Non-Alcoholic Fatty Liver Disease: What the Primary Care Physician Needs to Know

Anita Wong, MD
UCLA Family Medicine Grand Rounds
April 17, 2024

Disclosures

None

Outline

- Epidemiology
- Definitions: NAFLD vs MAFLD/MASLD
- Pathophysiology of NAFLD
- Evaluation of NAFLD
- Treatment for NAFLD
- NAFLD in Special Populations

Epidemiology

- Non-alcoholic fatty liver disease (NAFLD) is the most common form of liver disease in the US
- Prevalence of NAFLD in the US is estimated to be 25-30%
- It is projected that 100 million people in the US will have NAFLD by 2030 with direct medical costs of $103 billion annually
- Cirrhosis secondary to NAFLD is predicted to become the leading indicator for liver transplantation in adults by 2030

Definitions

Non-Alcoholic Fatty Liver Disease

Non-Alcoholic Fatty Liver (NAFL)

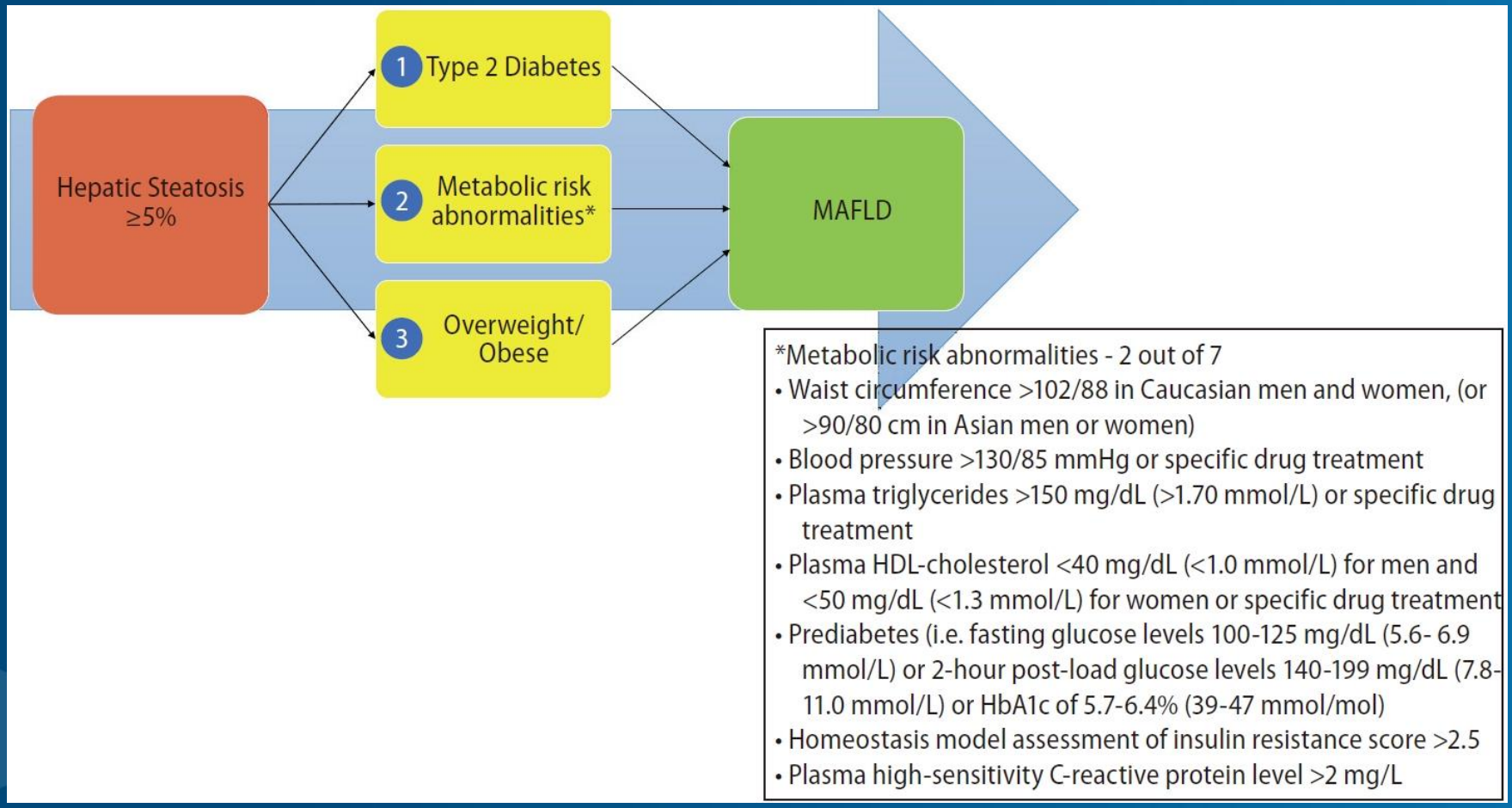
- 5% or greater hepatic steatosis without evidence of hepatocellular injury or fibrosis
- Follows a more indolent course

Non-Alcoholic Steatohepatitis (NASH)

- 5% or greater hepatic steatosis with hepatocellular injury and inflammation
- Fibrosis may or may not be present
- Patients are at risk of progression to cirrhosis and development of hepatocellular carcinoma

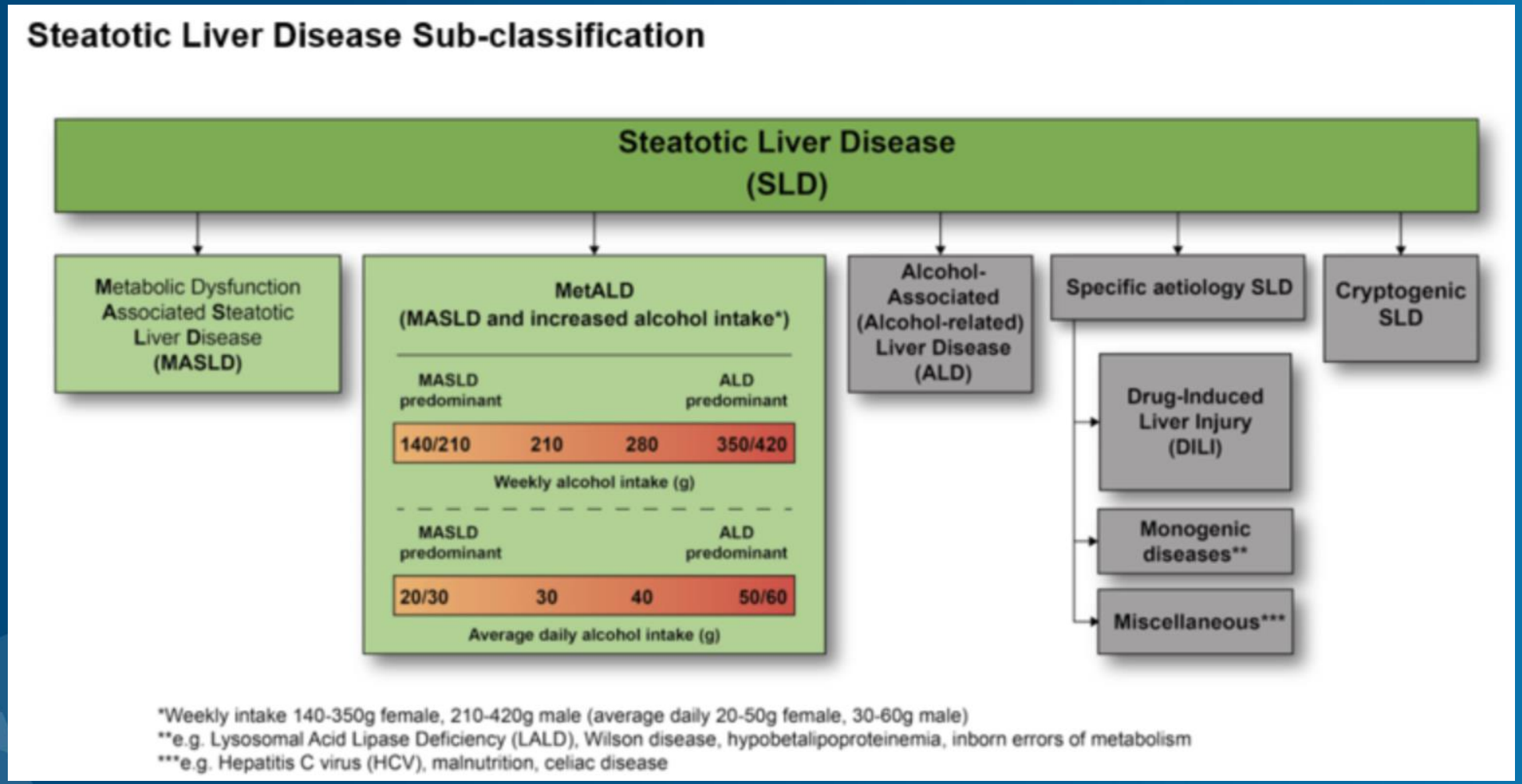
*Non-alcoholic: defined as < 14 standard drinks/week (< 30 g/day) for men and < 7 drinks/week (< 20 g/day) for women

