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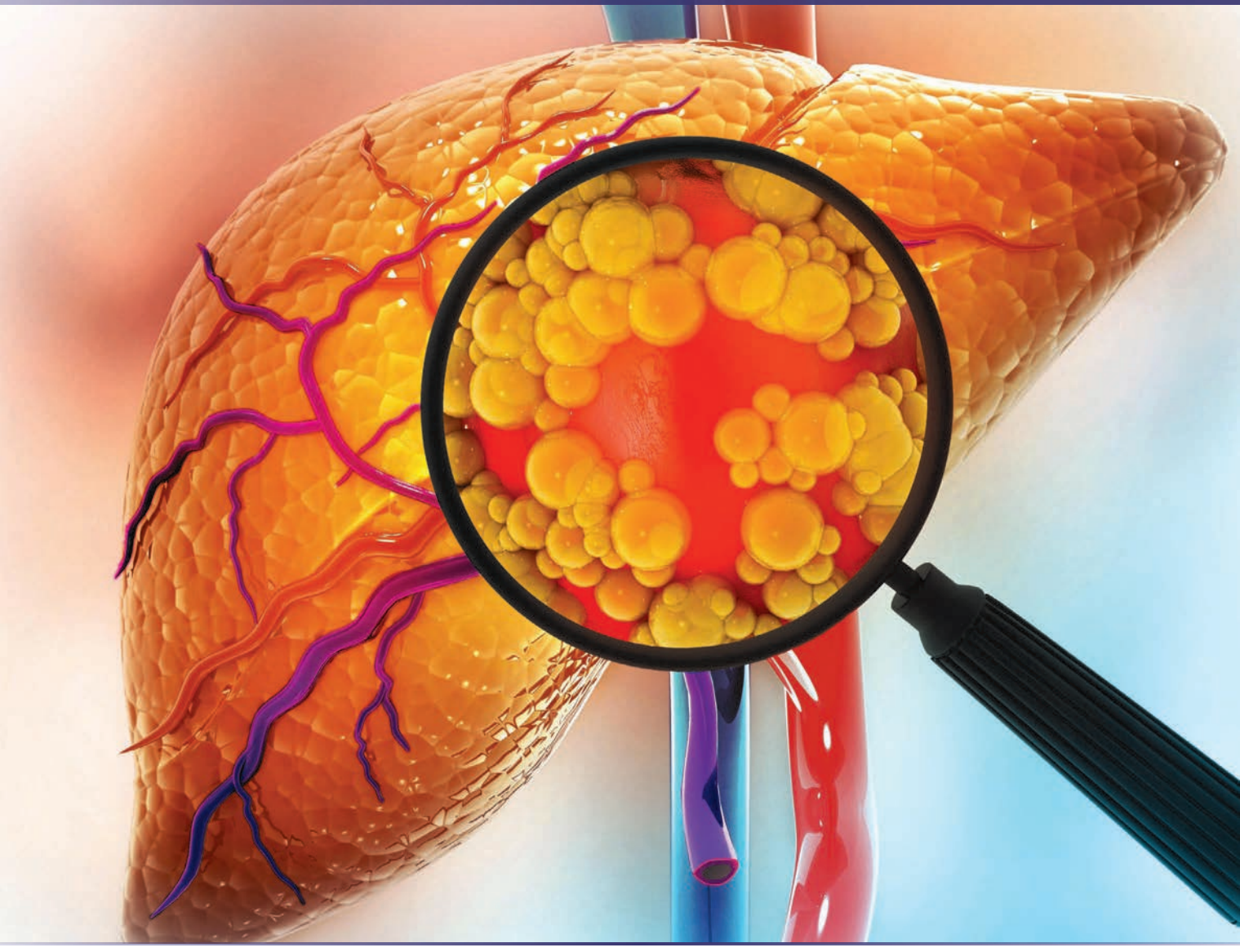

Clinical Consult in NASH: Are Your Patients at Risk?

Based on a Medscape Education Online Activity

CME INFORMATION

CME/ABIM MOC/CE
Release Date: 11/13/2023
Expiration Date: 11/13/2024

TARGET AUDIENCE

This activity is intended for primary care physicians, gastroenterologist, diabetologist & endocrinologists, nurse practitioners, and physician assistants.

