Non-alcoholic Fatty Liver Disease (NAFLD)

Sarah Wilson, MD

Outline

- Definitions and Epidemiology
- Role of Primary Care Providers
- Diagnosis
- When to refer to specialist
- Treatment

Clinical Practice Guidelines

American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings

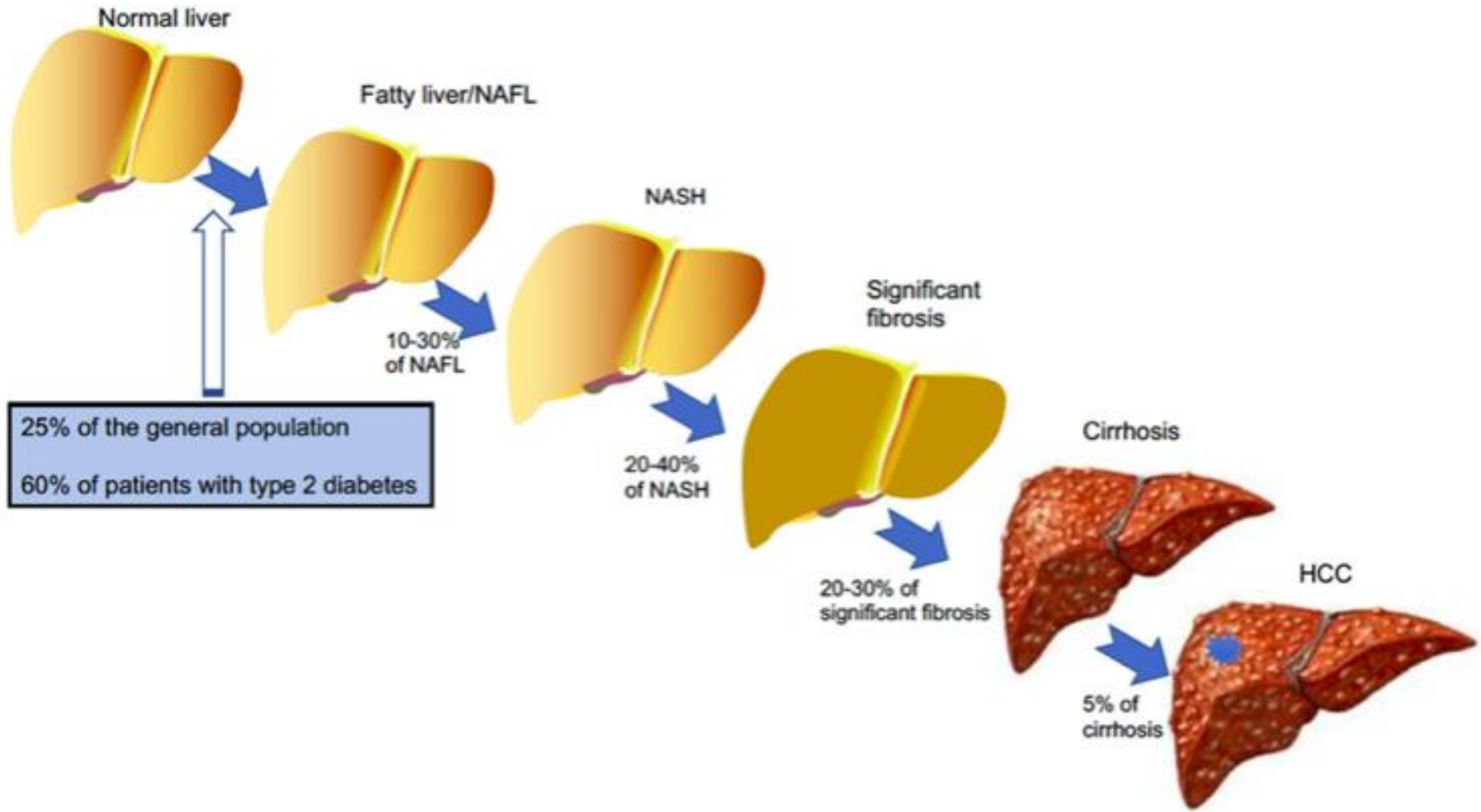
Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD)

