nutritionsource/healthy-eating-plate/

Slide credit: clinicaloptions.com

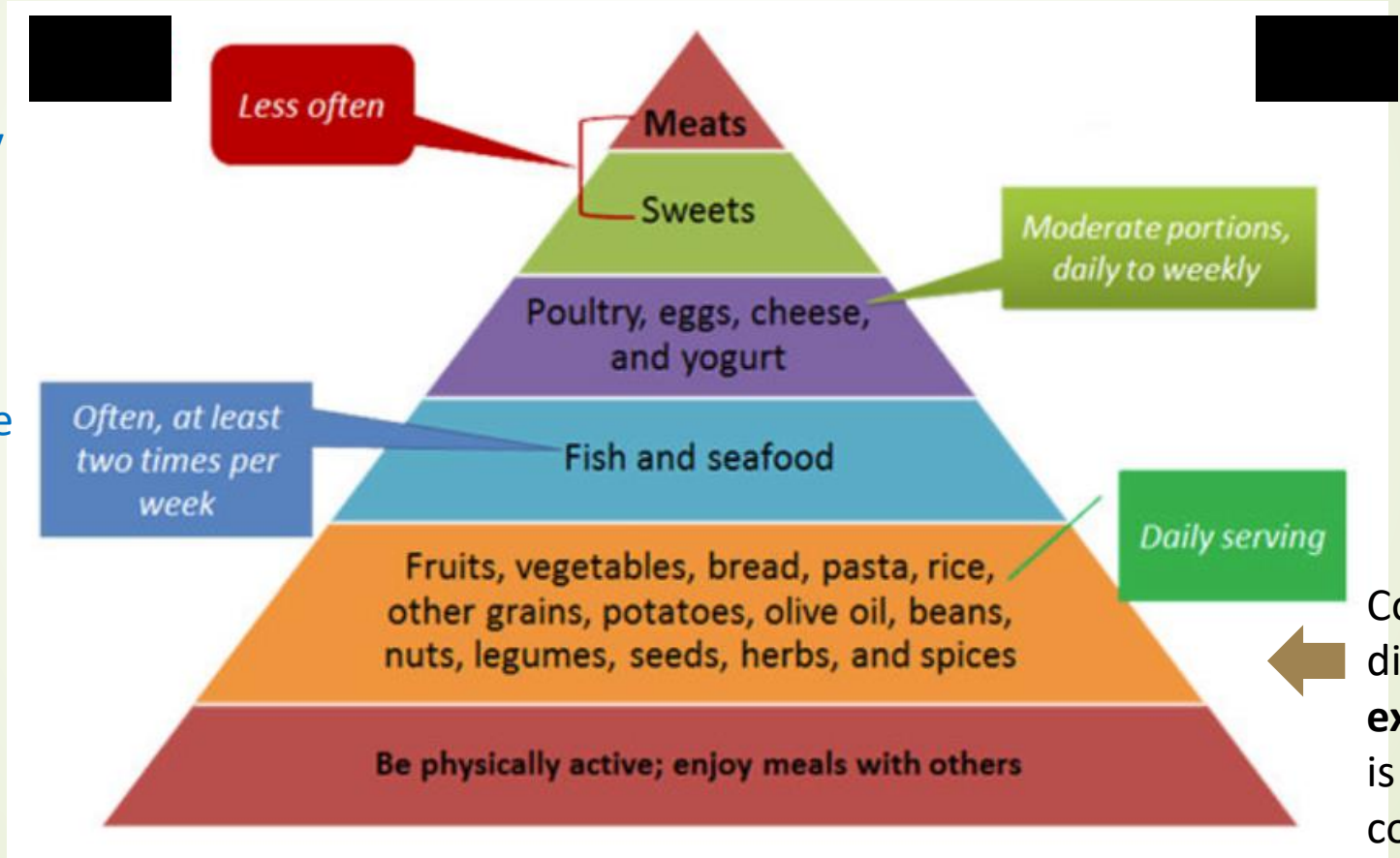
# The Mediterranean Diet Pyramid

***High in:***

- Monounsaturated, omega-3/omega-6 fatty acids
- Polyphenols
- Dietary fiber, prebiotics
- Plant proteins
- Water as drink of choice

