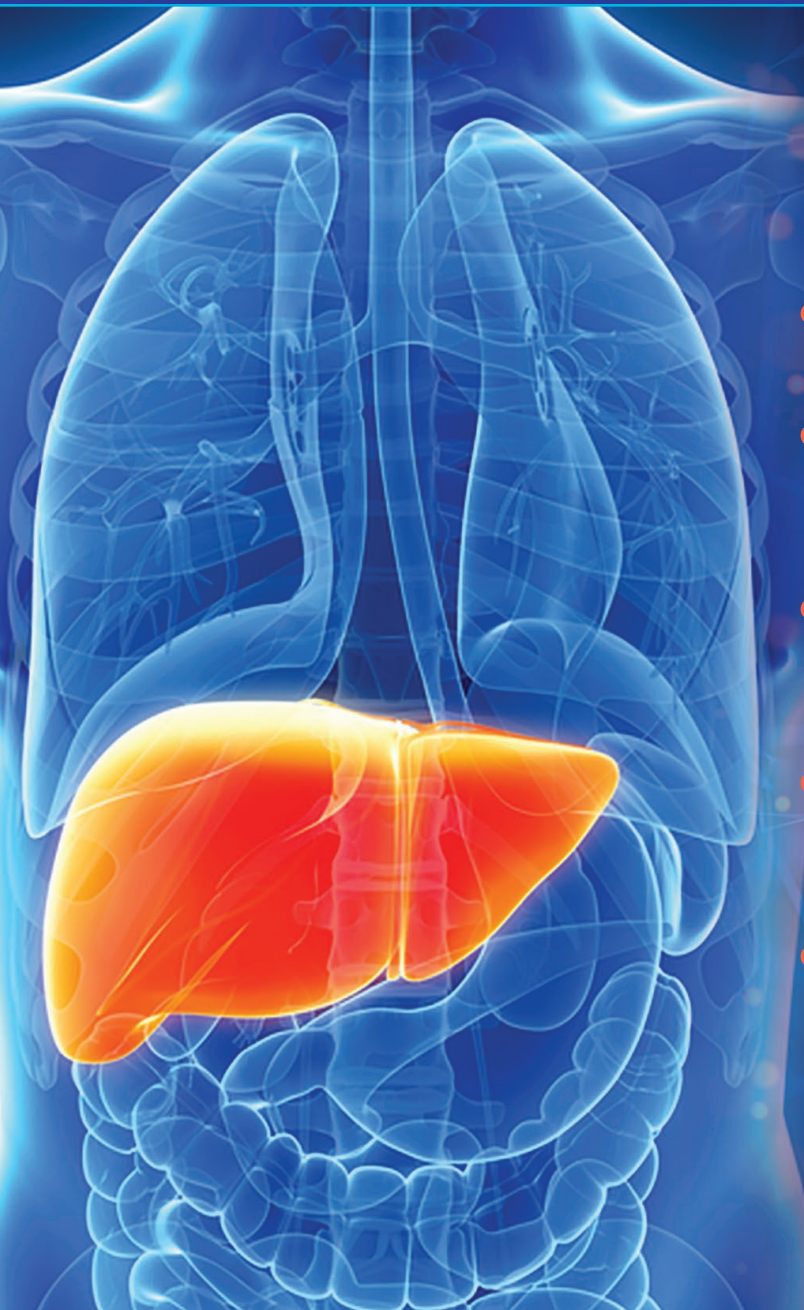


NASH: Emerging Diagnosis, Identification of Complications, and Evolving Treatment Strategies



- **Introduction**
- **What Is NASH, and Why Is Its Prevalence Increasing?**
- **Diagnosing and Assessing NAFLD/NASH**
- **Looking Ahead: A Promising Pipeline**
- **Managing NAFLD/NASH**

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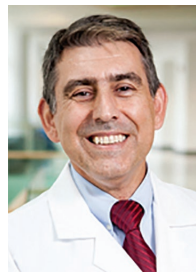
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Introduction

Nonalcoholic fatty liver disease (NAFLD) is now the most common liver disorder in Western countries and is a major cause of liver disease worldwide. Prevalence in the United States is estimated to be between 10% and 30%.¹ Actual figures may be higher, however, since the only way to conclusively diagnose NAFLD and its most progressive form—nonalcoholic steatohepatitis (NASH)—is by liver biopsy. The annual direct medical costs for NAFLD in the United States alone are estimated at \$103 billion.²

Much of the reason for the increasing incidence and prevalence of NAFLD is its inextricable connection with metabolic comorbidities, including obesity, type 2 diabetes (T2D), hyperlipidemia, hypertension, and metabolic syndrome (MetS). Many patients with NAFLD are also at high risk for cardiovascular disease.

Approximately 60% of biopsied patients diagnosed with NAFLD also have NASH.³ NASH—which can progress to cirrhosis, liver cancer, liver failure, and death—is now the second most common indication for orthotopic liver transplant in the United States.⁴ It is poised to overtake chronic hepatitis C virus infection as the leading cause of transplantation, as a large number of patients with hepatitis C are being cured by newer antiviral regimens.⁴⁻⁶

Accurate diagnosis and optimal management of NAFLD/NASH have been hindered by a number of factors. There are no reliable screening tools. Clinicians might not be up to date with screening algorithms and practice guidelines. Approaches for referring patients to specialists are often ad hoc. And as of this writing (June 2019), no pharmacologic agents are approved by the US Food and Drug Administration for the treatment of NAFLD and NASH, although, as discussed below, promising preliminary data on emerging agents have been published.

As the epidemics of metabolic entities such as obesity, T2D, MetS, and dyslipidemia continue to grow, so will the clinical and economic burden of NAFLD/NASH. With a number of promising agents for these diseases in late stages of the development pipeline, identification of appropriate patients for management is more important than ever.

In this supplement, we will consider several key issues: why the incidence of NAFLD/NASH is increasing, what we can do to stem the tide, which populations—if any—should be screened, which methods are most appropriate for noninvasive evaluation of patients, and what we need to know about available and emerging therapies.

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Target Audience

This activity has been designed to address the educational needs of physicians in the field of gastroenterology and hepatology who are actively treating patients with nonalcoholic steatohepatitis (NASH). Primary care physicians, physician assistants, and nurse practitioners who are treating patients with NASH will also benefit.

Educational Needs

The increasing global prevalence of nonalcoholic fatty liver disease (NAFLD) and NASH parallels the rise in the incidence of metabolic syndrome and its components, especially obesity (including overweight). NAFLD/NASH has become the second leading cause of liver transplantation in the United States and may soon become the leading cause. Clinicians should be aware of the latest scientific findings about the risk factors for, and pathophysiology of, NAFLD/NASH. Understanding the mechanisms of disease is the basis for designing and deploying an appropriate therapeutic strategy—including lifestyle and use of medications—to slow its progression and improve patient outcomes. Clinicians should also be familiar with new agents now in clinical trials that may provide more options for managing NAFLD/NASH in the near future.