Kenneth Cusi, MD, FACE, FACP, Co-Chair [1,*], Scott Isaacs, MD, FACE, FACP, Co-Chair [2], Diana Barb, MD, ECNU [3], Rita Basu, MD [4], Sonia Caprio, MD [5], W. Timothy Garvey, MD, MACE [6], Sangeeta Kashyap, MD [7], Jeffrey I. Mechanick, MD, ECNU, MACE, FACP, FACN [8], Marialena Mouzaki, MD, MSc [9], Karl Nadolsky, DO, FACE, DABOM [10], Mary E. Rinella, MD, AASLD Representative [11], Miriam B. Vos, MD, MSPH [12], Zobair Younossi, MD, AASLD Representative [13]

DEFINITIONS AND EPIDEMIOLOGY

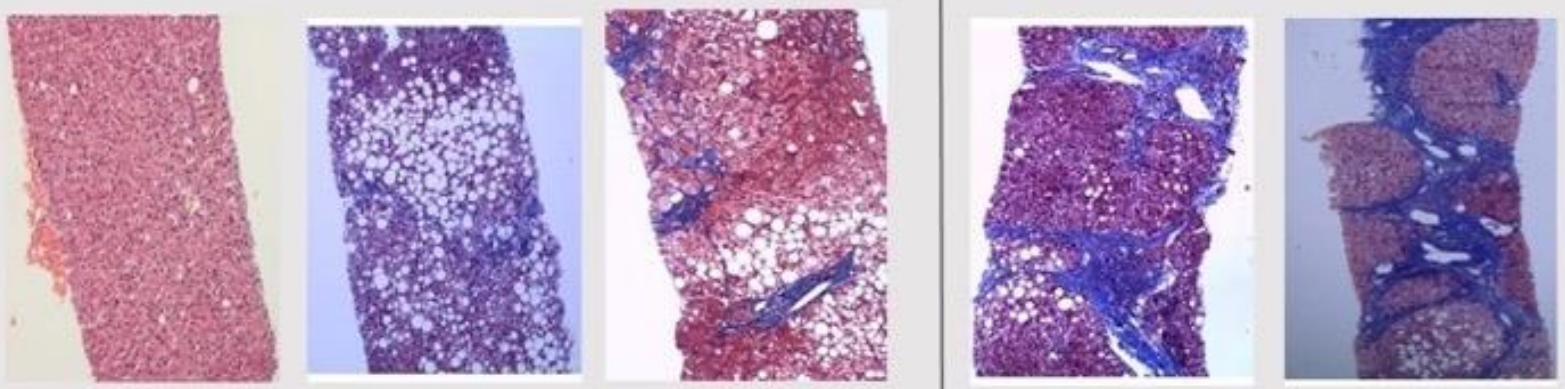
NAFLD vs. NASH

- **Nonalcoholic fatty liver disease (NAFLD):** Broad spectrum of liver disease, ranging from hepatic steatosis to steatohepatitis to cirrhosis
  - In the absence of significant alcohol consumption or presence of secondary causes of fatty liver disease
- **Nonalcoholic steatohepatitis (NASH):** Presence of > 5% or more of hepatic steatosis with inflammation and hepatocyte injury, with or without evidence of fibrosis



https://www.frontiersin.org/articles/10.3389/fendo.2018.00649/full

Stages of Hepatic Fibrosis



F0	F1	F2	F3	F4
No fibrosis	Perisinusoidal fibrosis	Perisinusoidal with portal/periportal fibrosis	Bridging fibrosis	Cirrhosis

https://www.clearvuehealth.com/questions/what-is-nash-fibrosis/

Major Risk Factors

- Obesity/Metabolic syndrome
  - 25-30% prevalence of NASH
- Type 2 Diabetes/Insulin resistance
  - 55% prevalence of NAFLD
  - 30-40% prevalence of NASH

Co-morbidities

- Hepatic
  - Cirrhosis
  - Hepatocellular carcinoma
- Extra-hepatic
  - Cardiovascular disease
    - Major cause of morbidity and mortality
  - Hypertension
  - Non-hepatic cancer

ROLE OF PRIMARY CARE PROVIDERS

Despite the increasing prevalence of NAFLD and potential for increased morbidity and mortality…

- It is estimated that < 5% of persons with NAFLD are aware of their liver disease
- Studies have shown that there is a knowledge gap regarding NAFLD among endocrinologists and PCPs, resulting in
  - Underestimation of prevalence of NAFLD in high risk groups
  - Underutilization of medications with proven efficacy in NASH
  - Underdiagnosis and low referral rates to gastroenterologists and hepatologists for management

Role of Primary Care Providers

- Screen patients who are at high risk of clinically significant fibrosis and cirrhosis
- Manage cardiometabolic risk factors
- Recommend lifestyle modifications
- Initiate appropriate medical therapy with proven efficacy
- Identify patients that should be referred to a gastroenterologist or hepatologist for management

DIAGNOSIS

Who should be screened?