Metabolic dysfunction-associated fatty liver disease (MAFLD)

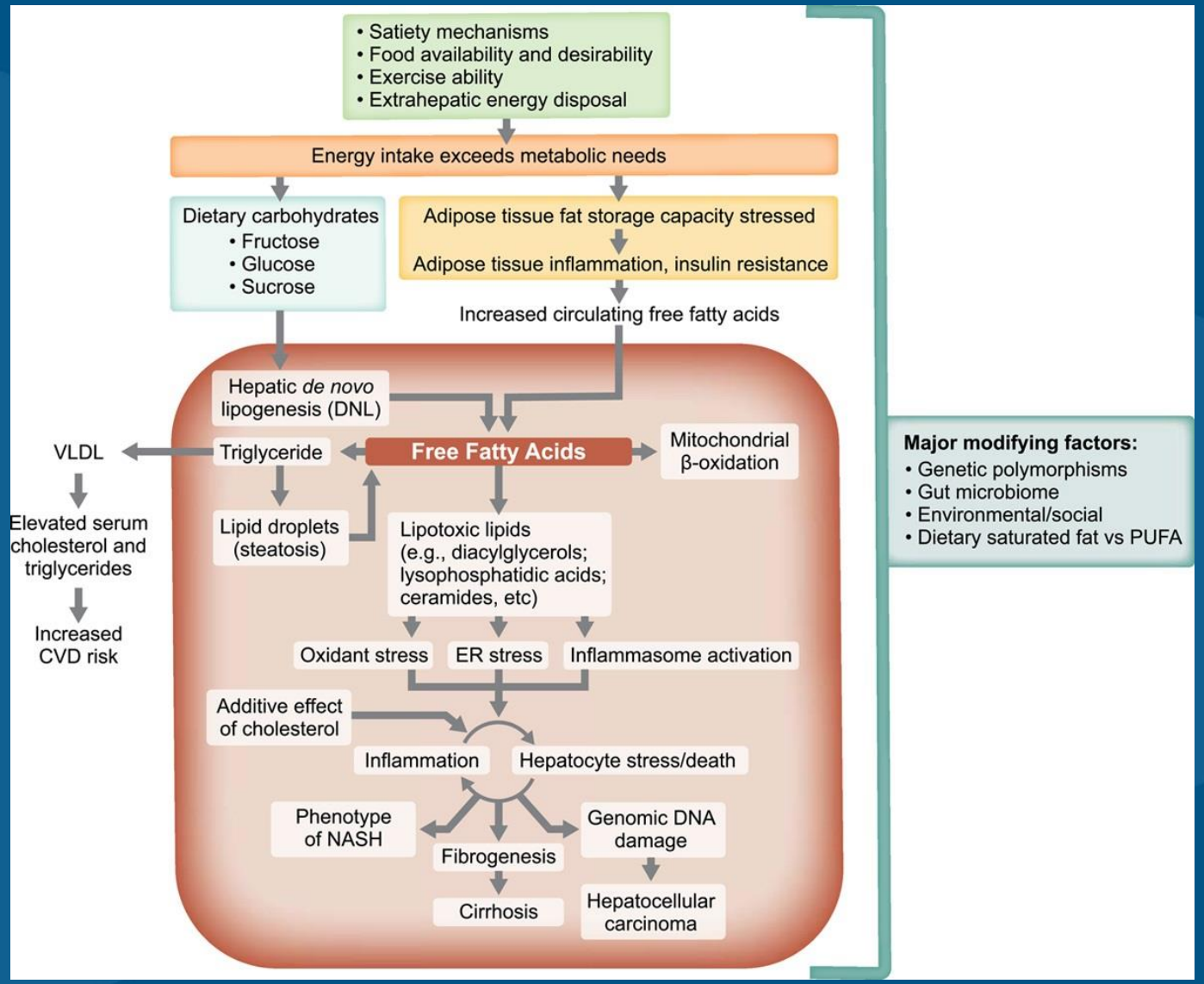


https://www.e-cmh.org/journal/view.php?doi=10.3350/cmh.2022.0367

Metabolic dysfunction-associated steatotic liver disease (MASLD)



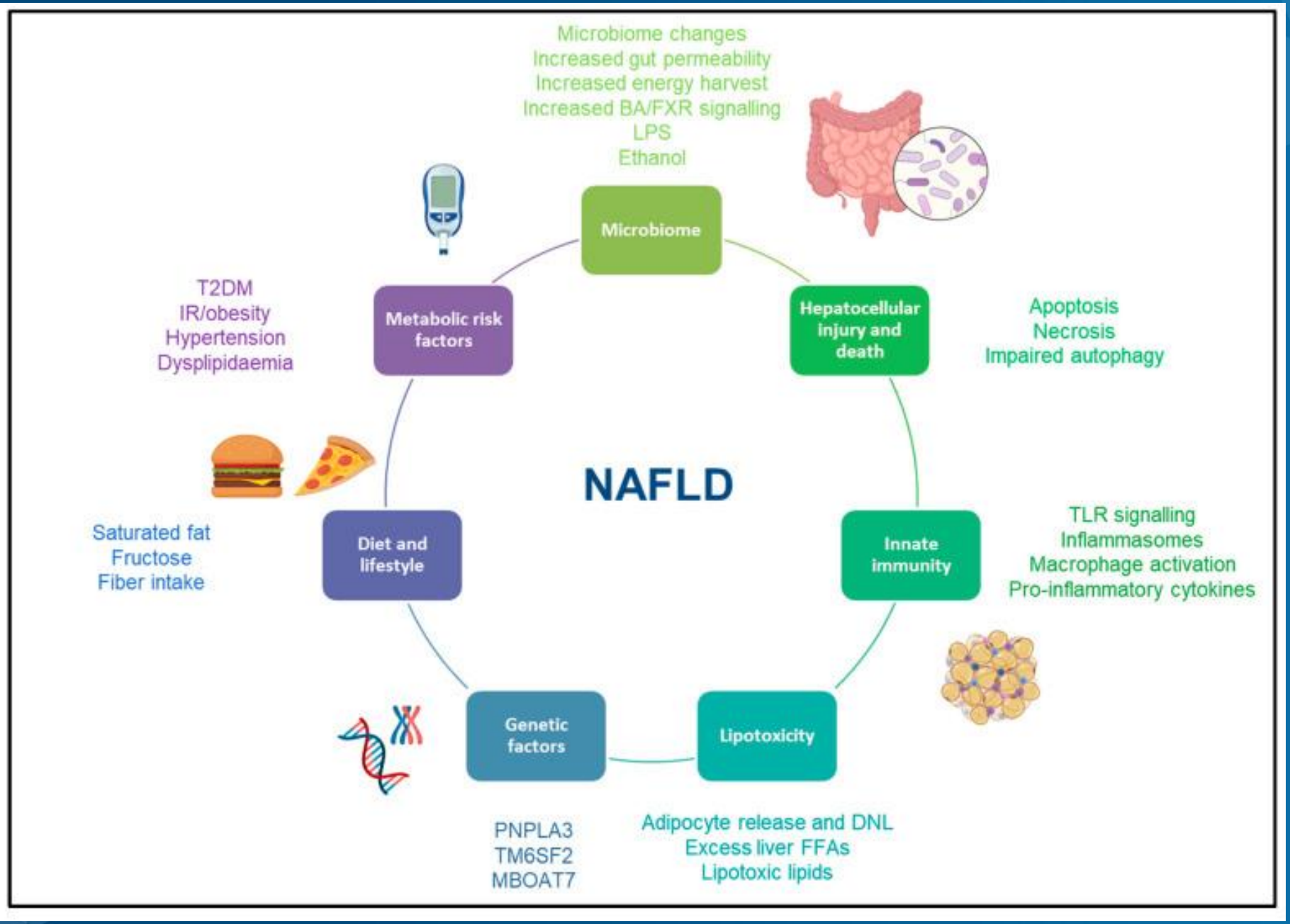
AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology77(5):1797-1835, May 2023.