Learning Objectives

At the conclusion of this program, participants should be better able to:

- Describe at least two factors contributing to the increasing prevalence of NAFLD/NASH
- Explain the process for screening for NAFLD/NASH in patients with metabolic risk factors
- Identify a practical stepwise approach to the evaluation of patients with suspected NAFLD/NASH that includes referral to hepatologists
- Describe a comprehensive management strategy for NAFLD/NASH that incorporates lifestyle strategies and approved therapeutic agents
- Discuss the mechanisms of action and trial data on emerging therapeutic agents for the management of NAFLD/NASH

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What Is NASH, and Why Is Its Prevalence Increasing?

According to published guidelines, NAFLD is defined as excessive hepatic fat accumulation with insulin resistance, steatosis in >5% of hepatocytes (by histologic analysis or proton density fat fraction >5.6% by proton magnetic resonance spectroscopy or quantitative fat/water selective magnetic resonance imaging), and the absence of secondary causes of hepatic fat accumulation (Table 1).^{6,7}

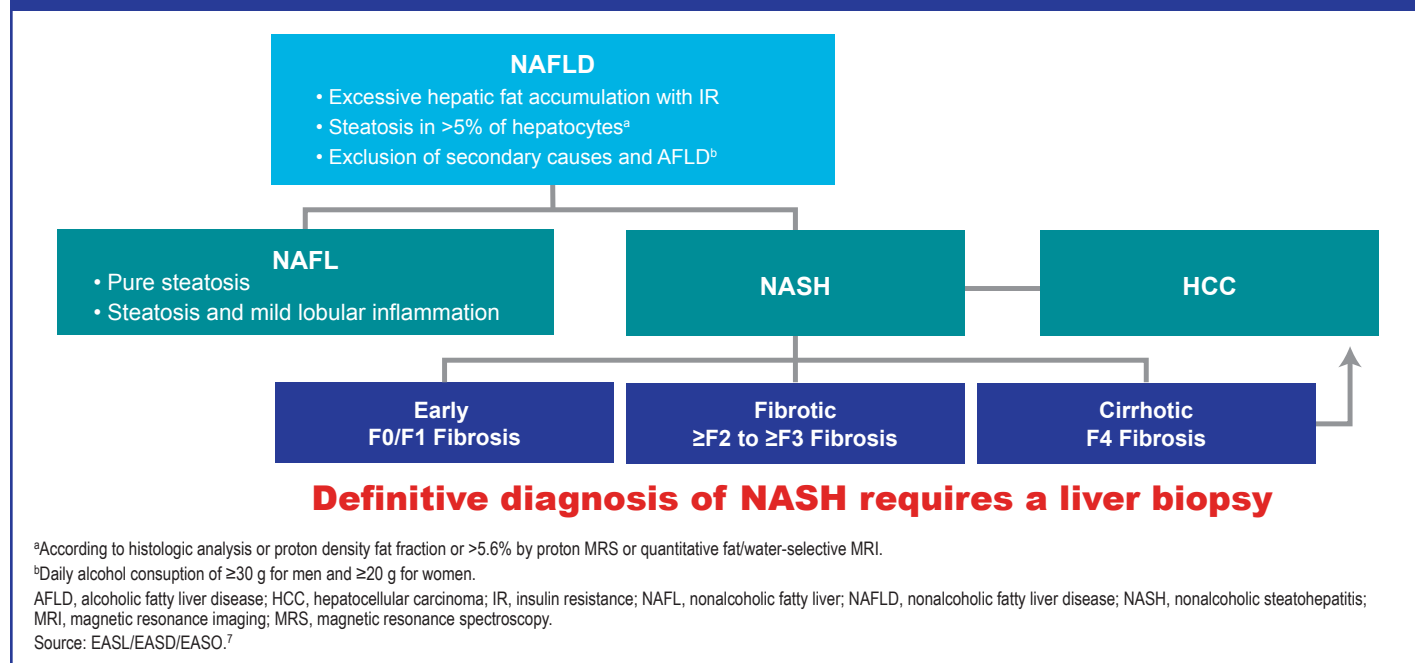
NAFLD encompasses both nonalcoholic fatty liver (NAFL), which is either pure steatosis or steatosis and mild lobular inflammation, and NASH, which is defined as the presence of ≥5% hepatic steatosis (HS) and inflammation with hepatocyte injury (eg, ballooning) with or without fibrosis (Figure 1).^{6,7} Up to about 40% of those with steatosis will develop NASH with mild fibrosis within 8 to 13 years (Figure 2).⁸

Table 1. Secondary Causes of Steatosis

Macrovascular	Microvascular
• Abetalipoproteinemia • Excessive alcohol consumption (≥30 g for men, ≥20 g for women) • Hepatitis C virus infection (genotype 3) • Lipodystrophy • Parenteral nutrition • Petrochemicals (eg, vinyl chloride) • Starvation • Steatogenic medications (eg, amiodarone, corticosteroids, methotrexate, tamoxifen) • Wilson disease	• Acute fatty liver of pregnancy • HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count) • Inborn errors of metabolism (eg, cholesterol ester storage disease, lecithin-cholesterol acyltransferase [L-CAT] deficiency, Wolman disease) • Medications (eg, valproate, antiretrovirals) • Reye syndrome

Source: Chalasani N et al.⁶

Figure 1. What Is NASH (vs NAFLD and NAFL)?



According to a 2013 survey of Wisconsin-based primary care physicians, 85% underestimate the population prevalence of NAFLD and less than half (46%) screen patients with diabetes and obesity for NAFLD.

– Said A et al. Ann Hepatol. 2013;12:758-765.

NASH and MetS: Inextricably Linked

The prevalence of NAFLD/NASH is increasing chiefly because of a parallel rise in the prevalence of MetS and its components. So closely linked are NAFLD and MetS that current practice guidelines for the management of NAFLD recommend that all patients with steatosis be screened for MetS, independent of liver enzyme levels, and that all patients with obesity or MetS be screened for NAFLD with liver enzymes tests and/or ultrasound (Table 2).^{6,7}

Obesity (including overweight) is the most common and well-documented risk factor for NAFLD.⁶ According to the Centers for Disease Control and Prevention, about 40% of adults aged ≥20 years are obese; that percentage rises to almost 72% when those who are overweight are

included.⁹ Furthermore, obesity affects about 20% of adolescents aged 12 to 19 years, 18% of children aged 6 to 11, and 14% of children aged 2 to 5 years.⁹

More than 95% of patients undergoing bariatric surgery have NAFLD.^{6,10} Similarly, up to two-thirds of patients with T2D and about half of people with dyslipidemia have NAFLD (Figure 3 on page 6).^{6,10-14}

In addition to increasing the risk for liver transplantation, NAFLD/NASH places patients at greater risk for hepatocellular carcinoma (HCC). Cirrhosis is a preneoplastic condition, and obesity and T2D are known risk factors for HCC regardless of the presence of cirrhosis.¹⁵ NAFLD accounted for 35% of all HCC cases in 2010 and is rapidly becoming the leading cause of HCC in developed countries.^{16,17}