- Obesity and/features of metabolic syndrome
- Pre-diabetes or Type 2 Diabetes
- Hepatic steatosis on imaging study
- Persistently elevation plasma aminotransferase levels (> 6 months)
- Persons undergoing bariatric surgery

Diagnosis

- Liver biopsy
- Biomarkers
  - Liver enzymes
  - FIB-4 Index
- Imaging
  - Abdominal Ultrasound
  - Elastography

Liver Biopsy

- **Gold Standard** for diagnosis of NASH
  - Allows direct visualization of liver parenchyma
  - Liver fibrosis stage indicating severity of fibrosis
- Limitations
  - Invasive and costly
  - Many more non-invasive strategies have been developed

Liver Transaminases

- ALT is higher in patients with T2DM and NAFLD
  - However, this has limited accuracy as liver enzymes can be normal in patients with NAFLD

	Sensitivity	Specificity
NASH		
ALT 1x ULN	*75%*	*47%*
ALT 0.5x ULN	*100%*	*11%*
Fibrosis		
ALT 1x ULN	*64%*	*47%*
ALT 0.5x ULN	*93%*	*10%*

- Limitations:
  - Does not reflect the severity or stage of the disease
  - Does not confirm the diagnosis

Fibrosis-4 (FIB-4) Index

- Preferred initial noninvasive test
- Components: age, AST, ALT, and platelet count
  - Score > 2.67 = High risk for advanced fibrosis
  - Score < 1.3 = Advanced fibrosis is excluded
  - Score of 1.3-2.67 = Indeterminate
- Patient's with an indeterminate or high risk score should be considered for further evaluation with imaging

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
ALT Alanine aminotransferase	Norm: 1 - 35	U/L
Platelet count	Norm: 150 - 350	× 10^3/μL

Result:

Please fill out required fields.

About the Creator

Dr. Richard Sterling

Are you Dr. Richard Sterling?

Also from MDCalc...

Related Calcs

- NAFLD Fibrosis Score
- HIV CKD Prediction
- MELD Score (Original)