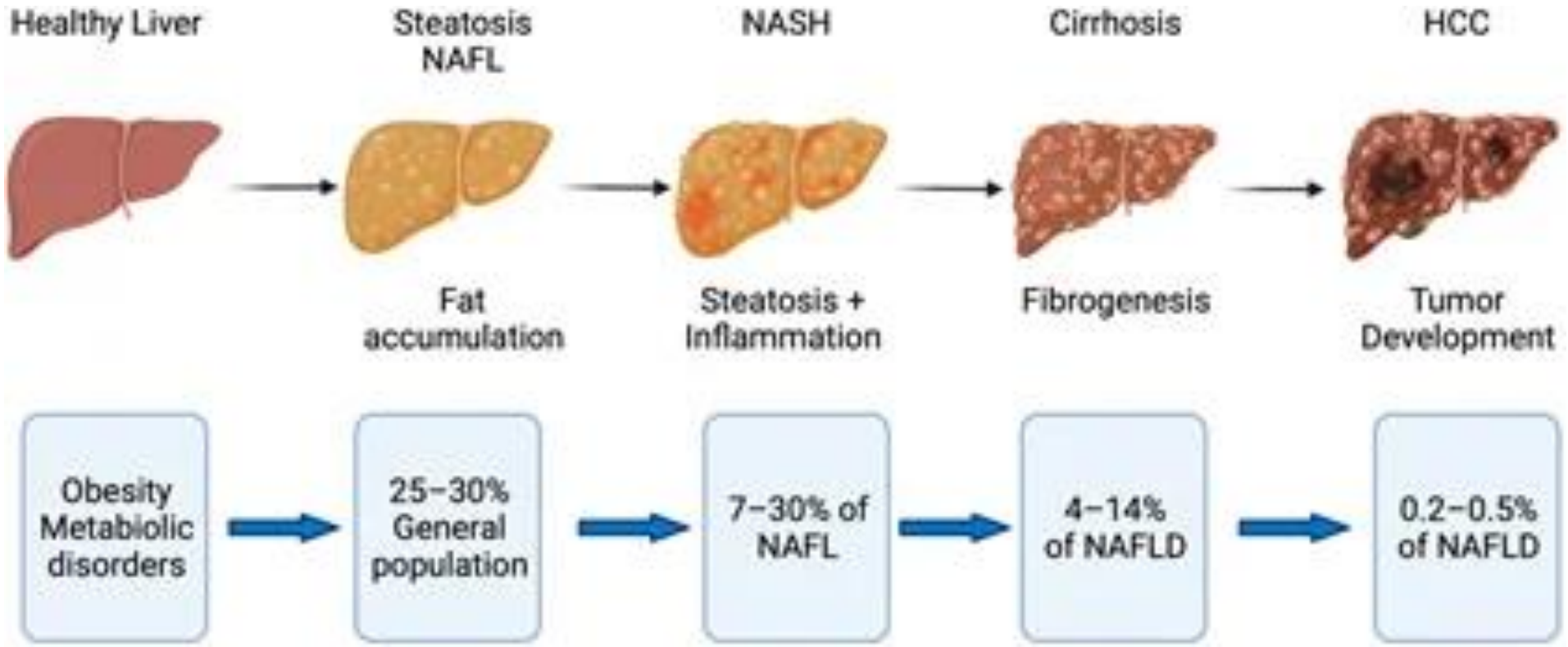


Pathophysiology

- A primary disease driver may be an oversupply of fat to adipocytes, exceeding triglyceride storage of liver cells
- Leads to cell stress, which activates inflammatory pathways and causes insulin resistance
- Genome-wide association studies have identified genetic variants associated with risk of progression to fibrosis (PNPLA3, IFNL4)

AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology77(5):1797-1835, May 2023.


Microbiome changes
Increased gut permeability
Increased energy harvest
Increased BA/FXR signalling
LPS
Ethanol
Microbiome
Hepatocellular injury and death
Apoptosis
Necrosis
Impaired autophagy
Innate immunity
TLR signalling
Inflammasomes
Macrophage activation
Pro-inflammatory cytokines
Lipotoxicity
Adipocyte release and DNL
Excess liver FFAs
Lipotoxic lipids
Genetic factors
PNPLA3
TM6SF2
MBOAT7
Diet and lifestyle
Saturated fat
Fructose
Fiber intake
Metabolic risk factors
T2DM
IR/obesity
Hypertension
Dysplipidaemia
NAFLD



https://www.news-medical.net/whitepaper/20221116/A-Gene-based-strategy-to-prevent-the-progression-of-Non-Alcoholic-Fatty-Liver-Disease-%28NAFLD%29.aspx

Your patient is a 45 yo M with a PMH of type 2 diabetes, hyperlipidemia, obesity (BMI 40) who denies any alcohol use. He has no family history of liver disease that he knows of. What should you order for this patient to evaluate for NAFLD?

A) LFTs

B) Abdominal US

C) A and B

D) None of the above

Your patient is a 45 yo M with a PMH of type 2 diabetes, hyperlipidemia, obesity (BMI 40) who denies any alcohol use. He has no family history of liver disease that he knows of. What should you order for this patient to evaluate for NAFLD?