Table 2. Guideline Recommendations for NAFLD Screening

	AASLD ¹	EASL ²
Population screening	✗	✗
With diabetes/obese	✗	✓
Family members	✗	✗

• All individuals with steatosis should be screened for features of MetS, independent of liver enzyme levels (Evidence Level A1)
• Because NAFLD is the main reason for unexpectedly elevated liver enzymes, all individuals with persistently abnormal liver enzyme levels should be screened for NAFLD (A1)
• In patients with obesity or MetS, screening for NAFLD by liver enzyme testing and/or ultrasound should be part of their routine workup. In high-risk individuals (eg, age ≥50 years, T2D, MetS), case finding of advanced disease (ie, nonalcoholic steatohepatitis with fibrosis) is advisable (A2)
AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; NAFLD, nonalcoholic fatty liver disease.
Sources: 1. Chalasani N et al⁶; 2. EASL/EASD/EASO.⁷

Figure 2. The Path to Cirrhosis: Natural History of NAFLD Over 8-13 Years

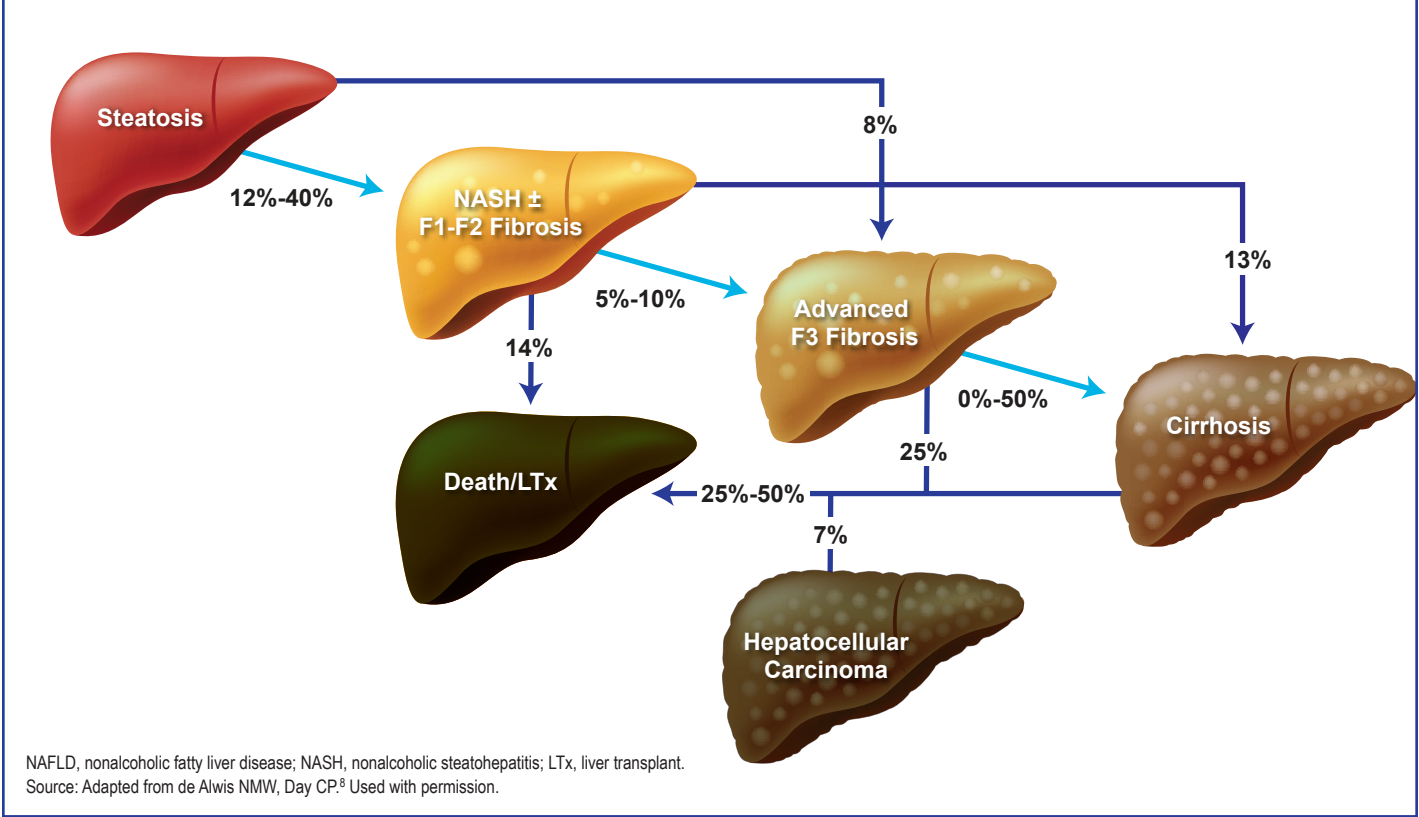
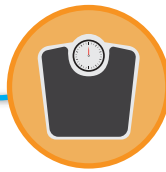


Figure 3. Why Is NASH Increasing?

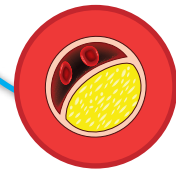
T2D, Obesity, Hyperlipidemia: A Perfect Storm



**Up to two-thirds
of those with
T2D have NAFLD¹**



Obesity
(most common risk factor for NAFLD)
**Up to 95% of those undergoing
bariatric surgery have NAFLD^{2,3}**



**About 50% of those
with hyperlipidemia
have NAFLD^{4,5}**

NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; T2D, type 2 diabetes.

Sources: Adapted from 1. Chalasani N et al⁶; 2. Sasaki A et al¹⁰; 3. Subichin M et al¹²; 4. Assy N et al¹³; 5. Wu KT et al.¹⁴

A Genetic Component

Lifestyle factors—especially sedentary behavior and consuming a high-calorie Western diet that includes excess saturated fats, refined carbohydrates, sugar-sweetened beverages, and high fructose intake—play a significant role in the development of weight gain and obesity, dyslipidemia, T2D, and, in turn, NAFLD/NASH. But genetics also plays a role.

Perhaps the most-researched and best-supported genetic association is with *PNPLA3*, the presence of which can lead to increased triglyceride accumulation and fibrosis.¹⁸ Krawczyk and colleagues found that the *PNPLA3* genetic variant was significantly associated with the risk of developing steatosis grades S2 and S3 and fibrosis stage F2 to F4.¹⁹ Other researchers have found a connection between the variant and an increased risk for the development of HCC.^{20,21}

Another important genetic association is with *TM6SF2*, which is associated with increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), and intrahepatic triglyceride content, but lower serum triglyceride levels.¹⁸

People with the *TM6SF2* gene variant are more prone to developing NAFLD involving advanced fibrosis, but they are less prone to cardiovascular disease.