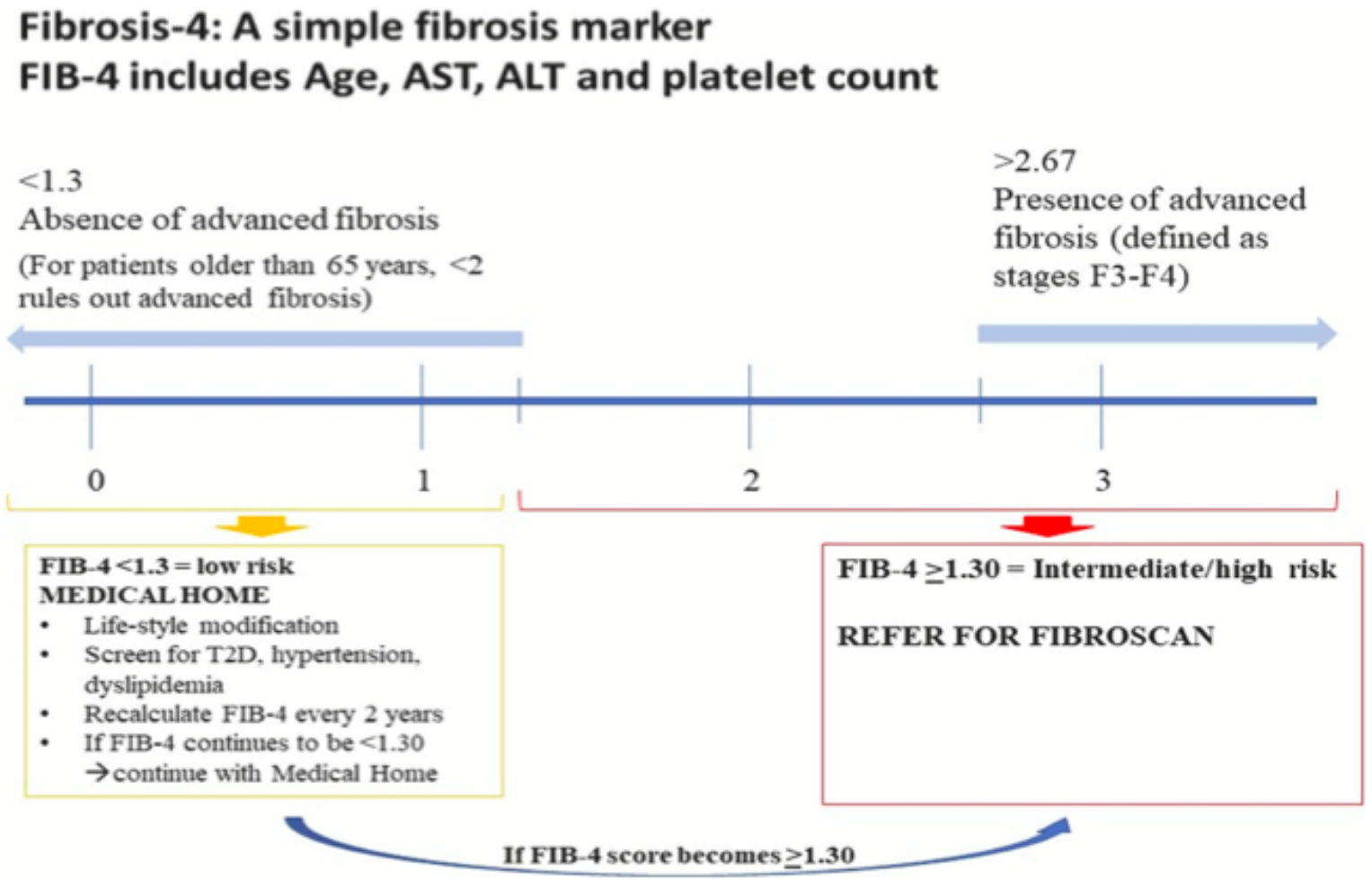


Fig. 2. Clinical use of FIB-4 to screen for NAFLD-related liver fibrosis in patients with T2D. https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis.

Abdominal Ultrasound

- 4-point qualitative scoring system to grade severity of NAFLD
  - Normal, mild, moderate, and severe
- Benefits:
  - Commonly available, affordable, and easy to use
  - Accuracy > 80%
  - Effective in patients with DM
- Limitations:
  - Operator-dependent technique
  - Unable to quantify amount of steatosis present, provide information on staging of NALFD-related fibrosis, cannot detect mild hepatic steatosis (<30% steatosis)
  - Sensitivity reduced by presence of severe obesity

Vibration controlled transient elastography (TE)

- Considered the preferred imaging study in recent AACE guidelines
- Uses ultrasound-based device that measures shear wave velocity as a surrogate of liver stiffness (more stiff = more fibrotic)
- Examples: Fibroscan

Steatosis – Vibration controlled transient elastography (TE)

- Benefits:
  - Includes two probes (M and XL) depending on body habitus
  - High accuracy for detecting both steatosis and fibrosis when compared to liver biopsy
  - Well studied in patients with DM
- Limitations:
  - Less widely available
  - May produce unreliable results in cases of acute hepatic inflammation, congestion, cholestasis, ascites, or portal vein thrombosis
  - Contraindicated in pregnancy and intracardiac devices
  - Limited results in patients with Obesity

WHEN TO REFER?

When should a patient be referred to a liver specialist?

- Persistent elevation in ALT or AST
- Hepatic steatosis on imaging
- Indeterminate or high risk FIB-4 score
- Clinical evidence of advanced liver disease (ascites, hepatic encephalopathy, esophageal varices, or evidence of hepatic synthetic dysfunction)

TREATMENT

Weight Loss!!