GOAL STATEMENT

The goal of this activity is for learners to be better able to identify patients with risk factors for nonalcoholic steatohepatitis (NASH) and take appropriate next steps.

LEARNING OBJECTIVES

Upon completion of this activity, participants will:

Have increased knowledge regarding the
- Consequences of untreated NASH
- Evidence-based risk stratification criteria for patients with nonalcoholic fatty liver disease (NAFLD)

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Clinical Consult in NASH: Are Your Patients at Risk?

Based on a Medscape Education Online Activity

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ABSTRACT

Nonalcoholic steatohepatitis, or NASH,[a] is the most severe form of nonalcoholic fatty liver disease (NAFLD). If left untreated, NASH can develop into advanced liver disease, such as cirrhosis. Moreover, patients with NASH and cirrhosis are also at increased risk of developing hepatocellular carcinoma. Therefore, early detection and intervention are key components to prevent disease progression, particularly in the primary care setting where many patients with NASH are typically encountered.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a term used to describe a condition caused by the presence of fat in the liver among individuals who drink little to-no alcohol, and includes nonalcoholic steatohepatitis (NASH).[1,a] According to the American Association for the Study of Liver Diseases (AASLD), NASH, a component of NAFLD, is a liver disease marked by inflammation and cellular injury (ballooning) that may or may not be accompanied by fibrotic changes.[1] In the United States alone, it is estimated that the prevalence of individuals with NAFLD is ~80 million,[2,3] with NASH likely affecting ~20% to 30% of these individuals.[2,4] If left untreated, ~10% of patients with NASH may develop cirrhosis,[3] currently the 9th leading cause of death for Americans.[5] Consequently, NASH poses a significant health problem that must be addressed. Clinicians must remain vigilant because early diagnosis allows for appropriate and prompt interventions to be implemented, thus limiting the number of patients who develop cirrhosis and, therefore, optimizing clinical outcomes. Furthermore, in its earliest stages, NAFLD and NASH are usually asymptomatic.[1] As a result, diagnosis of NAFLD/NASH requires a high degree of vigilance. This is of germane interest to primary care physicians (PCPs) and other primary care health professionals, as research suggests they are most likely to first encounter and treat patients with NAFLD/NASH in their clinical practice.[6-8] As such, this article will focus on considerations and best practices for the early identification and diagnosis of NAFLD/NASH in the clinical setting.

CAUSES & RISK FACTORS OF NAFLD/NASH

In order to diagnose and treat NAFLD/NASH, healthcare professionals must be familiar with the causes and clinical risk factors associated with the condition. Comorbidities that place patients at an elevated risk for developing NAFLD include a spectrum of metabolic and cardiovascular diseases (CVD), such as obesity, type 2 diabetes, hyperlipidemia/dyslipidemia, and/or hypertension, collectively termed the metabolic syndrome.[9-11] Patient-related factors contributing to the risk of developing NAFLD include older age, Hispanic or Asian ethnicity, postmenopausal status in women, and comorbid conditions such as obstructive sleep apnea.[4,12-15]

Less common conditions associated with NAFLD include chronic hepatitis C infection, diseases that cause individuals to store fat improperly (endocrine disorders; eg, hypothyroidism, hypogonadism), and a history of using or being exposed to certain medications and substances, such as corticosteroids, chemotherapeutics (eg, tamoxifen), and antiarrhythmics. It is also important to note that low and moderate alcohol use can contribute to fatty liver disease progression and may increase the probability of advanced fibrosis.[1,8] Taken together, it is imperative that clinicians have a high vigilance for NAFLD and document a detailed medical history, perform a careful physical examination, and order appropriate diagnostic tests as part of the initial evaluation of patients at high risk of NAFLD.[1,8]

It is difficult to predict which patients with NAFLD will develop NASH. In fact, the distinction is determined by diagnostic liver biopsy,[1,8] which is uncommonly performed. Yet, the distinction is important because the portion of patients with NASH are the ones who are at most risk

[a]Recently, the AASLD published new guidance on updated nomenclature to describe fatty liver disease and includes the use of the terms metabolic dysfunction-associated steatohepatitis (MASH) and metabolic dysfunction-associated liver disease (MAFLD), to be more inclusive of patients with this condition independent of alcohol intake and pattern of usage. However, in this article, we will use the terms NASH and NAFLD for better clarity.