***Low in:***

- Saturated and trans fat
- Animal protein
- Simple sugars

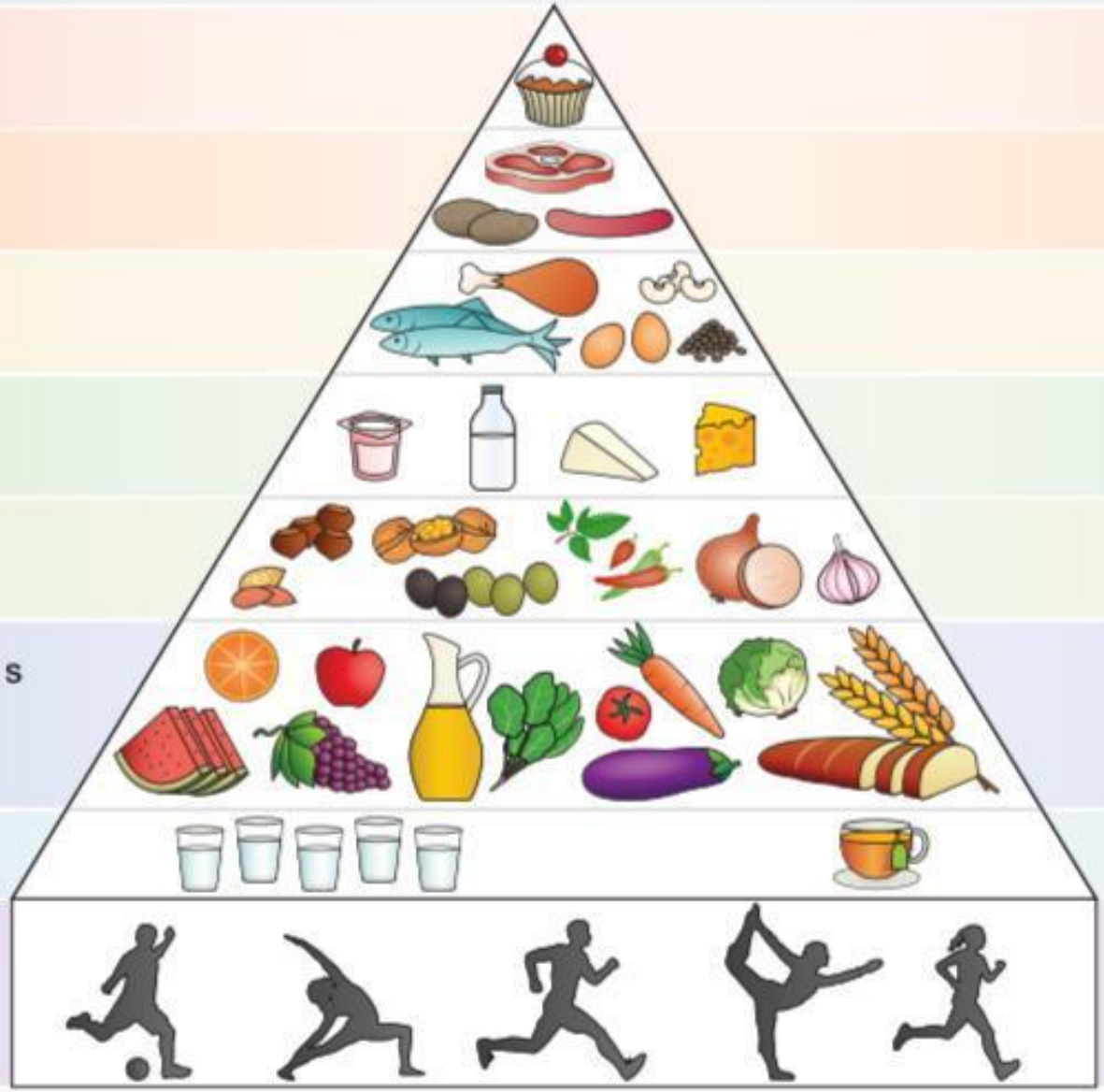



Could be adapted to different cultures but **extra virgin olive oil** is an essential component

Gray. Nutritional Recommendations for Individuals with Diabetes. 2019. endotext.org.