A) LFTs

B) Abdominal US

C) A and B

D) None of the above

Screening for NAFLD

- American Association for the Study of Liver Diseases (AASLD) guidelines
- **Routine screening for NAFLD is not recommended**, even in high-risk adults, because of uncertainties surrounding diagnostic tests and treatment options
  - LFTs are often normal in patients with NAFLD
  - Liver US are not reliable at low hepatic steatosis levels (< 20%) seen in early NAFLD
- However, incidental findings suggestive of NAFLD in high-risk patients **should initiate prompt evaluation**

Evaluation of NAFLD

Presentation is usually incidental finding on labs/imaging

Symptoms

- Often asymptomatic
- Patients may complain of fatigue, RUQ abdominal pain or fullness, pruritus

Abnormal liver function tests

- Alcohol use: AST/ALT > 1.5
- NAFLD: AST/ALT < 0.8
- As NAFL progresses to NASH with fibrosis, the AST/ALT ratio increases

Evaluation of NAFLD

History and Physical

Lifestyle

- Diet
- Physical activity
- Increase in weight
- Alcohol intake

Associated Conditions

- Diabetes
- Hypertension
- Hyperlipidemia
- Sleep apnea

Viral Hepatitis Risk Factors

- Drug use (IV and sniffing)
- History of blood transfusions
- Sexual history

Family History

- Cardiovascular disorders
- Metabolic disorders
- Chronic liver disease

Vital Signs

- Blood pressure
- Weight/BMI
- Waist circumference

Physical Exam

- Often unremarkable
- Central obesity
- Hepatosplenomegaly

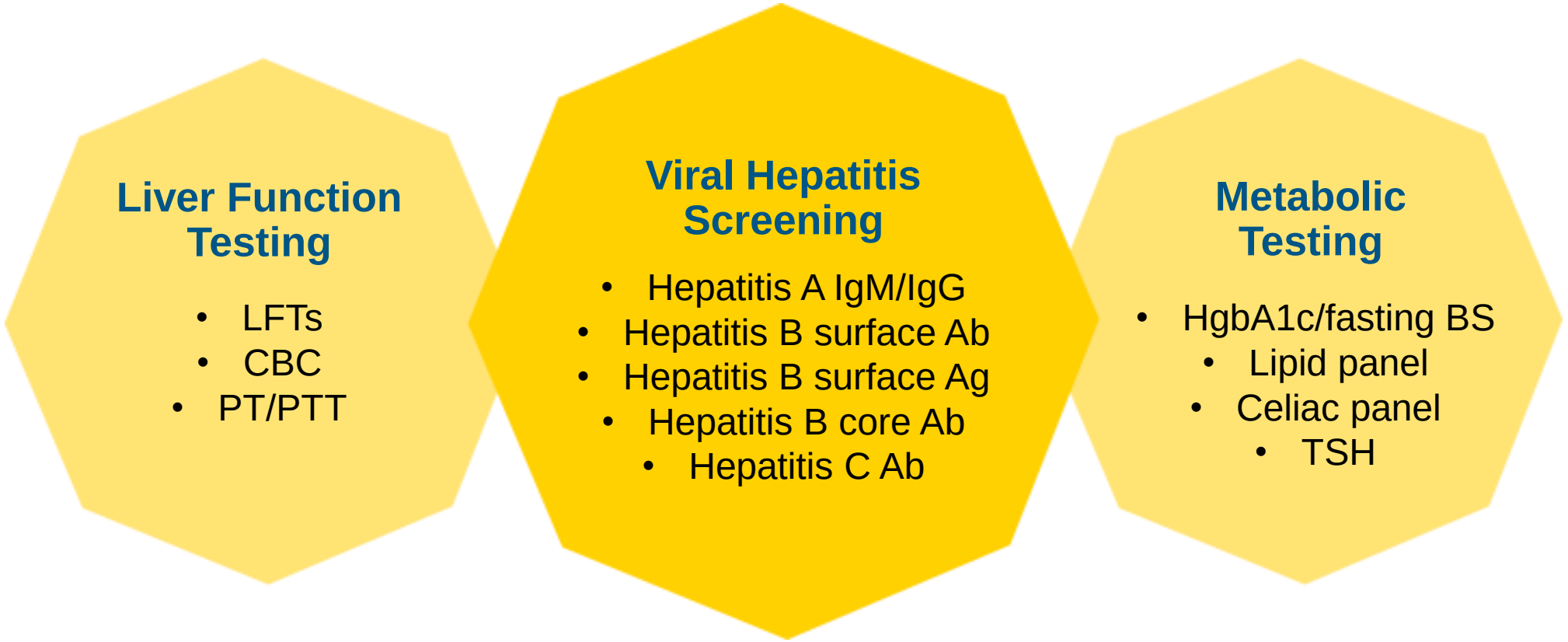
Evaluation of NAFLD

Medications that can cause hepatic steatosis

- Amiodarone
- Aspirin
- Chemotherapy drugs
  - 5-Fluorouracil
  - Tamoxifen
  - Irinotecan (Camptosar)
  - Cisplatin
  - Asparaginase (Erwinaze)
- Cocaine
- Glucocorticoids
- Methotrexate
- NSAIDs
- Tetracycline
- Valproic acid

Evaluation of NAFLD

Laboratory Testing



Evaluation of NAFLD: Differential Diagnosis

α_1- Antitrypsin Deficiency

- α_1- antitrypsin level
- Liver biopsy

Autoimmune Hepatitis

- Antinuclear Ab (ANA)
- Smooth muscle Ab
- Liver/kidney microsomal Ab

Hereditary Hemochromatosis

- CBC
- Ferritin and transferrin saturation level
- Hemochromatosis genetic testing (HFE)
- Liver biopsy with staining for iron

Wilson's Disease

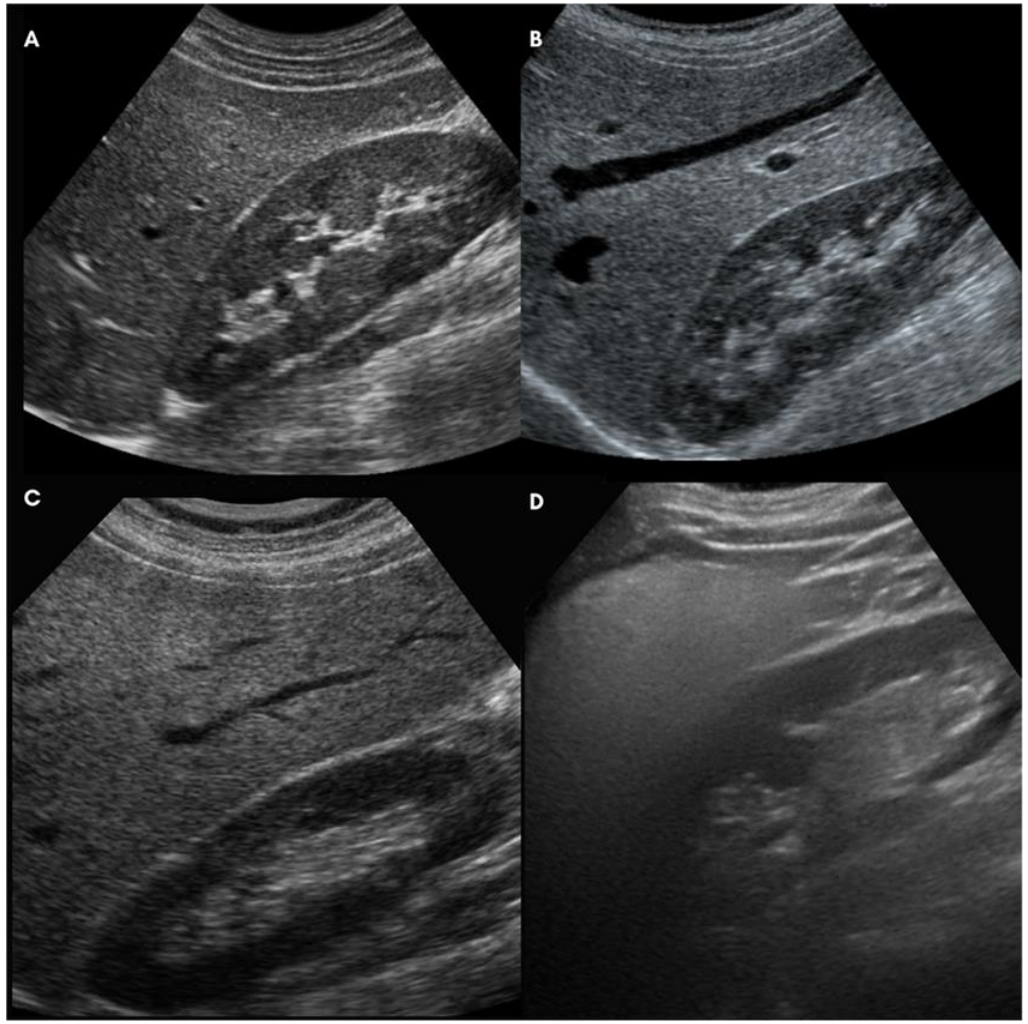
- Ceruloplasmin level
- 24-h urinary Cu
- Liver biopsy