for complications of chronic liver disease and liver-related outcomes.[1]

CONSEQUENCES OF UNMANAGED NASH

Overall, the most common causes of death for patients with NAFLD are CVD, nonhepatic malignancy, and chronic liver disease.[1,16,17] As mentioned, patients with NAFLD who have NASH are at higher risk of developing cirrhosis if not adequately managed.[1] Patients with NAFLD/NASH-associated cirrhosis are also at elevated risk for developing hepatocellular carcinoma (HCC; NASH-related cirrhosis cumulative incidence rate for developing HCC, 2.4% over 7 years to 12.8% over 3 years).[18] Regarding CVD, patients with NAFLD/NASH have an elevated risk for future complications including coronary heart disease, heart failure, stroke, and arrhythmia.[19]

DETECTING AND MONITORING NASH IN THE CLINIC

Signs & Symptoms

Initial suspicion for NAFLD/NASH is established by considering the diagnosis in patients with risk factors for the condition, as mentioned above, and other clinical features that may present. This includes the detection of increased liver enzymes (up to 4x the upper limits of normal) or abnormal liver imaging (by ultrasonography or cross-sectional imaging, such as computed tomography [CT] or magnetic resonance imaging [MRI]).[1,20-22] It must be emphasized that normal levels of liver enzymes are frequently observed in patients with NAFLD/NASH, including those with advanced fibrosis, so the astute clinician cannot be misled.[1,23] Moreover, patients with NAFLD/NASH may present to the clinic with either very mild or nonspecific symptoms (eg, right upper quadrant pain or discomfort, fatigue, abdominal bloating, and sleep disturbances), but most have no symptoms at all—this has led to NAFLD/NASH being dubbed as the "silent liver disease."[24,25] Therefore, clinicians must be prudent in assessing each patient and exercise their best clinical judgment when managing patients at risk for NAFLD/NASH. Early recognition and prompt intervention are crucial to preventing or delaying the development of advanced liver disease. The AASLD recommends targeted screening for advanced fibrosis among high-risk populations such as those with T2D, obesity with metabolic complications, family history of cirrhosis due to NAFLD/NASH, or significant alcohol use.[1] Consensus recommendations from an expert panel assembled by the American Gastroenterological Association (AGA) also supports screening of individuals with evidence of steatosis on any imaging modality or those with elevated aminotransferases.[8]

Testing Modalities

In addition to physical examination and laboratory testing, clinicians have several techniques available for assessing and screening for the presence of NAFLD/NASH and its complications. The AASLD and the AGA expert panel recommend noninvasive testing (NIT) modalities for assessing hepatic fibrosis in patients with NAFLD in the primary care setting to screen patients for suspected fatty liver disease.[1,8] If a liver biopsy is unavailable so that NASH can be graded and staged in a patient with NAFLD, the chief factor that indicates if a patient with NAFLD/NASH is at increased risk for progressive liver disease is whether or not they are developing significant hepatic fibrosis. Although liver biopsy is the gold standard to determine if a patient has hepatic fibrosis, it is an invasive test and is plagued by significant complications, high cost, and other inherent limitations related to risk (invasiveness), resource utilization, and technical issues (sampling error, interobserver sample interpretation). Diagnostic tools for the initial diagnosis assessment of NAFLD/NASH are summarized below in **TABLE 1**.[26-31]

NITs

Specific NITs have been developed and use different combinations of patient demographics, biomarkers indicative of liver function, and/or imaging findings to yield a predictive measure of hepatic fibrosis that enables the risk stratification or prediction of adverse liver-related outcomes.[1,8,9,32-44] Commonly used NITs (summarized below in **TABLE 2**) can be subdivided into 3 different categories: simple scores, proprietary serum tests, and imaging techniques.

Once NAFLD is confirmed, clinicians should have a low threshold for referring patients to specialty care (eg, gastrointestinal specialist, hepatology) when there are elevated liver enzymes or when there is suspicion of significant fibrotic liver disease. When any NIT suggests at least S2 hepatic fibrosis (https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4), patients should be referred.[1,8,30,41] Patients with low risk can be followed by primary care.