According to European practice guidelines, carriers of the *PNPLA3* I148M and the *TM6SF2* E167K variants may have NAFLD that is not associated with features of insulin resistance. Nevertheless, because these individuals have a higher liver fat content and an increased risk for NASH, practitioners may consider genotyping in selected patients, although doing so is not universally recommended.⁷

Additional variants, such as the glucokinase regulatory gene (*GCKR*), have been reported to contribute to the development of NASH and fibrosis.²² Connections with other variants, such as *MBOAT7*, are not as clear.^{23,24}

Genetic factors help to explain the existence of “lean NAFLD,” or NAFLD in the presence of a body mass index (BMI) <25 kg/m². The prevalence of lean NAFLD in the United States is approximately 7.8%, and lean NAFLD makes up about 17% of all NAFLD cases.²⁵

NASH

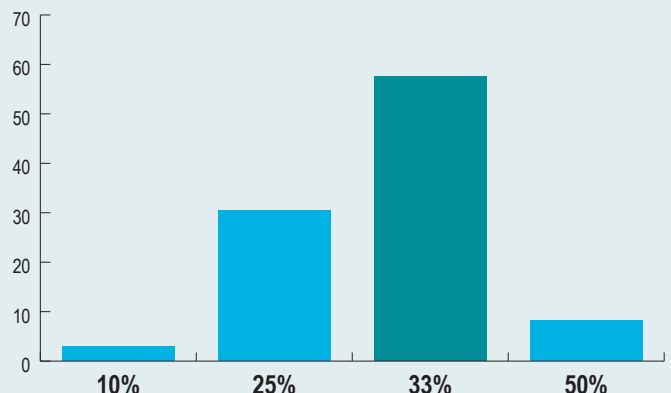
Where We Are and Where We Need to Be

In March 2019, the educational material in this supplement was presented by the author, Nikolaos Pyrsopoulos, MD, in a satellite symposium at the 6th Annual Digestive Diseases: New Advances Conference in Philadelphia, Pennsylvania. Among the approximately 100 attendees were gastroenterologists, primary care physicians, nurse practitioners, and physician assistants involved in the diagnosis, evaluation, management, and treatment of patients with digestive diseases.

As shown in this section, data collected from learners during the symposium revealed gaps in their knowledge of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH) and assessed their confidence in their ability to evaluate and manage patients with these conditions.

More than 40% of learners were unaware that one out of three Americans has NAFLD.

Q. What percentage of the US has nonalcoholic fatty liver disease (NAFLD)?



Diagnosing and Assessing NAFLD/NASH

Many clinicians find it challenging to diagnose and assess NAFLD/NASH. One reason is that patients do not exhibit symptoms until the latest stages of disease. Also, not all clinicians recognize the significance of metabolic risk factors. Contributing to the problem is the lack of proven cost-effective, noninvasive screening tools. Although liver biopsy is the gold standard for the diagnosis of steatohepatitis and fibrosis in patients with NAFLD, it is invasive, costly, associated with inherent risk, and has limitations in terms of sampling error.^{6,26}

Worse, while many (57%) gastroenterologists and hepatologists rely on elevated serum liver enzymes to determine the need for liver biopsy, experts agree that enzyme assays are not useful in diagnosing NAFLD.²⁷ In fact, the majority of patients with NAFLD have normal aminotransferase levels; normal levels do not rule out advanced disease.²⁸

And although imaging studies (ie, ultrasound, computed tomography [CT], magnetic resonance imaging [MRI], and transient elastography [TE]) are more sensitive, they can be unreliable at detecting low levels of disease. As such, their utility as screening tools is, at best, unproven.⁶

An analysis using a Markov model and involving 50-year-old adults looked at whether screening all individuals with T2D makes sense.²⁹ The researchers determined that, even though screening for NASH decreased the number of individuals who developed cirrhosis by 12.9% and resulted in an 11.9% decrease in liver-related deaths, such screening in all people with T2D was not cost-effective because of the adverse effects of currently available therapies.²⁹ They surmised that as better-tolerated, more-effective treatments for NASH become available, screening for NASH will become cost-effective.

Neither the American Association for the Study of Liver Diseases (AASLD) nor the European Association for the Study of the Liver

(EASL) recommend population screening or screening of family members for NAFLD (Table 2 on page 5).^{6,7} Still, the European practice guidelines state that it is important to identify NASH—particularly when it is associated with advanced fibrosis—in patients at risk (eg, age >50 years, T2D, or MetS) because of the prognostic implications.⁷ Up to one-third of patients with NASH progress to liver cirrhosis and other liver-related complications, such as HCC.²⁶

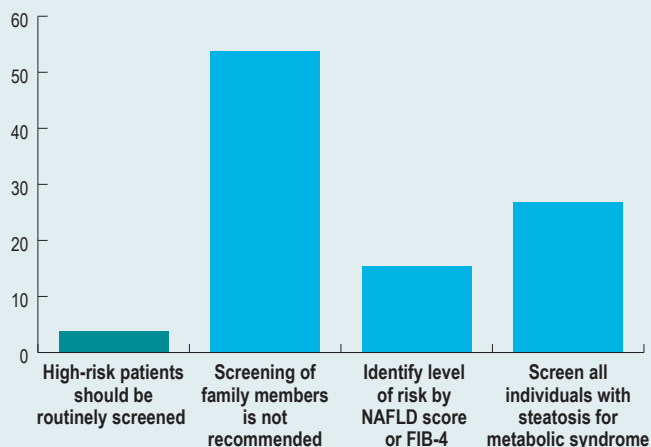
Survey Says: Confusion Abounds

- A recent national survey assessed awareness of NASH and associated practice patterns among US-licensed primary care physicians (PCPs) and specialists. Results showed that, while nearly half (49%) of the 152 PCPs who responded reported they were aware of both NAFLD and NASH, they were unaware of the differences between the two conditions.¹
- Despite their lack of awareness, 58% of the PCPs were treating patients with either of these entities; PCPs who said they were unfamiliar with NASH reported treating an average of 3.7 patients and said that they would continue to do so.¹
- Although specialists were generally more knowledgeable about NAFLD/NASH, not all specialists reported that they were familiar with and following current diagnostic and treatment guidelines.²

References: 1. Polanco-Briceno S, Glass D, Stuntz M, Caze A. Awareness of nonalcoholic steatohepatitis and associated practice patterns of primary care physicians and specialists. *BMC Res Notes*. 2016;9:157. 2. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2018;67:328-357.

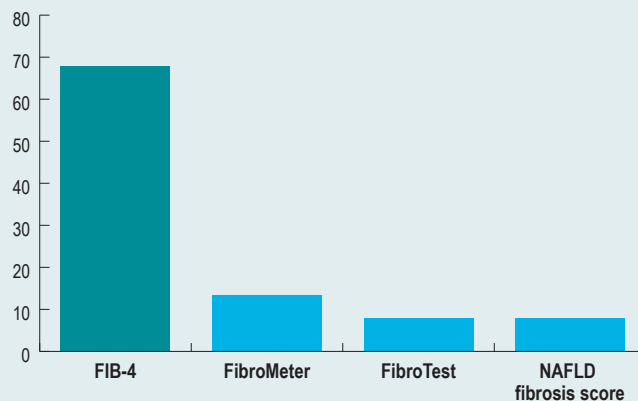
Very few learners were aware that screening of high-risk patients is not a current strategy recommended by the American Association for the Study of Liver Diseases (AASLD).