Slide credit: clinicaloptions.com

# Mediterranean diet pyramid



**Weekly**

Sweets ≤2 s

Potatoes ≤3 s

Red meat ≤2 s
Processed meat ≤1 s

White meat 2 s
Fish/Seafood ≥2 s

Eggs 2-4 s
Legumes ≥2 s

**Daily**

Dairy 2 s
(preferably low fat)

Olives/Nuts/Seeds 1-2 s

Herbs/Spices/Garlic/Onions
(less added salt)
Variety of flavours

**Every meal**

Fruits 1-2 Vegetables ≥2 s
Variety of colours/textures
(Cooked/raw)

Olive oil
Bread/Pasta/Rice/Couscous
Other cereals 1-2 s
(preferably whole grain)

Water and herbal infusions

Regular physical activity
Adequate rest
Conviviality

Biodiversity and seasonality
Traditional, local and eco-friendly products
Culinary activities

s, servings

# physical activity

- Guidelines recommend over 150 minutes a week of moderate intensity physical activity over 3–5 sessions including a combination of aerobic and resistance training (activity that strengthen the muscles)

- **Aerobic exercise ("cardio")** strengthens your heart and lungs and improves the way your body uses oxygen.
  - It normally uses the large muscle groups, is rhythmic in nature and can be maintained for at least 10 minutes. Examples include brisk walking, swimming, cycling, dancing.
- **Resistance exercise** strengthens the muscles and improves muscle tone and bulk. It includes any exercise where the muscles contract against a force and can include lifting weights, use of resistance bands or pushing against your body weight.

- Regular moderate exercise at least five times per week for a total of 150 min per week or an increase in activity level by more than 60 min per week can prevent or improve NAFLD

- Others suggest that more vigorous exercise is needed to improve NASH histology, with even higher intensity exercise needed to reduce fibrosis,

# Pharmacotherapy in NAFLD Reserved for Patients With NASH and Fibrosis

Slide credit: clinicaloptions.com

**Q3.3 What medications have proven to be effective for the treatment of liver disease and cardiometabolic conditions associated with NAFLD or NASH?**

**R3.3.1a** Pioglitazone and GLP-1 RAs are recommended for persons with T2D and biopsy-proven NASH.

**Grade A; High Strength of Evidence; BEL 1**

**R3.3.1b** Clinicians must consider treating diabetes with pioglitazone and/or GLP-1 RAs when there is an elevated probability of having NASH based on elevated plasma aminotransferase levels and noninvasive tests.

**Grade A; High Strength of Evidence; BEL 1**

**R3.3.2** To offer cardiometabolic benefit in persons with T2D and NAFLD, clinicians must consider treatment with GLP-1 RAs, pioglitazone, or SGLT2 inhibitors; however, there is no evidence of benefit for treatment of steatohepatitis with SGLT2 inhibitors.

**Grade A; High Strength of Evidence; BEL 1**

**R3.3.3** Due to the lack of evidence of efficacy, metformin, acarbose, dipeptidyl peptidase IV inhibitors, and insulin are not recommended for the treatment of steatohepatitis (no benefit on hepatocyte necrosis or inflammation) but may be continued as needed for the treatment of hyperglycemia in persons with T2D and NAFLD or NASH.

**Grade B; High Strength of Evidence; BEL 1; downgraded due to the use of surrogate outcome measures in many of the studies**

**R3.3.4** Vitamin E can be considered for the treatment of NASH in persons without T2D, but there is not enough evidence at this time to recommend for persons with T2D or advanced fibrosis.

**Grade B; High Strength of Evidence; BEL 1; downgraded due to risk/benefit**

**R3.3.5** Other pharmacotherapies for persons with NASH cannot be recommended at the present time due to the lack of robust evidence of clinical benefit.

**Grade A; High Strength of Evidence; BEL 1**

## Q3.4 What obesity pharmacotherapies have proven benefit for the treatment of liver disease and cardiometabolic conditions associated with NAFLD or NASH in adults?

**R3.4.1** Clinicians should recommend the use of obesity pharmacotherapy as adjunctive therapy to lifestyle modification for individuals with obesity and NAFLD or NASH with a goal of at least 5%, preferably ≥10 %, weight loss, as more weight loss is often associated with greater liver histologic and cardiometabolic benefit, when this is not effectively achieved by lifestyle modification alone.

**Grade B; Intermediate Strength of Evidence; BEL 1; downgraded due to small sample sizes used in studies and short duration of trials**

**R3.4.2** For chronic weight management in individuals with a BMI of ≥27 kg/$m^2$ and NAFLD or NASH, clinicians should give preference to semaglutide 2.4 mg/week (best evidence) or liraglutide 3 mg/day.