Invasive Techniques

The use of liver biopsy should be reserved for specific clinical scenarios, mainly when the diagnosis is in doubt, or when NITs have yielded indeterminate results.[1,45] According to AASLD guidance, a liver biopsy may be considered in patients who might benefit the most (eg, those at elevated risk for NASH and advanced fibrosis) from having diagnostic and prognostic information available. Additionally, a biopsy may be used to determine whether a patient might benefit from pharmacologic treatment that aims primarily to improve liver disease.[1,9]

TABLE 1. Tools for Diagnosis of NAFLD and NASH[26-31]

Method	Sensitivity	Specificity	Comments
Liver enzyme testing[26]	• ALT: 45% • GGT: 63%	• 85% • 65%	• Not reliable for diagnosis
Ultrasound[27,28]	• 85% • Any degree: 61% • Cutoff ≥ 20% of fat: 100%	• 94% • 100% • 90%	• Inexpensive and accessible, but cannot distinguish fibrosis/steatosis
CT without contrast[29]	• Cutoff for significant steatosis using the liver/spleen ratio, > 30%: 79%	• 97%	• Better in morbid obesity, but affected by iron, fibrosis, and less accurate with less steatosis
MRI[30]	• Cutoff PDFF 6.4%, grade ≥ 1: 86% • Cutoff PDFF 17.4%, grade ≥ 2: 64%	• 83% • 96% • Raw specificity (83% cross-validated): 100%	• Detects mild steatosis, quantifies hepatic fat most accurately
Liver biopsy[31]	• Sensitivity for bridging fibrosis: 85%[a,b]	• Specificity for bridging fibrosis: 89%[a,b]	• The gold standard, but invasive and subject to sampling error

[a]Based on paired biopsies assessed with Brunt scores 3 and 4. Brunt scores 3 and 4 are defined in the publication as "bridging fibrosis."

[b]Study to assess the sampling error of liver biopsy and its impact on diagnosis and staging of NASH. Patients with NAFLD (n = 51) underwent percutaneous liver biopsy with 2 samples collected. The agreement between paired biopsy specimens was assessed by the percentage of discordant results and by the Kappa reliability test.

Abbreviations: ALT, alanine transaminase; CT, computed tomography; GGT, γ-glutamyl-transpeptidase; MRI, magnetic resonance imaging; PDFF, proton-density fat fraction.

ROLE OF THE MULTIDISCIPLINARY TEAM IN THE ASSESSMENT & MANAGEMENT OF NAFLD/NASH

As noted earlier, the multidisciplinary care team involved in the management of patients with NAFLD/NASH may include PCPs, advanced practice providers, as well as specialists such as gastroenterologists, endocrinologists, hepatologists, cardiologists, and surgeons.[1,8,46,47] In addition, nutritionists, dieticians, and behavioral medicine specialists are important members of the care team; the need for a health psychologist can be assessed on an individual basis.[1] These individuals must come together and collaborate to optimally address the needs and challenges of the patient. This includes developing a tailored approach or individual care plan suited to meet the clinical goals of the patient to manage their liver and associated comorbid conditions.[1,8]

CLINICAL PEARLS FOR THE CLINICIAN

Once a diagnosis of NAFLD/NASH is established, the multidisciplinary care team should work with the patient using a shared decision-making model to identify appropriate interventions.[1] According to current AASLD guidelines, patients with fatty liver on imaging, and low-risk fibrosis on NIT such as FIB-4 (FIB-4 index, < 1.3)[1] should be monitored in the primary care setting. The AASLD and AGA expert panel agree on more frequent testing for high-risk individuals: every 1 to 2 years in those with prediabetes/T2D or at least 2 metabolic risk factors, even if the initial FIB-4 score < 1.3 (AASLD) and annually in patients with T2D (AGA).[1,8] Lifestyle management interventions should be implemented, including alcohol abstinence, establishing a diet conducive to controlling serum glucose and lipids, and weight loss.[1] Patients should be followed with annual liver panel testing and screening for fibrosis with NIT methods (eg, FIB-4; elastography, when FIB-4 > 1.3).[1] However, such patients do not require referral to a specialist.