- Goal of at least 5%, but preferably 10% weight loss
  - More weight loss = greater liver histologic and cardiometabolic benefit
- Dietary modification: calorie reduction and restriction of saturated fat, starch, and added sugars
  - Adopt healthy eating patterns such as the Mediterranean diet
- Increase physical activity
- Consider bariatric surgery
  - Not recommended in patients with cirrhosis

Pharmacotherapy – Patients with T2DM

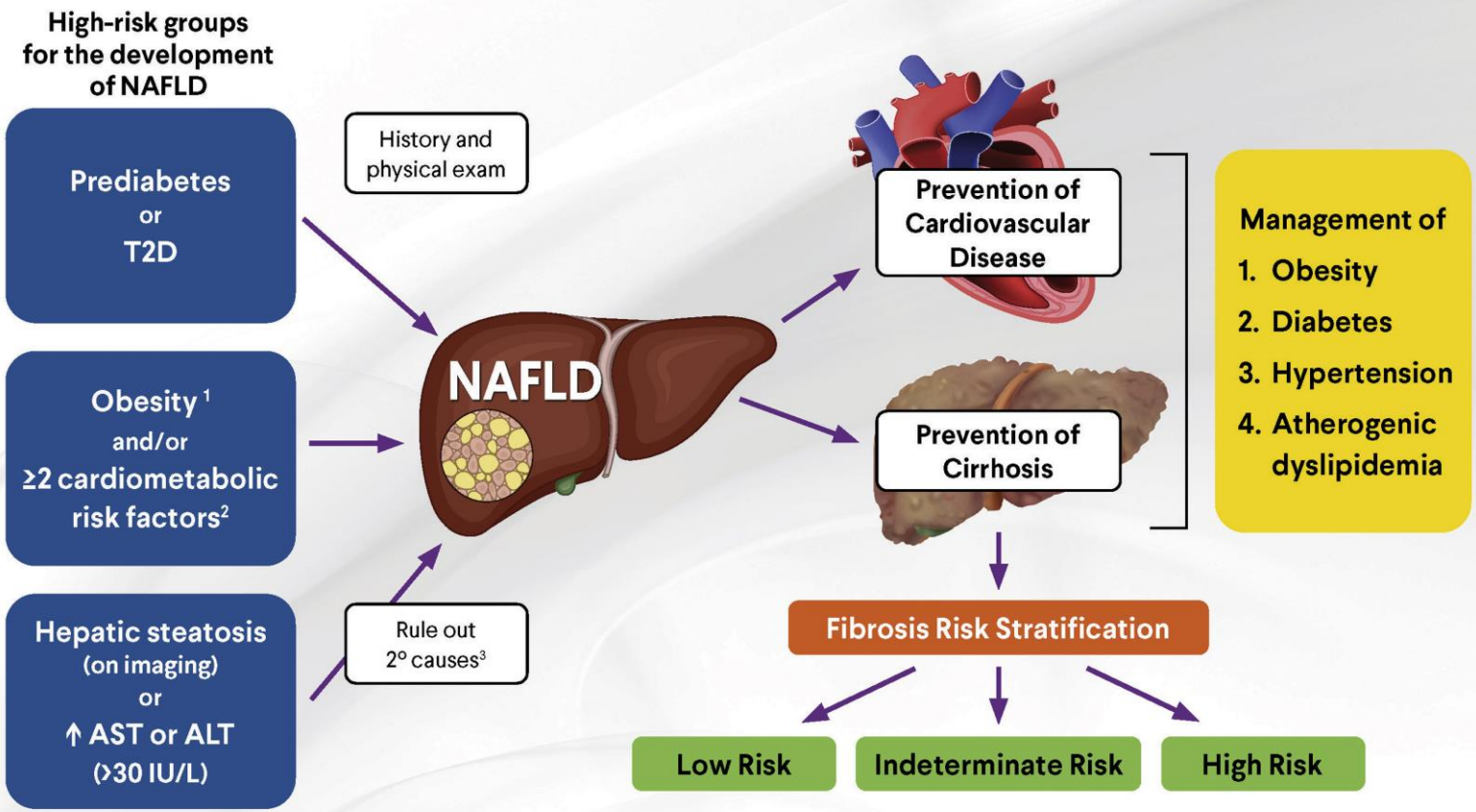
- **Pioglitazone** and **GLP-1 receptor agonists** have shown efficacy in treatment of steatohepatitis (NASH)
- SGLT-2 inhibitors do not provide benefit for treatment of steatohepatitis, but may offer cardiometabolic benefit
- Other diabetes medications (metformin, acarbose, insulin, DPP4 inhibitors) have no benefit on treatment of steatohepatitis, but can be continued if needed for treatment of hyperglycemia

Pharmacotherapy – Obesity

- Use as adjunctive to lifestyle modification to achieve weight loss goal
- Semaglutide 2.4 mg weekly has best evidence
  - Can also consider Liraglutide 3 mg/day