**Grade B; High/Intermediate Strength of Evidence; BEL 1; downgraded due to different formulations and doses used in the semaglutide and liraglutide NASH trials**

**R3.4.3** Clinicians must consider obesity pharmacotherapy (with preference to semaglutide 2.4 mg/week [best evidence] or liraglutide 3 mg/day) as adjunctive therapy to lifestyle modification for individuals with obesity and NAFLD or NASH to promote cardiometabolic health and treat or prevent T2D, CVD, and other end-stage manifestations of obesity.

**Grade A; High/Intermediate Strength of Evidence; BEL 1**

**Q3.5 What is the effect of bariatric surgery on liver disease and cardiometabolic conditions associated with NAFLD or NASH in adults?**

**R3.5.1** Clinicians should consider bariatric surgery as an option to treat NAFLD **(Grade B; Intermediate/Weak Strength of Evidence; BEL 2**) and improve cardiometabolic health **(Grade A; High/Intermediate Strength of Evidence; BEL 2; upgraded based on the cardiometabolic and all-cause mortality benefits in all persons with or without NAFLD)** in persons with NAFLD and a BMI of ≥35 kg/m$^2$ (≥32.5 kg/m$^2$ in Asian populations), particularly if T2D is present. It should also be considered an option in those with a BMI of ≥30 to 34.9 kg/m$^2$ (≥27.5 to 32.4 kg/m$^2$ in Asian populations)
**(Grade B; Intermediate/Weak Strength of Evidence; BEL 2).**

**R3.5.2** For persons with NASH and compensated cirrhosis, clinicians should exercise caution in recommending bariatric surgery, which should be highly individualized if prescribed and performed at experienced centers
**(Grade B; Intermediate/Weak Strength of Evidence; BEL 2).**

In persons with decompensated cirrhosis, bariatric surgery should not be recommended due to limited evidence and potential for harm
**(Grade B; Intermediate/Weak Strength of Evidence; BEL 2).**

**R3.5.3** Endoscopic bariatric and metabolic therapies and orally ingested devices should not be recommended in persons with NAFLD due to insufficient evidence.
**Grade C; Intermediate/Weak Strength of Evidence; BEL 2; downgraded due to the quality of studies and small sample sizes**

Medications to Treat Diabetes and Their Efficacy for the Treatment of Nonalcoholic Fatty Liver Disease

| Medication | Liver fat | Disease activity (steatohepatitis/NAS) | Studies |
|---|---|---|---|
| Metformin | Unchanged | Neutral | (298-302) |
| Pioglitazone | Decreased | Improved[a] | (97, 98, 280-282) |
| Insulin | Decreased | Effect unknown | (177, 178, 306) |
| GLP-1 RAs (semaglutide and liraglutide) | Decreased | Improved[a] | (99, 286-288) |
| SGLT2 inhibitors (dapagliflozin, empagliflozin, and canagliflozin) | Decreased | Effect unknown | (28, 294-297) |
| DPP-IV inhibitors (sitagliptin and vildagliptin) | Unchanged (in RCTs) | Effect unknown | (286, 303-305) |

Abbreviations: DPP-IV = dipeptidyl peptidase IV; GLP-1 RAs = glucagon-like peptide11 receptor agonists; NAS = nonalcoholic fatty liver disease activity score; RCTs = randomized controlled trials; SGLT2 = sodium-glucose cotransporter 2.

[a] The effect on hepatic fibrosis of diabetes medications that improve steatohepatitis has been overall small, although some individual studies[98,281] and meta-analyses of available RCTs[283,284] report a decrease in fibrosis with pioglitazone.

# *What Medications Have Proven to Be Effective for the Treatment of Liver Disease and Cardiometabolic Conditions Associated With NAFLD or NASH?*

- Pioglitazone or GLP-1 RAs are recommended for persons with T2D and biopsy-proven NASH.

  Grade A; High Strength of Evidence; BEL ,

- ✓ Clinicians must consider treating diabetes with pioglitazone and/or GLP-1 RAs when there is an elevated probability of having NASH based on elevated plasma aminotransferase levels and noninvasive tests.

- ✓ To offer cardiometabolic benefit in persons with T2D and NAFLD, clinicians must consider treatment with GLP- 1 RAs, pioglitazone, or SGLT2 inhibitors; however, there is no evidence of benefit for treatment of steatohepatitis with SGLT2 inhibitors.

- Due to the lack of evidence of efficacy, metformin, acarbose, dipeptidyl peptidase IV inhibitors, and insulin are not recommended for the treatment of steatohepatitis (no benefit on hepatocyte necrosis or inflammation) but may be continued as needed for the treatment of hyperglycemia in persons with T2D and NAFLD or NASH.