Patients with advanced liver disease are at increased risk for HCC. Although such patients should be followed by a specialist, it should be noted that, according to AASLD guidance, the standard of care is to implement screening for liver cancer using semiannual liver imaging (ultrasound, CT scan, or MRI). Serum alfa fetoprotein measurements every 6 months should also be considered.[48]

Recommendations & Emerging Approaches

While there are currently no US Food and Drug Administration–approved pharmacologic approaches to manage NAFLD/NASH, a few new and emerging agents show promise for treating patients with fatty liver disease.[1,8] The recently updated AASLD guidance recommends

TABLE 2. Commonly Used NITs for Assessing NAFLD/NASH[1,8,9,32-44]

Test Type	Simple Scores	Proprietary Serum Tests	Imaging Techniques
Clinical utility	Use information from standard liver tests and patient data	Test biomarkers associated with fibrosis stage	Focus on liver stiffness
What is the assay?	• FIB-4 (Fibrosis-4) test ○ Uses a combination of patient age, platelet count, AST, and ALT ○ Reference values[36]: ■ < 1.30, indicates a low risk for advanced fibrosis ■ 1.30 to 2.67, indicates intermediate risk for advanced fibrosis ■ > 2.67, indicates high risk for advanced fibrosis • NFS (NAFLD fibrosis score) test ○ Composite score of age, hyperglycemia, body mass index, platelet count, albumin, and AST/ALT ratio ○ Reference values[37]: ■ > -1.455, indicates absence of advanced fibrosis ■ > 0.675, indicates the presence of advanced fibrosis • APRI (aspartate aminotransferase/ platelet ratio index) test ○ Aspartate transaminase to platelet ratio ○ Reference values[38]: ■ 0.5, indicates fibrosis ■ 1.5, indicates cirrhosis	• Noninvasive blood test that measures 3 direct markers of fibrosis: hyaluronic acid (HA), procollagen III amino-terminal peptide (PIIINP), and tissue inhibitor of matrix metalloproteinase 1 (TIMP-1) ○ Reference values[39]: ■ 7.7, excludes fibrosis ■ 9.8, indicates fibrosis ■ 11.3, indicates cirrhosis • Blood test measuring alpha-2-macroglobulin, haptoglobin, GGT, apolipoprotein A1, total bilirubin, and ALT ○ Reference values[40]: ■ < 0.3, the probability of cirrhosis is low ■ 0.30 to 0.70, intermediate risk for cirrhosis ■ ≥ 0.70, indicates cirrhosis	• Transient elastography • MRE (magnetic resonance elastography)

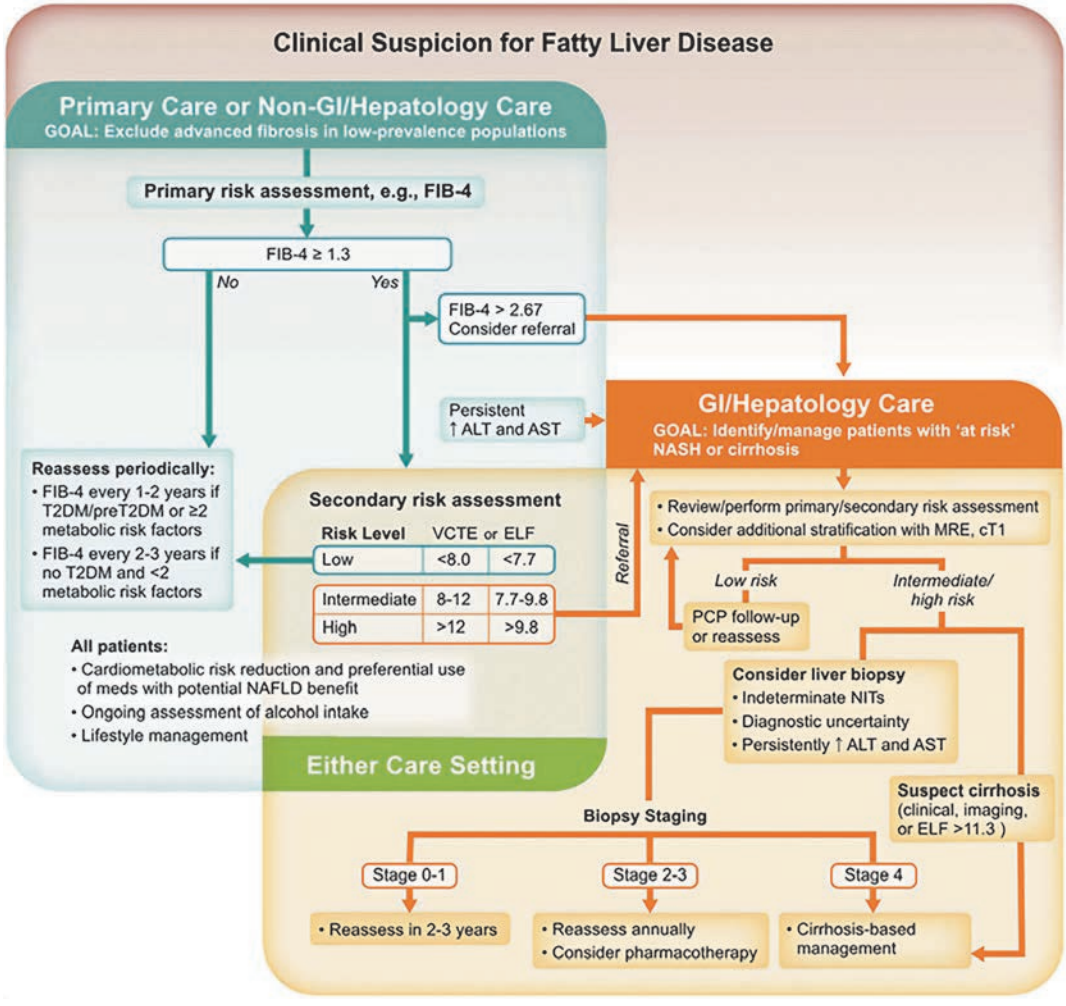
Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; GGT, γ-glutamyl-transpeptidase.