SUMMARY

Management Algorithm for NAFLD – Overview

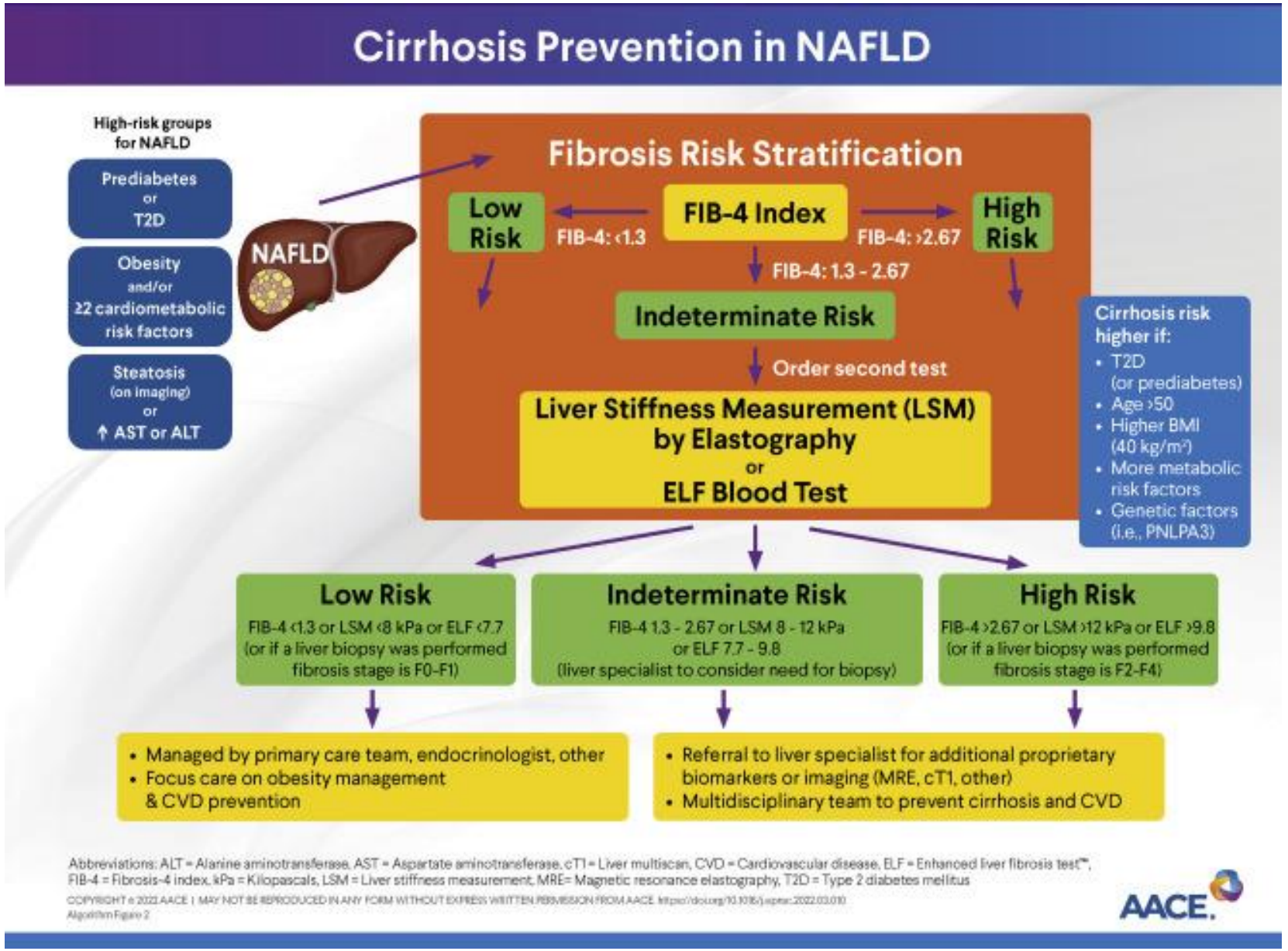


Abbreviations: ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, T2D = Type 2 diabetes mellitus

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.