Q. Which of the following approaches is not one of the current strategies recommended by the AASLD for the diagnosis of NAFLD?



However, most learners correctly identified FIB-4 as the panel with the highest sensitivity for predicting fibrosis in NAFLD.

Q. Which of the following diagnostic panels has the highest sensitivity for predicting fibrosis in NAFLD?



continued on page 13

A survey by Rinella et al reported that liver biopsy is performed less often than needed for making treatment decisions by both gastroenterologists and hepatologists; only 24% of respondents routinely performed liver biopsy in patients with suspected NAFLD.¹ Both groups of specialists rely on elevated aminotransferase levels to identify patients for biopsy, and they perceive that biopsy in many cases is unnecessary because results will not alter management.

Reference: Rinella ME, Lominadze Z, Loomba R, et al. Practice patterns in NAFLD and NASH: real life differs from published guidelines. *Therap Adv Gastroenterol.* 2016;9:4-12.

In addition, the amount of fibrosis at the time of diagnosis is the most important determining factor of mortality in patients with NAFLD/NASH.³⁰ People with simple steatosis rarely die of liver-related causes, whereas those with NASH have an approximate 3-fold increase in liver-related mortality (from 1.7% to 8.6%).³¹ And with potent antifibrotic agents for the treatment of NASH on the horizon, accurately assessing liver fibrosis becomes even more relevant for identifying appropriate candidates for treatment and clinical trials.²⁶

Noninvasive Diagnosis

Noninvasive diagnosis of NAFLD relies largely on either predictive models or the identification of biomarkers.

As for predictive models, the NAFLD Fibrosis Score (NFS) (naflscore.com) and the FIB-4 Index are commonly used tools. The NFS calculates the likelihood of fibrosis using age, BMI, the presence or absence of impaired fasting glucose/diabetes, and levels of AST, ALT, platelets, and albumin.³² According to the original investigation of the method, by applying a low cutoff score of -1.455 , advanced fibrosis can be accurately excluded (negative predictive values of 93% and 88% in the estimation and validation groups, respectively).³² By applying a high cutoff score of $+0.676$, the presence of advanced fibrosis can be accurately diagnosed (positive predictive value of 90% and 82% in the estimation and validation groups, respectively).³² As a result, the authors of the original investigation indicated that by applying this model, a liver biopsy was avoided in 549 (75%) of 733 patients; prediction was correct in 496 cases (90%).³²

Similarly, the FIB-4 calculator uses patient age, AST and ALT levels, and platelet count to estimate the extent of liver scarring. A FIB-4 score <1.45 has a negative predictive value of 90% for advanced fibrosis and a sensitivity of 70%. These patients require nothing more than retesting every 2 years. A score >3.25 has 97% specificity and a positive predictive value of 65% for advanced fibrosis. These patients optimally should be evaluated for liver biopsy. In the patient cohort in which the formula was first validated, at least 70% of patients had values <1.45 or >3.25 . These individuals may have avoided liver biopsy with an overall accuracy of 87%.³³ It is the approximately 30% of patients whose results fall between the two values who may or may not have bridging fibrosis and for whom the need for liver biopsy is unclear.

With regard to the determination of serum biomarkers, the Enhanced Liver Fibrosis (ELF) panel is not currently available in the United States. Clinicians in this country can use the FibroMeter test, which determines the existence and extent of fibrosis based on the age and weight of the patient and levels of AST, ALT, platelets, ferritin, and glucose. Reported sensitivity and specificity are 79% and 96%, respectively.³⁴

Another alternative is FibroSURE (aka FibroTest). This test uses 10 serum markers (alpha2-macroglobulin, ALT, apolipoprotein A1, AST, GGT, glucose, haptoglobin, total bilirubin, total cholesterol,

and triglycerides) to calculate scores for fibrosis, steatosis, and NASH. Reported sensitivity and specificity are 77% and 98%, respectively.³⁵

Vibration-controlled transient elastography (VCTE) is the technology used by the FibroScan device to assess liver stiffness. Such devices use pulse echo ultrasound to measure the speed with which a mechanically induced 50 Hz frequency shear wave passes through the liver. High shear wave speed correlates with high liver stiffness. Tapper et al reported that the optimal liver stiffness measurement cutoff for advanced fibrosis was 9.9 kilopascals with 95% sensitivity and 77% specificity, but 27% of the patients had unreliable results.³⁶ Another study yielded a lower failure rate of 10.5%.³⁷

Magnetic resonance elastography (MRE) is another noninvasive technique that is MRI-based and that uses a vibration source to produce low-frequency mechanical waves in the liver to generate quantitative images showing tissue stiffness. In one study, MRE was superior to VCTE at identifying fibrosis $\geq$ stage 2, but the methods performed equally well at identifying fibrosis $\geq$ stage 3.³⁷

Other Imaging Methods

Steatosis should be documented whenever NAFLD is suspected. Ultrasound, which is less expensive than the gold standard MRI, may be used for this purpose, although it is not very sensitive with low levels of disease or high BMIs. Nevertheless, the European guidelines recommend it as a first-line diagnostic procedure for imaging of NAFLD, stating that serum biomarkers and scores may be used as alternatives when imaging is not available or feasible.⁷

Limited Guidance

As stated earlier, fibrosis is the most important prognostic factor in NAFLD/NASH. The European practice guidelines indicate that biomarkers, fibrosis scores, and TE are acceptable noninvasive procedures to identify those at low risk for advanced fibrosis/cirrhosis.⁷ These guidelines also state that the NAFLD Activity Score (NAS) should not be used to diagnose NASH, but rather to evaluate disease severity after diagnosis.

Similarly, the AASLD guidelines report that the NFS and the FIB-4 Index “are clinically useful tools for identifying patients with NAFLD that have a higher likelihood of having bridging fibrosis (stage 3) or cirrhosis (stage 4).”⁶ AASLD also notes that VCTE and MRE are clinically useful tools for identifying advanced fibrosis in patients with NAFLD.

When to Refer Patients for Biopsy or Management

One challenge in knowing when to refer patients for liver biopsy is that many of the methods used to diagnose and assess steatosis and fibrosis are limited by cost, availability, and accuracy. Different methods use different threshold values to indicate the degree of fibrosis. Although serum biomarkers that can help clinicians monitor the efficacy of treatment are becoming available, they often fail to discriminate lower levels of fibrosis. With no one single comprehensive noninvasive method available to accurately determine the presence and extent of fibrosis, practitioners often find themselves piecing together clues from the patient's history and physical exam, lab results, imaging findings, and assessment scores.