using daily vitamin E supplements (based on the phase 3 PIVENs randomized-controlled trial) in patients with confirmed NASH who do not have comorbid T2D or cirrhosis.[1,8,49] According to AASLD guidance, other agents that may be a good choice for individuals with NAFLD/NASH (+/- other comorbid conditions) include those with current indications for T2D and/or obesity, including pioglitazone (a peroxisome proliferator-activated receptor [PPAR]-γ agonist), liraglutide, semaglutide (glucagon-like peptide-1 receptor agonists [GLP-1RA]), tirzepatide (a glucagon-like peptide-1/glucose-dependent insulinotropic polypeptide receptor agonist), and sodium-glucose cotransporter-2 inhibitors.[1,9] It should be noted that the AASLD guidelines indicate that metformin, ursodeoxycholic acid, dipeptidyl peptidase-4, silymarin, and statins should not be used for the treatment of NASH, due to the lack of a meaningful histologic benefit with these agents. However, it is also important to note that statins are recommended for the management of CVD in patients with NAFLD/NASH.[1] Finally, the novel β-selective thyroid hormone receptor agonist, resmetirom, and the oral pan-PPAR agonist, lanifibranor, both in phase 3 clinical trials, aim to bring novel strategies into the pharmacologic armamentarium for managing patients with NASH in the near future.[50,51]

Final Thoughts

With newer technologies and advances in NAFLD/NASH research on the horizon, novel biomarkers and targeted therapies are expected to emerge and make their way into the clinic. Management will likely evolve to allow more

FIGURE 1. AASLD-Recommended Multidisciplinary Care Model for Diagnosing & Managing Patients With NAFLD[1]



Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; ELF, enhanced liver fibrosis test; FIB-4, Fibrosis-4; GI, gastrointestinal; MRE, magnetic resonance elastography; NAFLD, nonalcoholic fatty liver disease; NIT, noninvasive testing; PCP, primary care physician; T2DM, type 2 diabetes; VCTE, vibration-controlled transient elastography.

Rinella ME, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology*. 2023;77:1797-1835.

individualized approaches for the future treatment of patients with NAFLD/NASH. These advances will likely lead to rapid changes in the diagnostic and therapeutic paradigm for patients with NAFLD, providing clinicians and collaborating specialists with better tools to control this increasingly problematic global health concern (see **FIGURE 1** below for AASLD's multidisciplinary care model for identifying and managing patients with NAFLD)[1]; similar guidance has been published by the AGA expert panel on the management of NAFLD/NASH.[8] ●

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