Grade B

Vitamin E can be considered for the treatment of NASH in persons without T2D, but there is not enough evidence at this time to recommend for persons with T2D or advanced fibrosis.

Other pharmacotherapies for persons with NASH cannot be recommended at the present time due to the lack of robust evidence of clinical benefit

# What Obesity Pharmacotherapies Have Proven Benefit for the Treatment of Liver Disease and Cardiometabolic Conditions Associated With NAFLD or NASH in Adults?

- Clinicians should recommend the use of obesity pharmacotherapy as adjunctive therapy to lifestyle modification for individuals with obesity and NAFLD or NASH with a goal of at least 5%, preferably >10%, weight loss, as more weight loss is often associated with greater liver histologic and cardiometabolic benefit, when this is not effectively achieved by lifestyle modification alone. Grade B

- For chronic weight management in individuals with a BMI of >27 kg/m2 and NAFLD or NASH, clinicians should give preference to semaglutide 2.4 mg/week (best evidence) or liraglutide 3 mg/day.

Grade B

- In ***lean*** patients with NAFLD, lifestyle intervention, including exercise, diet modification, and avoidance of fructose- and sugar-sweetened drinks, to target a modest weight loss of 3%–5% is suggested.

- Clinicians must consider obesity pharmacotherapy (with preference to semaglutide 2.4 mg/week [best evidence] or liraglutide 3 mg/day) as adjunctive therapy to lifestyle modification for individuals with obesity and NAFLD or NASH to promote cardiometabolic health and treat or prevent T2D, CVD, and other end-stage manifestations of obesity. Grade A

# Weight Management in NAFLD

## Fibrosis Risk Stratification

| |  **Low Risk** FIB-4: <1.3 LSM <8 kPa ELF <7.7 |  **Indeterminate Risk** FIB-4: 1.3 - 2.67 LSM 8 - 12 kPa ELF 7.7 - 9.8 |  **High Risk** FIB-4: >2.67 LSM >12 kPa ELF >9.8 |
|---|---|---|---|
| General lifestyle changes | Decrease sedentary time and increase daily movement. Stress reduction through exercise and other methods. | | |
| Dietary recommendations | Creating an energy deficit is the priority with reduction of saturated fat, starch, & added sugars. Persons with cirrhosis need an individualized nutritional assessment and treatment plan. | | |
| Exercise | To improve cardiometabolic health, support weight loss and mitigate sarcopenia. Aerobic exercise for 30-60 min (3-5 days/week) + resistance training 20-30 min (2-3 times/week). | | |
| Alcohol intake | Minimize | Minimize | Avoid if F3 or cirrhosis (F4)[1] |
| Weight loss goal to treat NAFLD (if overweight or obesity)[2] | Greater weight loss associated with greater liver and cardiometabolic benefit. | | |
| Weight loss tools | Behavioral modification counseling. In person or remote programs. | Greater intensity of weight loss to reverse steatohepatitis and fibrosis. | Specialized obesity management, with a structured program, anti-obesity medications, bariatric surgery. |
| Medical therapy to treat obesity | Phentermine, phentermine/topiramate ER, naltrexone/bupropion, orlistat, liragluitde 3 mg/d, semaglutide 2.4 mg/wk | GLP-1 RA preferred for NASH.[3,4] | GLP-1 RA preferred for NASH.[3,4] |
| Bariatric surgery | Consider to treat obesity and comorbidities. | Strong consideration to treat steatohepatitis and fibrosis. | Stronger consideration to treat steatohepatitis and fibrosis. Avoid in decompensated cirrhosis. |

Abbreviations: GLP-1 RA = Glucagon-like peptide-1 receptor agonists, HCC = Hepatocellular carcinoma, NASH = Nonalcoholic steatohepatitis

1. Persons with confirmed cirrhosis based on biopsy or high likelihood based on LSM >13.6kPa from vibration controlled transient elastography (FibroScan®), ELF ≥9.8 or >5.0 kPa on MRE) should undergo HCC surveillance. Varices screening is recommended if LSM >20 kPa or platelet count of <150,000/mm$^3$.
2. These goals should only be taken as a broad guidance. NAFLD/NASH may also improve by changes in macronutrient content, exercise and other factors beyond magnitude of weight loss. All high-quality studies available limited to a maximum of 12 month duration.
3. No high-quality evidence for pharmacotherapy in persons with NASH cirrhosis. Treatment should be individualized and used with caution only by liver specialists.
4. Among GLP-1 RAs, semaglutide has the best evidence of benefit in persons with steatohepatitis and fibrosis.