Algorithm Figure 1

https://www.endocrinepractice.org/article/S1530-891X(22)00090-8/fulltext#secsectitle0010



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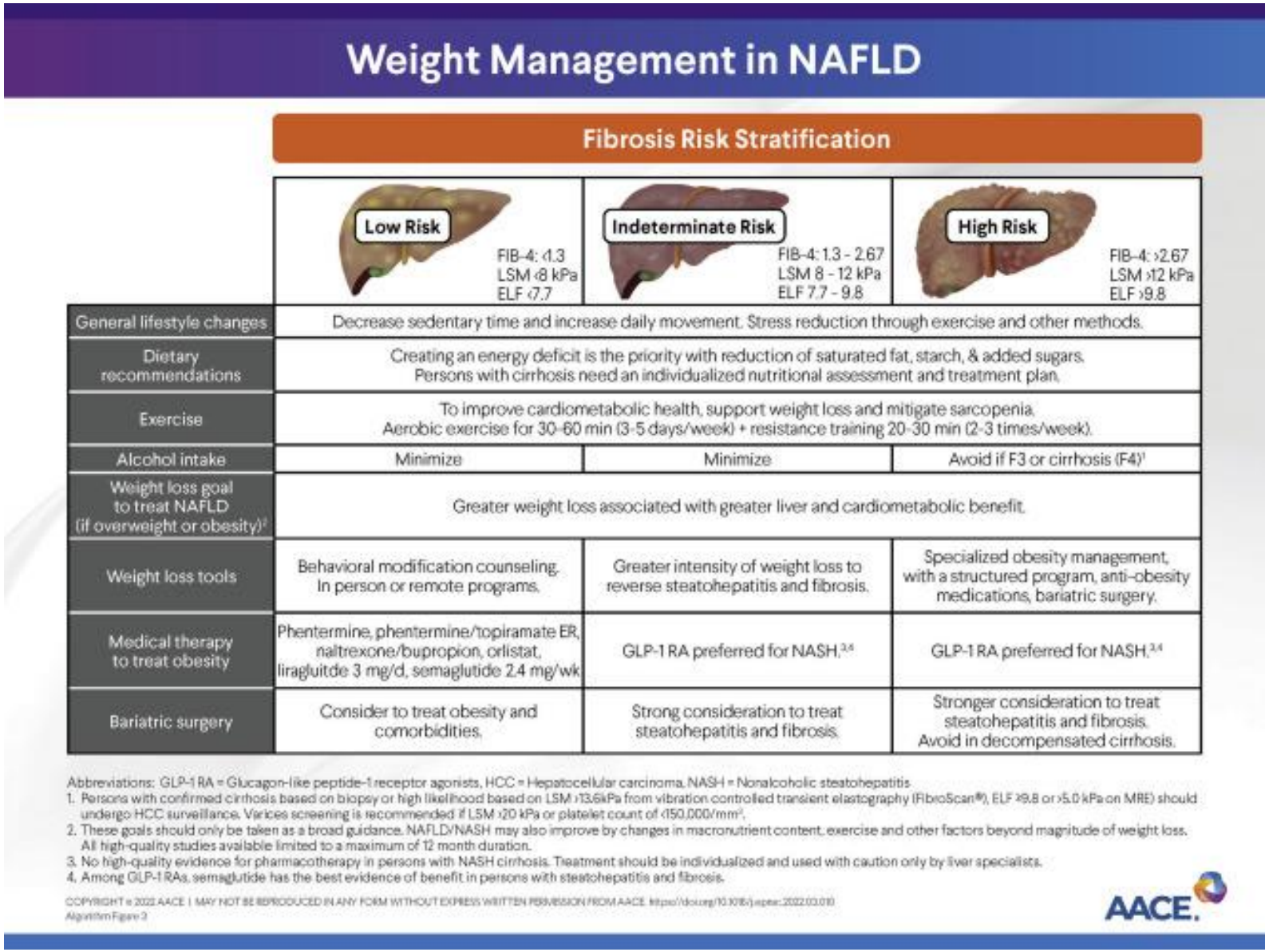
Weight Management in NAFLD



Fibrosis Risk Stratification

	Low Risk	Indeterminate Risk	High Risk
	FIB-4: <1.3 LSM <8 kPa ELF <7.7	FIB-4: 1.3 - 2.67 LSM 8 - 12 kPa ELF 7.7 - 9.8	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, liraglutide 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/mm³.
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.

Algorithm Figure 3

AACE.

https://www.endocrinepractice.org/article/S1530-891X(22)00090-8/fulltext#secsectitle0010

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.
3. Among GLP-1 RAs, semaglutide has the best evidence of benefit in persons with steatohepatitis and fibrosis.

Algorithm Figure 4

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WELL-AHEAD

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Project ECHO