Evaluation of NAFLD

Imaging

- Utrasonography
  - First line imaging: non-invasive, inexpensive and does not expose patient to radiation
  - Reliable for qualitative evaluation and detection of moderate to high amounts of fat in liver
  - Accuracy relies on intraobserver reproducibility and interobserver variability
  - Can be affected by patient's body habitus
  - Cannot reliably differentiate between steatosis and fibrosis

https://www.researchgate.net/figure/Ultrasound-grading-of-hepatic-steatosis-A-Normal-Liver-score-0-B-Mild-Steatosis_fig1_365133257



Ultrasound grading of hepatic steatosis: (A) Normal Liver (score 0); (B) Mild Steatosis (score 1-4); (C) Moderate Steatosis (score 5-8); (D) Severe Steatosis (score 9-12).

Table 4. Imaging Tests for the Evaluation of Nonalcoholic Fatty Liver Disease

Test	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*LR+**	*LR–**
Contrast-enhanced CT	84 to 87	75 to 86	59 to 72	92 to 94	1.4 to 2.7	0.06 to 0.09
Magnetic resonance imaging	96	93	85	98	5.9	0.02
Ultrasonography	60 to 100	77 to 95	52 to 89	82 to 100	1.1 to 8.6	∞ to 0.2
Unenhanced CT	88 to 95	90 to 99	79 to 98	95 to 98	3.7 to 40.7	0.02 to 0.05

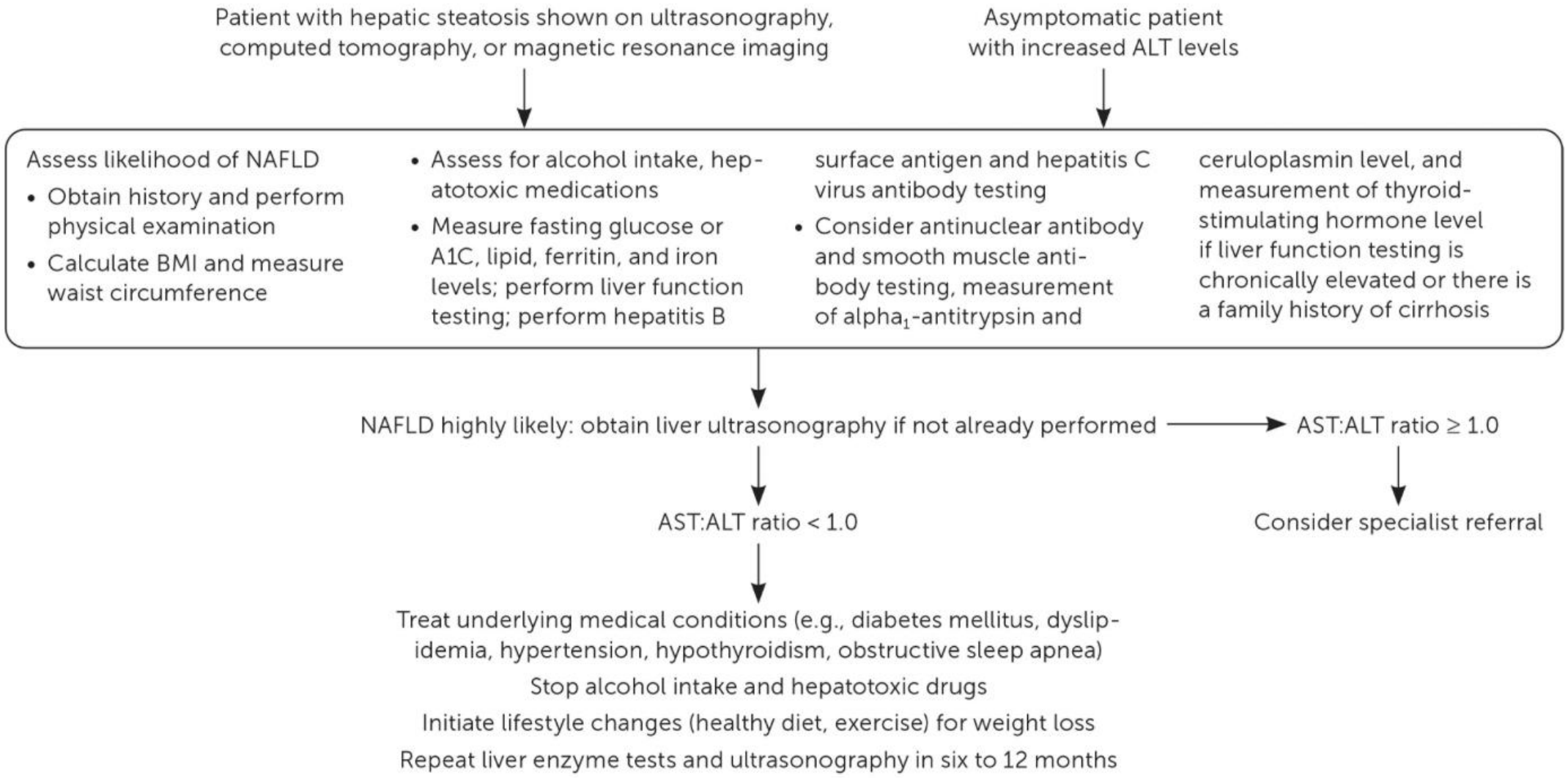
CT = computed tomography; LR– = negative likelihood ratio; LR+ = positive likelihood ratio; NPV = negative predictive value; PPV = positive predictive value.

**—Calculated using a prevalence of 30%.*

Information from references 17 through 19.

https://www.aafp.org/pubs/afp/issues/2013/0701/p35/jcr:content/root/aafp-article-primary-content-container/aafp_article_main_par/aafp_tables_content3.enlarge.html

Westfall EC, Jeske R, and Bader AR. Nonalcoholic Fatty Liver Disease: Common Questions and Answers on Diagnosis and Management. *Am Fam Physician.* 2020;102(9):603-612.



Which of the following patients identified with NAFLD should be screened for the presence of clinically significant fibrosis?

A) All patients identified with NAFLD should be screened
B) A patient with NAFLD and type 2 diabetes mellitus
C) A patient with NAFLD who drinks less than 1 alcoholic drink a day
D) A patient with NAFLD whose paternal grandfather had cirrhosis

Which of the following patients identified with NAFLD should be screened for the presence of clinically significant fibrosis?

A) All patients identified with NAFLD should be screened

B) A patient with NAFLD and type 2 diabetes mellitus

C) A patient with NAFLD who drinks less than 1 alcoholic drink a day

D) A patient with NAFLD whose paternal grandfather had cirrhosis

AASLD Guidelines: “Targeted screening of populations at increased risk of advanced liver disease is recommended to allow for interventions that may prevent future hepatic complications.”