As a result, the referral of patients with NAFLD/NASH usually involves an ad hoc approach, which often means that patients with advanced disease are overlooked while patients with minimal disease are referred unnecessarily.³⁸ That the prevalence of advanced fibrosis in people at risk for NAFLD is only about 5% underscores the need for accurate and appropriate referral pathways from primary to specialist care.³⁸

A reasonable strategy is to reserve liver biopsy for cases where there is a high suspicion of steatohepatitis or advanced fibrosis/cirrhosis or to rule out coexisting/alternative liver disease.

Looking Ahead: A Promising Pipeline

Many potential new agents for NAFLD/NASH are on the horizon. One class of investigational agents includes agonists of the bile acid–FXR axis (eg, obeticholic acid [OCA]). Other categories include peroxisome proliferator-activated receptor (PPAR) agonists, eg, elafibranor; pan-caspase inhibitors, eg, emricasan; immune modulators such as cenicriviroc; antifibrotics such as selonsertib, which is an apoptosis signal-regulating kinase 1 inhibitor, and simtuzumab, a monoclonal antibody that binds to lysyl oxidase (LOX)-like 2; and fibroblast growth factor analogs such as pegbelfermin (*BMS-986036*), a PEGylated human fibroblast growth factor 21 (FGF21) analog, and MK-3655 (NGM313), a humanized monoclonal antibody activator of beta-Klotho/fibroblast growth factor receptor 1c. More details on these investigational agents follow.

Given the complex pathophysiology of NASH, several emerging therapeutics involve combinations of agents, rather than singular compounds, as a strategy for simultaneously targeting different aspects of the disease. One example is the combination of selonsertib and simtuzumab.

Obeticholic Acid

OCA is a modified version of a bile acid that targets the FXR axis as an agonist (**Figure 4**).³⁹ It has been approved by the US Food and Drug Administration since 2016 for the treatment of primary biliary cholangitis in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.

OCA was first found to improve NAFLD histology and to reduce disease activity in the FLINT (Farnesoid X Nuclear Receptor Ligand Agonist Obeticholic Acid for Noncirrhotic, Nonalcoholic Steatohepatitis) trial.⁴⁰ This double-blind, placebo-controlled, parallel-group, randomized 72-week trial, conducted at US medical centers and involving patients with confirmed noncirrhotic NASH, compared treatment with OCA 25 mg/d (n=141) to that with placebo (n=142). The primary endpoint—a decrease in NAS by ≥ 2 points without worsening of fibrosis—was met in 45% of the OCA group and in 21% of the placebo group. OCA improved ALT, AST, bilirubin, fibrosis, GGT concentrations, and weight, but worsened alkaline phosphatase,

high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and total cholesterol. Adverse events were mild to moderate and similar between the two groups with the exception of pruritus; 23% of patients in the OCA group had pruritus vs 6% in the placebo group.⁴⁰

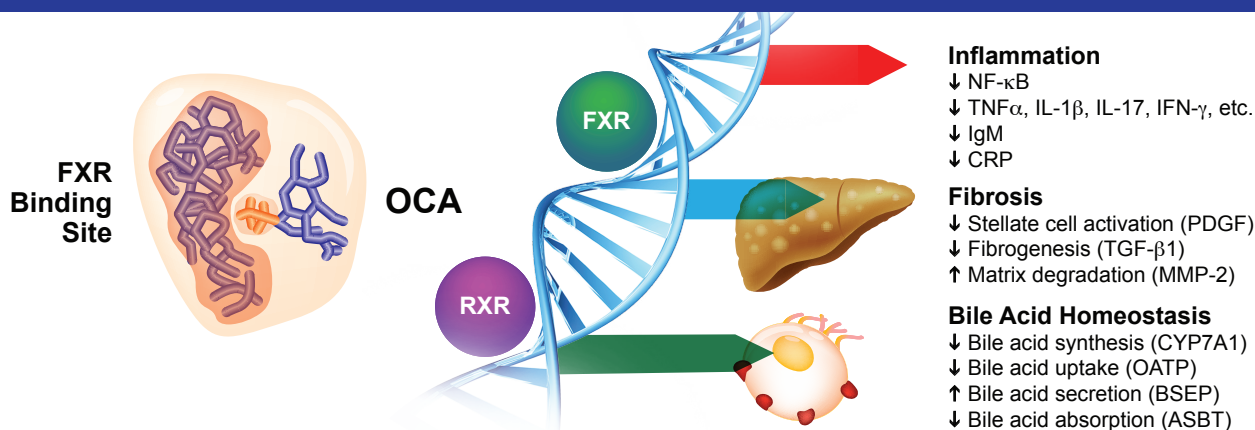
OCA is being studied in two ongoing phase 3 clinical trials. In the first and largest successful pivotal phase 3 study in patients with liver fibrosis due to NASH to date, REGENERATE (Randomized Global Phase 3 Study to Evaluate the Impact on NASH With Fibrosis of Obeticholic Acid Treatment), a double-blind, placebo-controlled, multicenter trial, is assessing the safety and efficacy of OCA on liver-related clinical outcomes in patients with NASH and fibrosis.^{41,42} Top-line results revealed in February 2019 and reported at the International Liver Congress 2019 in Vienna, Austria, confirmed that once-daily OCA 25 mg achieved the primary endpoint of the study by demonstrating statistically significant improvement in liver fibrosis without worsening of NASH at 18 months ($P=0.0002$).⁴³

The study compared OCA 25 mg (n=308), OCA 10 mg (n=312), and placebo (n=311) in a population with stage 2 or 3 liver fibrosis due to NASH. Primary endpoints were either improvement of fibrosis by ≥ 1 stage or with no worsening of NASH or resolution of NASH with no worsening of fibrosis on liver biopsy. Once-daily OCA 25 mg met the primary endpoint of improvement of fibrosis with no worsening of NASH in 23.1% of patients ($P=0.0002$ vs placebo).⁴³

Additional analyses of the per-protocol population (n=668) demonstrated that 13.3% of patients receiving OCA 25 mg/d for ≥ 15 months experienced a ≥ 2 -stage improvement in fibrosis vs 4.5% of the placebo group ($P=0.0008$).⁴⁴ In patients who experienced ≥ 1 -stage change in fibrosis, 38% of the OCA 25-mg group improved, whereas 13.1% worsened. By contrast, 23.2% of the placebo group improved, whereas 20.9% worsened.⁴⁴

Substantially more patients in the OCA 25-mg group experienced improvement in certain key underlying features of NASH. For example, a ≥ 1 -point improvement in hepatocellular ballooning was seen in 43.6% of patients receiving OCA 25 mg vs in 28.6% of patients receiving placebo ($P=0.0008$). And a ≥ 1 -point improvement in lobular inflammation was seen in 52.3% of patients receiving OCA 25 mg vs in 42.0% of patients receiving placebo ($P=0.03$).⁴⁵

Figure 4. Obeticholic Acid: A Modified Bile Acid and FXR Agonist



ASBT, apical sodium bile acid transporter; BSEP, bile salt export pump; CRP, C-reactive protein; FXR, farnesoid X receptor; IFN, interferon; IgM, immunoglobulin M; IL, interleukin; MMP-2, matrix metalloproteinase 2; NF- κ B, nuclear factor kappa B; OATP, organic anion transporting polypeptide; OCA, obeticholic acid; PDGF, platelet-derived growth factor; RXR, retinoid X receptor; TGF- β 1, transforming growth factor beta 1; TNF- α , tumor necrosis factor alpha.