- Bariatric surgery very effectively achieves weight loss and weight loss maintenance in patients with obesity,

The agreed criteria for the surgical management of obesity and metabolic disorders (BMI ≥4 0 kg/m2 or BMI ≥ 35 kg/m2 with complicating disorders, no resolution after medical treatment) are also applicable for NAFLD.

Patients with a BMI of 30–35 kg/m2 who also have T2D that is not adequately controlled by medical therapy may also be candidates for surgery.

# What Is the Effect of Bariatric Surgery on Liver Disease and Cardiometabolic Conditions Associated With NAFLD or NASH in Adults?

- Clinicians should consider bariatric surgery as an option to treat NAFLD (Grade B) and improve cardiometabolic health (Grade A; upgraded based on the cardiometabolic and all-cause mortality benefits in all persons with or without NAFLD) in persons with NAFLD and a BMI of >35 kg/m2 (>32.5 kg/m2 in Asian populations), particularly if T2D is present.

- NASH and compensated cirrhosis, clinicians should exercise caution in recommending bariatric surgery, which should be highly individualized if prescribed and performed at experienced centers (Grade B).

- In persons with decompensated cirrhosis, bariatric surgery should not be recommended due to limited evidence and potential for harm

- Reduction of liver fat content at 1 year was similar with sleeve gastrectomy compared with that of RYBG although the latter was found to be superior for remission of T2D.

- Of note, follow-up was too short to make strong conclusions.

- The average durability of weight loss induced by RYGB has been reported to be 21%, with 72% having more than 20% and 40% having more than 30% estimated weight loss at 10 years, compared with 11% and 4%, respectively, in nonsurgical matched controls.

- Endoscopic bariatric and metabolic therapies (EBMTs) should not be recommended in persons with NAFLD due to insufficient evidence. Grade C

- There are limited data for the treatment of NASH with EBMT. These therapies encompass devices such as intragastric balloon (IGB), endoscopic sleeve gastroplasty (ESG), and aspiration therapy by means of a gastrostomy

# Diabetes Management in NAFLD

## Fibrosis Risk Stratification

| |  **Low Risk** FIB-4: <1.3 LSM <8 kPa ELF <7.7 |  **Indeterminate Risk** FIB-4: 1.3 - 2.67 LSM 8 - 12 kPa ELF 7.7 - 9.8 |  **High Risk[1]** FIB-4: >2.67 LSM >12 kPa ELF >9.8 |
|---|---|---|---|
| General goal | Optimize glycemic control using preferred agents that reverse steatohepatitis, whenever possible. Prefer GLP-1 RA and SGLT2i in CVD. Prefer SGLT2i in CKD and HF. | | |
| Dietary recommendations | Glycemic load reduction via emphasis on whole food carbohydrates (vegetables, legumes, fruit) versus sugar/processed carbohydrates. | | |
| Individualize A1c target | ≤6.5% for persons without concurrent serious illness and at low hypoglycemic risk (>6.5% otherwise). | | In advanced cirrhosis[1], caution with risk of hypoglycemia and avoid oral agents[2] |
| Preferred diabetes pharmacotherapy | Consider agents that reduce liver fat (pioglitazone, GLP-1 RA, SGLT2i). | Strongly consider agents with efficacy in NASH: Pioglitazone and/or GLP-1 RA[3]. No evidence that SGLT2i improve steatohepatitis. | Strongly consider agents with efficacy in NASH: Pioglitazone and/or GLP-1 RA[3]. No efficacy data in cirrhosis. |
| Metformin, sulfonylurea, DPP-4i, acarbose and insulin | May continue but limited benefit on liver histology in NAFLD. | May continue but limited benefit on liver histology in NAFLD. | May continue (F2-F3) but avoid oral agents if advanced cirrhosis present. Cannot avoid insulin in patients with advanced liver cirrhosis – often only option |

Abbreviations: CKD = Chronic kidney disease, CVD = Cardiovascular disease, DPP-4i = Dipeptidyl peptidase 4, GLP-1 RA = Glucagon-like peptide-1 receptor agonists, HF = Heart failure, NASH = Nonalcoholic steatohepatitis, SGLT2i = Sodium-glucose cotransporter-2 inhibitors.