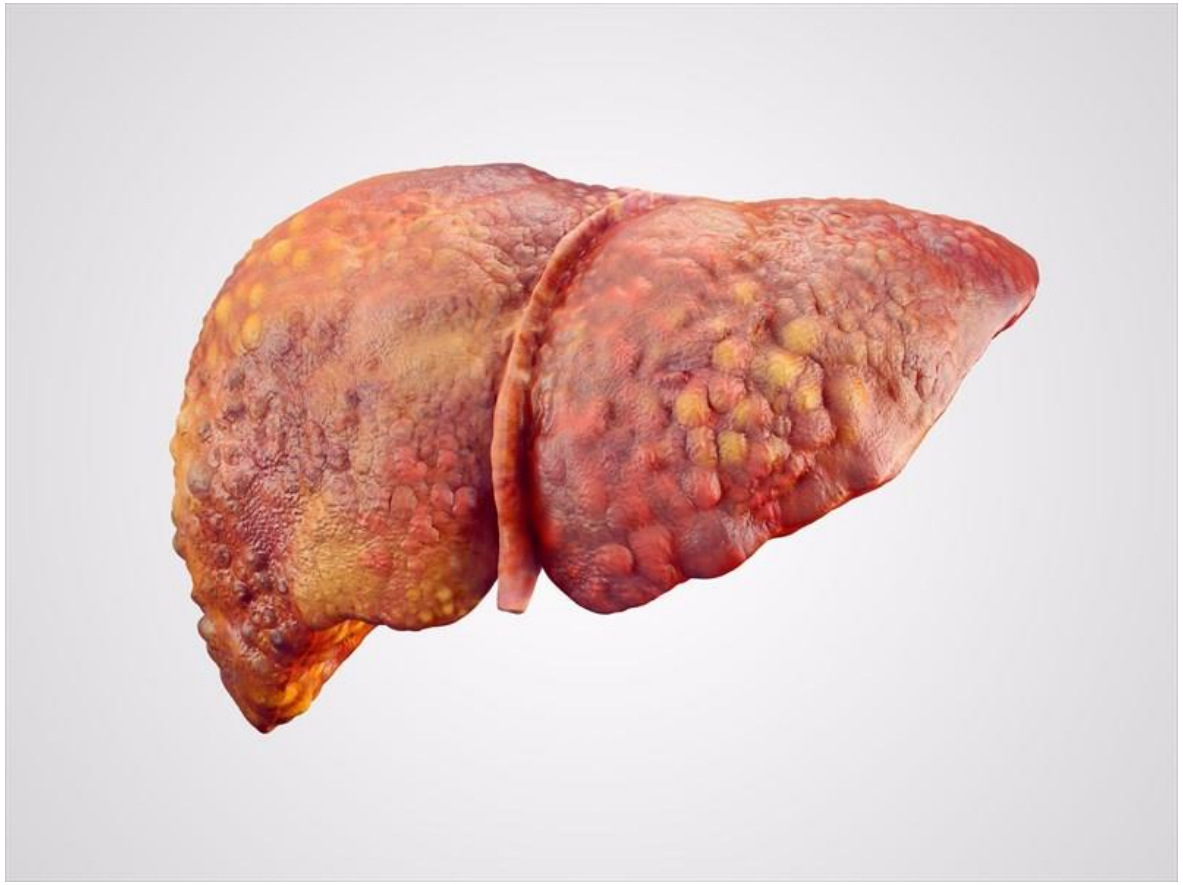
High Risk Populations

- Patients with type 2 diabetes mellitus
- Medically complex obesity
  - One obesity-related comorbidity
    - Dyslipidemia
    - Hypertension
    - Heart disease
    - Stroke
    - CKD/ESRD
    - OSA/obesity hypoventilation syndrome
  - Two or more metabolic risk factors (metabolic syndrome)
- NAFLD in the setting of moderate alcohol use
  - 20-50 g daily for females
  - 30-60 g daily for males
- First-degree relative of a patient with cirrhosis due to NAFLD/NASH (12x risk)

Liver Fibrosis Stages

Comparative Scoring Systems for Histologic Stage (Fibrosis)			
Score	**IASL**	**Batts-Ludwig**	**Metavir**
0	No Fibrosis	No Fibrosis	No Fibrosis
1	Mild fibrosis	Fibrous portal expansion	Periportal fibrotic expansion
2	Moderate fibrosis	Rare bridges or septae	Periportal septae (> 1 septum)
3	Severe fibrosis	Numerous bridges or septae	Portal-central septae
4	Cirrhosis	Cirrhosis	Cirrhosis

Clinically significant fibrosis is defined as stage F2 or more (this group is more likely to progress to cirrhosis)



NAFLD

Evaluation for Fibrosis

1. Non-invasive labs/scoring
2. Imaging
3. Liver biopsy

Evaluation of NAFLD Fibrosis

Non-invasive testing

1. Fibrosis-4 Index (FIB-4)
2. NAFLD Fibrosis Score (NFS)
3. Enhanced Liver Fibrosis Test (ELF)

FIB-4

Fibrosis-4 Index

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

FIB-4 Score	Approximate fibrosis stage*
<1.45	0-1
1.45-3.25	2-3
>3.25	4-6

Use

- Initially created to assess for cirrhosis in HCV and HIV co-infection, but has been validated for use in NAFLD
- Labs: CBC, LFTs
- Correlates with Ishak levels of fibrosis
  - 0-2: mild fibrosis -> monitor
  - 3-4: moderate fibrosis -> further workup
  - 5-6: severe fibrosis/cirrhosis -> refer to Hepatology

Pitfalls

- Initial study of patients around 40 yo
  - Overestimates in pts < 35 yo
  - Underestimates in pts > 65 yo
- High false positive rate (35% in one study), better at ruling out fibrosis than ruling in fibrosis

NFS

NAFLD Fibrosis Score

NAFLD-fibrosis score = -1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m2) + 1.13 × impaired fasting glucose (IFG)/diabetes (yes=1, no=0) + 0.99 × AST/ALT ratio – 0.013 × platelet ($\times 10^9$/L) – 0.66 × albumin (g/dL)

NAFLD Score	Correlated Fibrosis Severity
< -1.455	F0-F2
-1.455 – 0.675	Indeterminant score
> 0.675	F3-F4

Fibrosis Severity Scale

- F0 = no fibrosis
- F1 = mild fibrosis
- F2 = moderate fibrosis
- F3 = severe fibrosis
- F4 = cirrhosis

Use

- Useful for ruling out clinically significant fibrosis
- Labs: HgbA1c, CBC, LFTs, BMI
- Fibrosis severity
  - F0-F2: continue to monitor
  - Indeterminant score: further workup with imaging or biopsy
  - F3-F4: refer to Hepatology

Pitfalls

- High false positive rate (45% in one study), better at ruling out fibrosis
- Less reliable in patients with “lean” NAFLD (normal BMI)

ELF

Enhanced Liver Fibrosis Test

Use

- Blood tests that measures three direct markers of liver fibrosis
  - Hyaluronic acid (HA)
  - Type III procollagen peptide (PIINP)
  - Tissue inhibitor of matrix metalloproteinase 1 (TIMP-1)
- Uses Siemens Healthcare Diagnostics algorithm to determine risk of fibrosis

Pitfalls

- Significantly fewer false positives compared to FIB-4 and NFS (11% in one study)
- Expensive

Evaluation of NAFLD Fibrosis

Imaging: US Elastography

US Elastography (Fibroscan)