Source: Andrea Italia.³⁹

Researchers also observed dose-dependent reductions in liver enzymes. Almost two-thirds (65.6%) of the OCA 25-mg group with an elevated ALT level at baseline achieved a normal level vs slightly more than a third (37.3%) in the placebo group. Similarly, of those with elevated AST levels as baseline, 54.7% of the OCA 25-mg group achieved normal levels vs 29.3% of the control group.⁴⁵

Serious adverse events occurred with similar frequency across all three treatment arms: 14%, OCA 25 mg; 11%, OCA 10 mg; and 11%, placebo. Adverse events were generally mild to moderate. The most common adverse event was dose-related pruritus (51%, OCA 25 mg; 28%, OCA 10 mg; and 19%, placebo). Across all three treatment arms, the incidence of pruritus was highest during the first 3 months of treatment and then decreased. Consistent with previous study findings, LDL cholesterol levels increased in the OCA treatment groups, peaking with an increase of 22.6 mg/dL at 4 weeks; levels subsequently reversed and approached baseline at month 18. Triglyceride levels quickly and continually decreased in the OCA treatment arms throughout the 18-month period.⁴⁵ As of this writing, the study remains ongoing with more than 2,000 patients enrolled to confirm benefit on clinical outcomes.

The ongoing (as of June 2019) phase 3 REVERSE (Study Evaluating the Efficacy and Safety of Obeticholic Acid in Subjects With Compensated Cirrhosis Due to Nonalcoholic Steatohepatitis) trial is a randomized, double-blind, placebo-controlled, multicenter trial evaluating the safety and efficacy of OCA on histologic improvement in fibrosis with no worsening of NASH in patients with compensated cirrhosis due to NASH. In the first phase, which will last 1 year, patients will receive OCA 25 mg, OCA 10 mg, or placebo. In the second phase of the study, participants will have the choice to continue for another year, during which time all participants will receive OCA; no one will receive placebo.^{46,47}

Elafibranor

Elafibranor is a dual PPAR alpha and delta agonist that has been shown to improve insulin sensitivity, glucose homeostasis, and lipid metabolism and to reduce inflammation (**Figure 5**).⁴⁸

Researchers assessed the safety and efficacy of elafibranor in an international, randomized, double-blind, placebo-controlled trial of patients with NASH without cirrhosis.⁴⁸ Patients received either elafibranor 80 mg (n=93), elafibranor 120 mg (n=91), or placebo (n=92) daily for 1 year at sites in both Europe and the United States.

In intention-to-treat analysis, there was no significant difference between the elafibranor and placebo groups in the primary outcome, which was resolution of NASH without worsening of fibrosis. However, a greater proportion of patients in the 120-mg elafibranor group vs the placebo group had resolution of NASH without worsening of fibrosis (19% vs 12%; odds ratio [OR], 2.31; 95% CI, 1.02-5.24; $P=0.045$). And in post hoc analyses of patients with an NAS ≥ 4 (n=234), NASH resolved in 20% of the patients in the elafibranor 120-mg group vs in 11% taking placebo (OR, 3.16; 95% CI, 1.22-8.13; $P=0.018$). Patients with resolution of NASH after receiving elafibranor 120 mg had reduced liver fibrosis stages compared to those without NASH resolution. And patients in the elafibranor 120-mg group vs the placebo group had significantly lower liver enzymes, lipids, glucose profiles, and markers of systemic inflammation. Elafibranor was well tolerated and did not cause weight gain or cardiac events, but 7% of patients experienced a mild, reversible increase in serum creatinine.⁴⁸

Elafibranor is now being studied in NASH-RESOLVE-IT (Phase 3 Study to Evaluate the Efficacy and Safety of Elafibranor Versus Placebo in Patients With Nonalcoholic Steatohepatitis), a multicenter, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of elafibranor 120 mg vs placebo for 72 weeks in patients with NASH and fibrosis. Endpoints include histologic improvement and improvement in all-cause mortality and liver-related outcomes in patients with NASH and fibrosis. Top-line data are expected by the end of 2019.⁴⁹

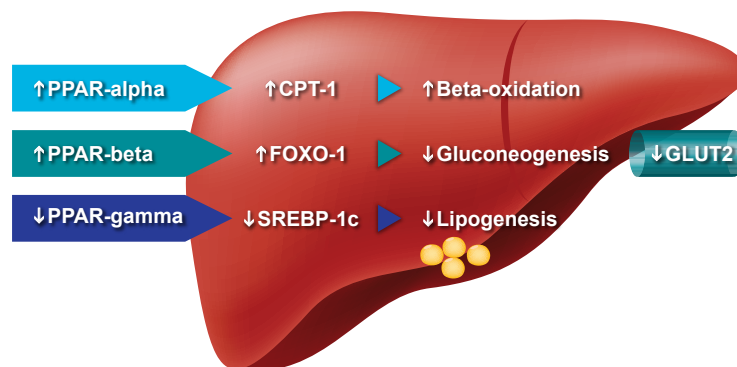
Emricasan

Emricasan, a pan-caspase inhibitor, is the subject of the ENCORE-PH (Emricasan, an Oral Caspase Inhibitor, in Subjects With Non-Alcoholic Steatohepatitis [NASH] Cirrhosis and Severe Portal Hypertension) trial, a 6-month phase 2b trial initiated at the end of 2016.^{50,51} It involved 263 patients with NASH and compensated (n=201) or early decompensated (n=62) liver cirrhosis and severe portal hypertension. The primary endpoint was change in mean hepatic venous pressure gradient (HVPG) from baseline to week 24 in any of 3 emricasan dosing groups (5 mg, 25 mg, or 50 mg twice a day) or in a group taking placebo twice daily.

Top-line results were reported at the end of 2018.⁵¹ Although changes in HVPG from baseline to week 24 showed trends consistently favoring emricasan compared with placebo, the primary endpoint was not reached. The amount of improvement in mean HVPG generally increased as baseline HVPG levels increased. Both the emricasan 25-mg and 50-mg groups achieved >10% improvement in mean HVPG compared with the placebo group in all HVPG cohorts from ≥ 13 mm Hg through ≥ 17 mm Hg, whereas placebo-treated patients experienced increases in mean HVPG. The greatest improvement was observed in patients with a baseline HVPG of ≥ 16 mm Hg.⁵¹

In addition, the phase 2b ENCORE-NF (Emricasan, a Caspase Inhibitor, for Evaluation in Subjects With Non-Alcoholic Steatohepatitis [NASH] Fibrosis) trial, initiated in the first quarter of 2016, involves approximately 318 patients with biopsy-confirmed NASH and stage 1 to 3 liver fibrosis who were randomized to receive either 5 mg of emricasan, 50 mg of emricasan, or placebo twice daily for 72 weeks. The primary endpoint was biopsy-based improvement in fibrosis by ≥ 1 stage without worsening of steatohepatitis. The secondary endpoint was resolution of steatohepatitis without worsening of fibrosis, NAS, or other components of the disease.^{52,53} Top-line results announced at the end of March 2019 revealed that emricasan did not reach the primary endpoint.⁵⁴