1. Advanced cirrhosis is defined as persons with cirrhosis based on biopsy and Child class B or C with clinical evidence of comorbidities (varices, portal hypertension, ascites, etc.).
2. Limited data on oral diabetes medications and GLP-1 RA in persons with cirrhosis. Avoid metformin. GLP-1 RA appear safe, insulin preferred. Avoid oral agents in advanced cirrhosis.

# Hypertension Management in NAFLD

## Fibrosis Risk Stratification

| |  **Low Risk** FIB-4: <1.3 LSM <8 kPa ELF <7.7 |  **Indeterminate Risk** FIB-4: 1.3 – 2.67 LSM 8 – 12 kPa ELF 7.7 – 9.8 |  **High Risk[1]** FIB-4: >2.67 LSM >12 kPa ELF >9.8 |
|---|---|---|---|
| General goal | Optimize BP control and improve cardiovascular health using preferred agents, whenever possible. Assess every 3 months and intensify therapy until goal achieved. | | |
| Goal (individualize) [2,3,4] | Systolic < 130 mm Hg / Diastolic < 80 mm Hg | Systolic < 130 mm Hg / Diastolic < 80 mm Hg | Systolic < 130 mm Hg / Diastolic < 80 mm Hg; individualize if decompensated cirrhosis |
| Dietary recommendations | In addition to general dietary recommendations, reduce sodium & increase high potassium foods (e.g., DASH diet). | | |
| Pharmacotherapy for hypertension[5] | First-line therapy: ACEIs and ARBs. | First-line therapy: ACEIs and ARBs. | Same but avoid ACEI or ARB if decompensated cirrhosis. |
| Intensification of therapy | Second agent: CCB, BB[6] or thiazide diuretic (as additional agents as needed). | | Same but individualize if decompensated cirrhosis. Use diuretics with caution (risk of excessive diuresis). |
| Additional options | Additional BP medication choices: alpha blockers, central agents, vasodilators, aldosterone antagonist. | | Same but individualize if decompensated cirrhosis. |

Abbreviations: ACEIs = Angiotensin-converting enzyme inhibitors, ARBs = angiotensin II receptor blockers, BB = beta blockers, CCB = calcium channel blockers.

1. Advanced cirrhosis defined as persons with cirrhosis based on biopsy and Child class B or C and clinical evidence of comorbidities (varices, portal hypertension, ascitis, etc.).
2. AACE recommends that BP control be individualized, but that a target of <130/80 mm Hg is appropriate for most persons.
3. Less-stringent goals may be considered for frail persons with complicated comorbidities or those who have adverse medication effects.
4. A more intensive goal (e.g., <120/80 mm Hg) should be considered for some persons if this target can be reached safely without adverse effects from medication.
5. If initial BP > 150/100 mm Hg start with dual therapy. (ACEI or ARB + CCB, BB or thiazide diuretic).
6. Prefer weight neutral beta-blockers: carvedilol, nebivolol.

# Atherogenic Dyslipidemia Management in NAFLD

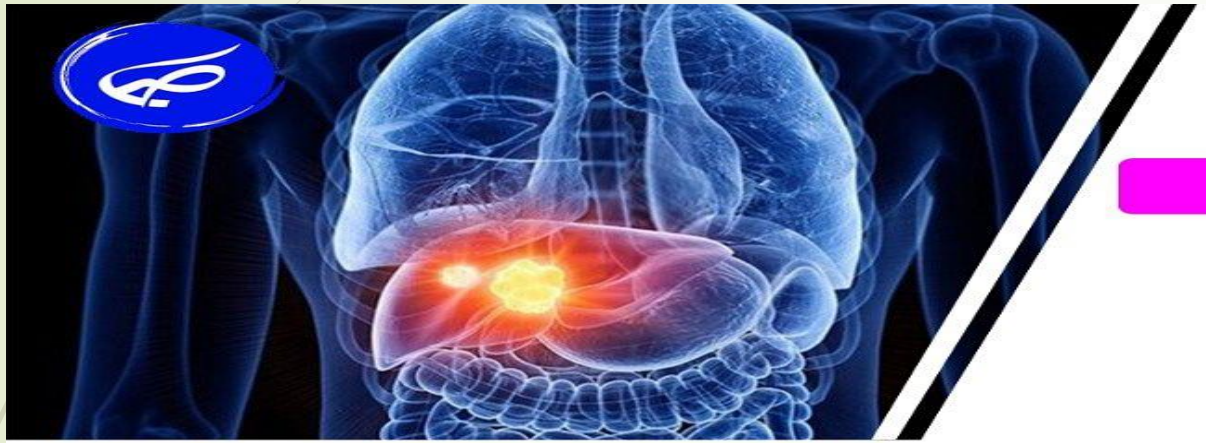
## Lipid risk levels are similar in the presence of NAFLD or NASH