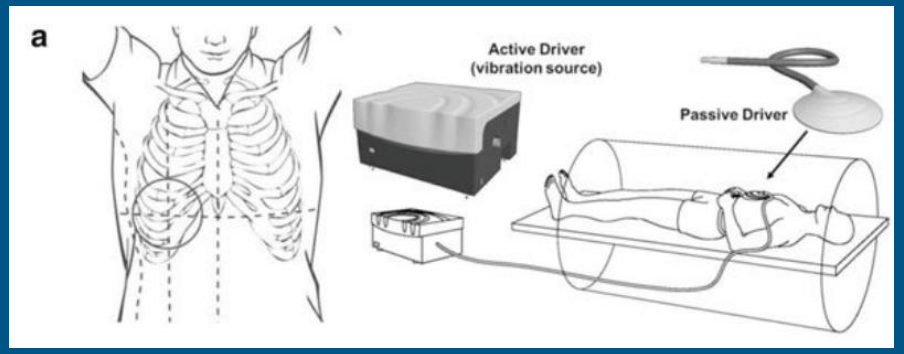
- US transient elastography
- Measures hepatic elasticity by quantifying shear wave speed from low frequency pulses transmitted through the liver
- Liver stiffness correlate with liver fibrosis stages
- Sensitivity of 91% and specificity of 75% for F γ 3 at cutoff value of 7.9 kPa

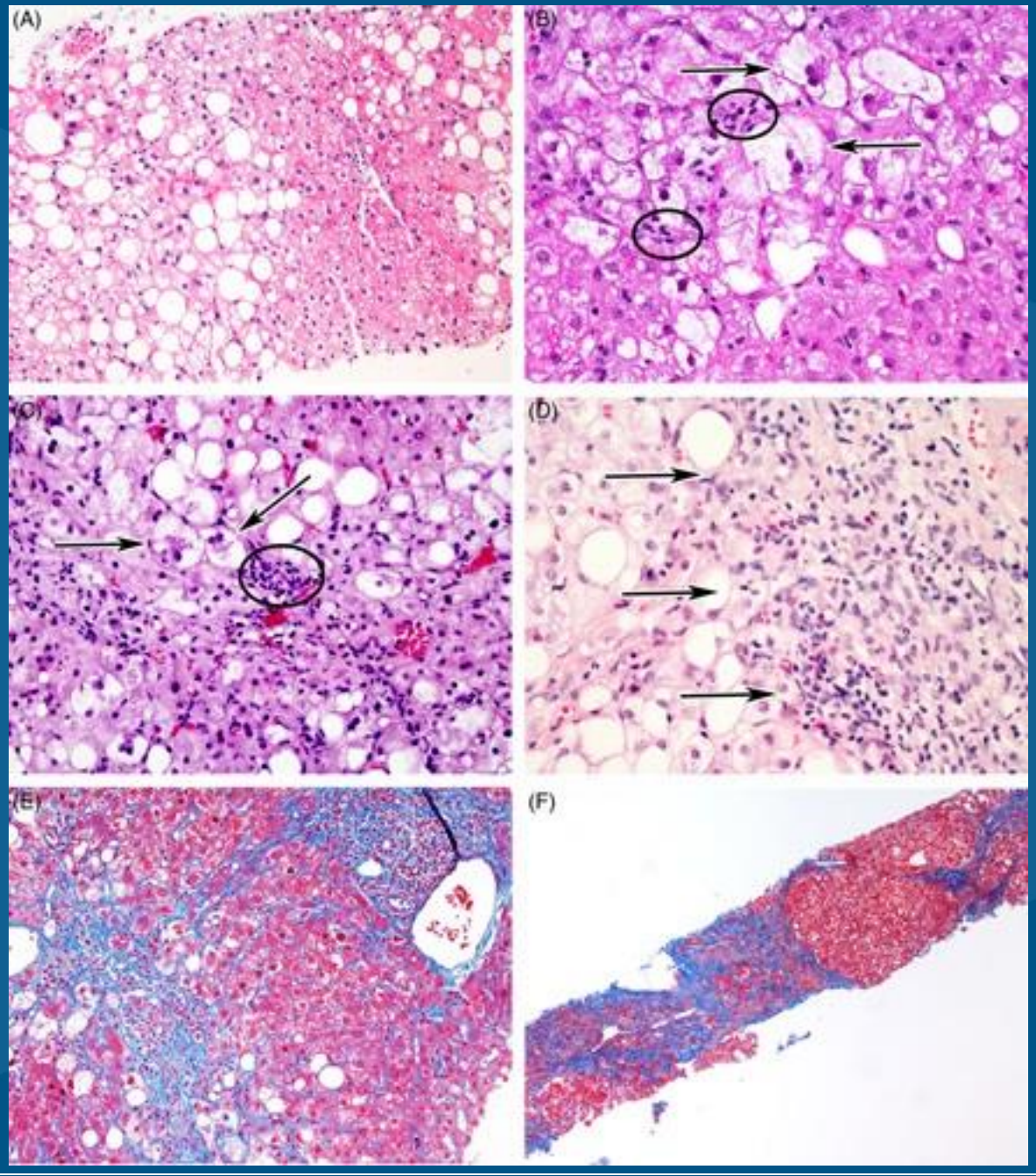
Evaluation of NAFLD Fibrosis

Imaging: Magnetic Resonance Elastography

MR Elastography (MRE)

- Uses modified phase-contrast MRI sequence and external mechanical actuator to induce and visualize tissue shear waves
- Most accurate non-invasive biomarker of fibrosis in NAFLD
- Sensitivity of 89.7% and specificity of 87.1% for F γ 2 at cutoff value of 3.05 kPa
- Low availability and high cost





Evaluation of NAFLD Fibrosis: Liver Biopsy

- Gold standard of diagnosis
  - Reserved for unknown or unclear etiology of liver disease (considering other etiologies besides NAFLD)
  - Distinguishing between NAFL and NASH
  - Risks
    - Increases mortality from 0.009 to 0.14%
    - Intraperitoneal hemorrhage
    - Only assesses small portion of liver

(A) Hepatic steatosis without inflammation or fibrosis

(B) Multiple ballooned hepatocytes and mild lobular inflammation

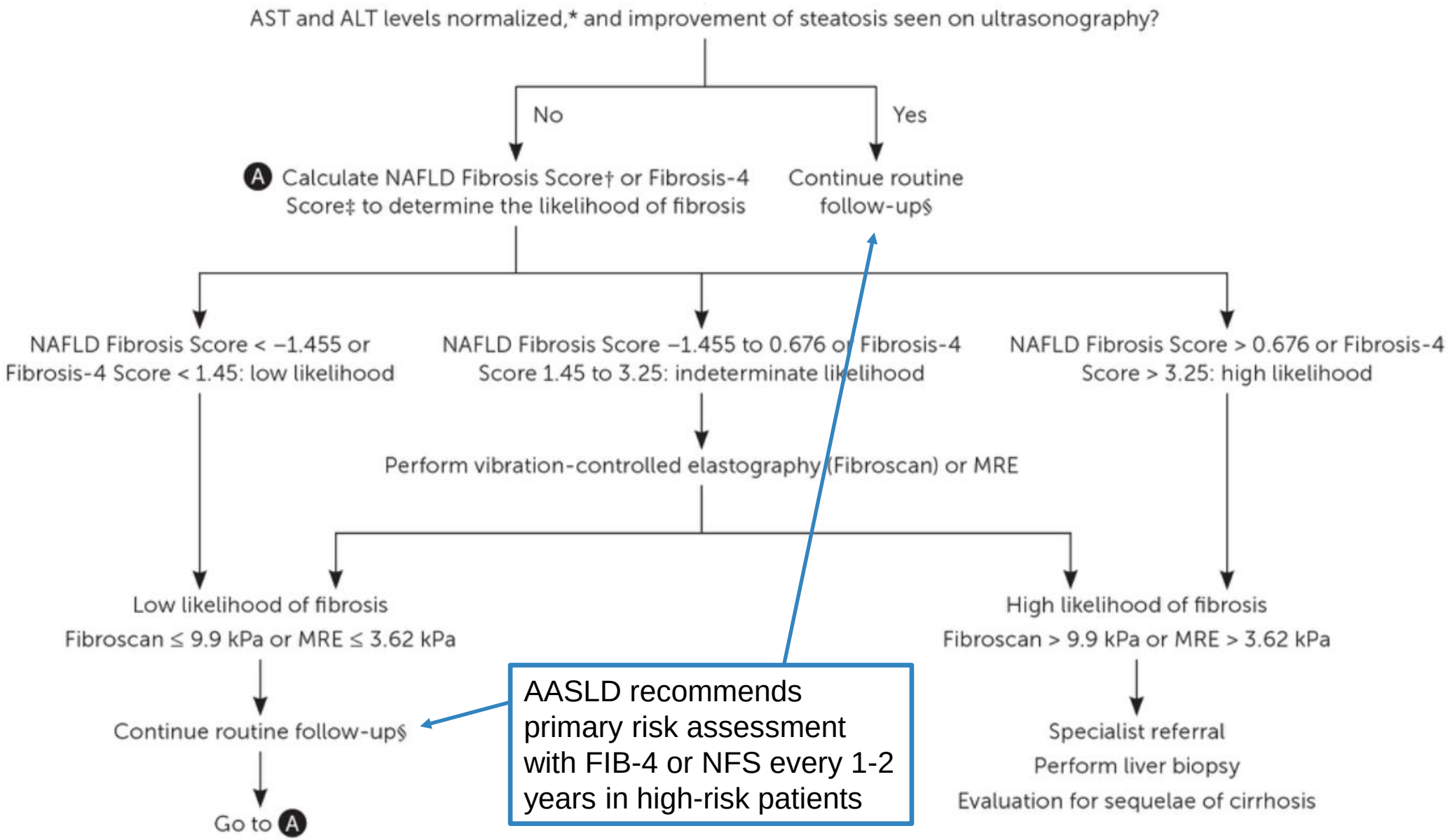
(C) Ballooned hepatocytes with moderate lobular inflammation

(D) Significant portal inflammation

(E) Dense perisinusoidal and periportal fibrosis

(F) Cirrhosis with nodule formation

Westfall EC, Jeske R, and Bader AR. Nonalcoholic Fatty Liver Disease: Common Questions and Answers on Diagnosis and Management. *Am Fam Physician.* 2020;102(9):603-612.



AASLD recommends primary risk assessment with FIB-4 or NFS every 1-2 years in high-risk patients

Treatment Options for NAFLD

What can we do as primary care physicians?

NAFLD: Treatment

1. Lifestyle interventions
2. Bariatric surgery
3. Medications

Lifestyle Interventions

Weight loss

- Weight loss 3-5% improves steatosis
- > 10% weight loss usually required to improve NASH and fibrosis

Diet

- Goal is calorie deficit
- Limit fructose consumption (refined carbohydrates, sugary beverages)
- Some evidence for Mediterranean diet in reducing fat around liver
- Coffee consumption (3+ cups a day) may reduce liver fibrosis

Exercise

- Regular moderate exercise for 30 minutes 5x a week (150 min a week)

Bariatric Surgery

- Bariatric surgery should be considered as a therapeutic option in patients who meet criteria for metabolic weight loss surgery
  - Effectively resolves NAFLD or NASH in the majority of patients without cirrhosis
  - Reduces mortality from CVD and malignancy
- The role of bariatric surgery is less in NASH cirrhosis
  - The type, safety, and efficacy of bariatric surgery in patients with well-compensated NASH cirrhosis is not established and requires a careful benefit–risk assessment
  - Decompensated cirrhosis should be considered an absolute contraindication for bariatric surgery due to increased risk and unproven liver-related benefit, unless performed in conjunction with liver transplantation at experienced centers

Medications

- There are currently no FDA-approved drugs for the treatment of NASH at any disease stage
- There are medications approved for other indications that have shown benefits for NASH in clinical trials and should be considered under specific circumstances

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

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

AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology77(5):1797-1835, May 2023.

Medications

- **Semaglutide** can be considered for its approved indications (T2DM/obesity) in patients with NASH, as it confers a cardiovascular benefit and improves NASH
- **Pioglitazone** improves NASH and can be considered for patients with NASH in the context of patients with T2DM
- **Vitamin E** can be considered in select individuals as it improves NASH in some patients without diabetes
- Available data on **semaglutide**, **pioglitazone**, and **vitamin E** do not demonstrate an antifibrotic benefit, and none has been carefully studied in patients with cirrhosis
- **Metformin**, **ursodeoxycholic acid**, **dipeptidyl peptidase-4**, **statins**, and **silymarin** are well studied in NASH and should not be used as a treatment for NASH as they do not offer a meaningful histological benefit

NAFLD in Special Populations

NAFLD in Lean Individuals

- Lean: defined as BMI < 25 kg/m^2 or < 23 kg/m^2 in Asian individuals
- Prevalence: 4.1% in US, 19% in Asia
- Compared to healthy controls, lean subjects with NAFLD have increased metabolic comorbidities, visceral adiposity, and decreased muscle mass
  - Genetic factors likely play a significant role (more common in Asian and Latinx patients)
  - No role for genetic testing at this time
- Management
  - Dietary modifications and exercise without weight loss

NAFLD in Pediatric Patients

- Prevalence: around 8% in non-obese children, up to 34% in obese children
  - Higher in male children, adolescents, Asian and Latinx ethnicity
  - Associated factors: impaired glucose tolerance, diabetes, panhypopituitarism, obstructive sleep apnea
- Some evidence of disease onset in perinatal period in children of mothers with gestational diabetes and high BMI
- Children with NAFLD had 14x the risk of progression to severe liver disease and death in a long-term retrospective cohort study following 66 children for 20 years

NAFLD in Pediatric Patients

- Presentation: more likely to have extrahepatic manifestations compared to adults
  - Hypertriglyceridemia
  - Hypertension
  - Premature atherosclerosis
  - Obstructive sleep apnea
  - Polycystic ovarian syndrome
- Screening
  - Consider screening with ALT beginning between 9-11 yo for all obese and overweight patients, especially with other risk factors
  - Earlier screening for children with severe obesity or panhypopituitarism

References

- Rinella ME et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology.* May 2023. *77(5);*1797-1835.
- Westfall EC, Jeske R, and Bader AR. Nonalcoholic Fatty Liver Disease: Common Questions and Answers on Diagnosis and Management. *Am Fam Physician.* 2020;102(9):603-612.
- Arnold, MJ. Nonalcoholic Fatty Liver Disease: Diagnosis and Management Guidelines from the AACE. *Am Fam Physician.* 2023;107(5):554-556.
- Gofton C et al. MAFLD: How is it different from NAFLD? Clin Mol Hepatol. 2023; 29(Suppl): S17-S31.
- Volpe SL et al. Once-Weekly Subcutaneous Semaglutide Improves Fatty Liver Disease in Patients with Type 2 Diabetes: A 52-Week Prospective Real-Life Study. *Nutrients*. 14(4673).
- Forlano R et al. Screening for NAFLD – Current Knowledge and Challenges. *Metabolites*. 2023 Apr; 13(4):536.
- Sterling RK, Lissen E, Clumeck N, et. al. Development of a simple noninvasive index to predict significant fibrosis patients with HIV/HCV co-infection. Hepatology 2006;43:1317-1325.
- Kjaergaard M et al. Using the ELF test, FIB-4 and NAFLD fibrosis score to screen the population for liver disease. *J Hepatology*. 2023 Aug; 79(2):277-286.
- Li Q et al. Current status of imaging in nonalcoholic fatty liver disease. *World J Hepatol*. 2018 Aug; 10(8):530-542.

UCLA David Geffen School of Medicine

Thank you!

Questions?