| | | | |
|---|---|---|---|
| General goal | Early intensive management of dyslipidemia needed to reduce cardiovascular risk. Intensify therapy until lipid goal is reached. | | |
| Dietary recommendations | Increase fiber intake (>25 g/d), prioritize vegetables, fruits whole grains, nuts, reduce saturated fat & added sugars (e.g., Mediterranean diet). | | |
| Lipid risk levels | **High CV Risk**[1]<br>≥2 risk factors and 10-year risk 10-20%<br>Diabetes or CKD ≥3<br>with no other risk factors | **Very high CV Risk**[1]<br>Established CVD<br>or 10-year risk >20%<br>Diabetes with >1 risk factor, CKD ≥3, HeFH | **Extreme CV Risk**[1]<br>Progressive CVD<br>CVD + diabetes or CKD ≥3 or HeFH<br>FHx premature CVD (<55 yrs male <65 yrs female) |
| LDL-C goal (mg/dL) | <100 | <70 | <55 |
| Non-HDL-C goal (mg/dL) | <130 | <100 | <80 |
| Triglycerides goal (mg/dL) | <150 | <150 | <150 |
| Apo B goal (mg/dL) | <90 | <80 | <70 |
| First line pharmacotherapy: Statins | Use a moderate-to-high intensity statin[2], unless contraindicated. Statins are safe in NAFLD or NASH but do not use in decompensated cirrhosis (Child C). | | |
| If LDL-C not at goal[3]: Intensify statin therapy | Use higher dose or higher potency statin. | | |
| If LDL-C not at goal (or statin intolerant)[4]: add 2nd agent, then add 3rd agent | Ezetemibe, PCSK9 inhibitor, bempedoic acid, colesevelam, inclisiran. | | |
| If triglycerides > 500 mg/dL | Fibrates, Rx grade omega 3 FA, icosapent ethyl (if diabetes, optimize glycemic control and consider pioglitazone).[5] | | |
| If TG 135-499 mg/dL on max statin dose | Emphasize diet (as above). | Add icosapent ethyl.[6] | Add icosapent ethyl.[6] |

Adapted from Handelsman Y, et al. Endocr Pract. 2020;26:1196-1224.

Abbreviations: CKD = Chronic kidney disease, CVD = cardiovascular disease, FA = Fatty acids, HeFH = Heterozygous familial hypercholesterolemia, HTN = Hypertension, Rx = Prescription

1. Major risk factors: age >40, DM, HTN, FHx of early CVD, low HDL C, elevated LDL, Smoking, CKD 3,4
2. High intensity statin therapy: rosuvastatin 20, 40 mg/d, atorvastatin 40, 80 mg/d.
3. Other lipid modifying agents should be used in combination with maximally tolerated statins if goals not reached: ezetimibe, PCSK9 inhibitor, bempedoic acid, colesevelam, or inclisiran.
4. Assess adequacy and tolerance of therapy with focused laboratory evaluations and patient follow up.
5. Niacin may lower triglycerides but does not reduce CVD and worsens insulin resistance. It may promote hyperglycemia in a population at high-risk of diabetes.
6. Icosapent ethyl 4g/d is recommended as an adjunct to maximally tolerated statin therapy to reduce risk of cardiovascular disease in high-risk persons.



## ۱۱ قاتل کبد چرب

۱. شربت خاکشیر
۲. عرق کاسنی
۳. عرق شاه تره
۴. آب لبو
۵.قهوه
۶. چای سبز
۷.گریپ فروت
۸.کلم بروکلی
۹.عرق خار مریم
۱۰.سویا
۱۱.زنجبیل

# Follow up

- Control examinations can include physical examination and blood test, as well as ultrasound and liver stiffness measurement, depending on your personal situation.
- – **NAFL** (isolated or simple fatty liver [steatosis]): ~every 2–5 years
- – ***NASH with no or minimal fibrosis*** (fibrosis below F2): once a year or every 2 years
- – ***NASH with significant fibrosis*** (fibrosis equal or higher than F2): at least once a year (probably better every 6 months)
- ***NASH (Cirrhosis):*** every 3–6 months

# Thank you for your attention