Figure 5. Elafibranor: A Dual Peroxisome Proliferator-Activated Receptor (PPAR) Compound



CPT-1, carnitine palmitoyltransferase 1; FOXO1, Forkhead Box O1; GLUT2, glucose transporter type 2; SREBP-1c, sterol regulatory element binding protein 1c.
Source: Ratziu V et al.⁴⁸

Lastly, the ENCORE-LF (Emricasan, a Caspase Inhibitor, for Treatment of Subjects With Decompensated NASH Cirrhosis) study was initiated in the second quarter of 2017.⁵⁵ It involves approximately 210 patients with decompensated NASH cirrhosis. Top-line results are expected sometime in 2019.⁵¹

Genicriviroc

Genicriviroc (CVC) is an oral immunomodulator that acts as an antagonist of C-C chemokine receptor types 2 and 5.

The AURORA (Phase 3 Study for the Efficacy and Safety of CVC for the Treatment of Liver Fibrosis in Adults With NASH) trial, which, as of this writing, is recruiting patients, is designed to evaluate the efficacy and safety of genicriviroc in adults with NASH with liver fibrosis.⁵⁶ Participants will receive either one 150-mg tablet of CVC or placebo daily. The primary outcome measures are improvement in fibrosis ≥ 1 stage and no worsening of steatohepatitis, and the superiority of CVC compared with placebo on the composite endpoint of histopathologic progression to cirrhosis, liver-related clinical outcomes, and all-cause mortality.⁵⁷

A previous study, the phase 2b CENTAUR (Efficacy and Safety Study of Genicriviroc for the Treatment of Nonalcoholic Steatohepatitis [NASH] in Adult Participants With Liver Fibrosis) study, also looked at the efficacy and safety of CVC in a population of adult patients with NASH with liver fibrosis.^{58,59} The randomized, placebo-controlled trial, which took place at 81 clinical sites, included 289 patients randomized for 1 year to receive either CVC (a 150-mg tablet once per day) or placebo. After year 1, half of the patients who had received placebo were re-randomized to receive CVC or stay on placebo for year 2.

The primary outcome measure was histologic improvement in NAS score (defined by ≥ 2 -point improvement in NAS with ≥ 1 -point reduction in either lobular inflammation or hepatocellular ballooning) with no concurrent worsening of fibrosis stage at year 1. Secondary outcomes were resolution of steatohepatitis and no worsening of fibrosis, and improvement in fibrosis by ≥ 1 stage and no worsening of steatohepatitis.⁵⁹

Upon the conclusion of year 1, the primary endpoint of NAS improvement and resolution of steatohepatitis was not met. A similar proportion of subjects in the CVC group and the placebo group achieved the primary outcome (16% vs 19%, respectively; OR, 0.82; 95% CI, 0.44-1.52; $P=0.52$). But the participants taking CVC were twice as likely as those taking placebo to achieve improvement in fibrosis stage by ≥ 1 stage and no worsening of steatohepatitis (20% vs 10%, respectively; OR, 2.20; 95% CI, 1.11-4.35; $P=0.02$).⁵⁹

Safety profiles were similar between the CVC and placebo groups. The only drug-related treatment-emergent adverse events grade >2 and with greater than 2% frequency were fatigue (2.8%) and diarrhea (2.1%).⁵⁹ In the placebo patients who crossed over to receive CVC during year 2, 20% of patients receiving CVC vs 13% of patients receiving placebo achieved the primary endpoint.⁵⁷

Selonsertib

Selonsertib is another oral agent, but one that is an apoptosis signal-regulating kinase (ASK) 1 inhibitor. It is used with or without simtuzumab, a monoclonal antibody to LOX-like 2.

The safety and efficacy of selonsertib in combination with simtuzumab were tested in a phase 2 trial for NASH. Seventy-two participants with histologically proven NASH with a NAS of ≥ 5 and stage 2 or 3 fibrosis received either selonsertib 18 mg or 6 mg orally once daily, with or without simtuzumab 125 mg subcutaneously once weekly, or just simtuzumab 125 mg subcutaneously once weekly, for 24 weeks.⁶⁰

The primary histologic endpoints were improvement of fibrosis of ≥ 1 stage and progression to cirrhosis. The former histologic endpoint was

observed in 37%, 30%, and 20%, respectively, of the participants, whereas the latter histologic endpoint was met by 3%, 7%, and 20%, respectively. The primary magnetic resonance (MR)-based efficacy endpoints were $\geq 15\%$ reduction in MRE-measured liver stiffness and $\geq 30\%$ reduction in MR-proton density fat fraction (PDFF)-measured hepatic fat. The former MR-based endpoint was met by 20%, 32%, and 0%, respectively, of the participants, whereas the latter MR-based endpoint was met by 26%, 13%, and 10%, respectively.⁶⁰

One of five serious adverse events in the selonsertib $\pm$ simtuzumab groups was deemed related to the study drug. Treatment was discontinued because of adverse events in three participants in the selonsertib $\pm$ simtuzumab groups vs none in the simtuzumab-alone group.⁶⁰

Selonsertib failed the phase 3 STELLAR 4 (Safety and Efficacy of Selonsertib in Adults With Compensated Cirrhosis Due to Nonalcoholic Steatohepatitis [NASH]) trial.⁶¹ In this study of 883 patients with compensated cirrhosis due to NASH, only a slightly higher percentage of patients receiving selonsertib 18 mg achieved the primary endpoint (a ≥ 1 stage improvement of fibrosis without worsening of NASH) than those receiving placebo, and even fewer of those receiving selonsertib 6 mg did as well as those taking placebo.^{61,62}

Another phase 3 trial, the STELLAR 3 trial,⁶³ involving patients with bridging fibrosis due to NASH and investigating selonsertib in combination with cilofexor (a nonsteroidal FXR agonist) or firsocostat (an ACC inhibitor), also did not achieve the endpoints. Of 802 patients, 9.3% treated with selonsertib 18 mg ($P=0.42$ vs placebo) and 12.1% of patients treated with selonsertib 6 mg ($P=0.93$) achieved a ≥ 1 -stage improvement in fibrosis without worsening of NASH after 48 weeks of treatment vs 13.2% taking placebo. Selonsertib was generally well tolerated; safety results were consistent with prior studies.⁶⁴

The phase 2 ATLAS trial involving 395 participants is ongoing and is investigating selonsertib, cilofexor, firsocostat, and combinations in patients with bridging fibrosis or compensated cirrhosis due to NASH. Results are anticipated to be available by the end of 2019.⁶⁵

Pegbelfermin (aka BMS-986036)

Another agent in phase 2 study is pegbelfermin (BMS-986036), a PEGylated fibroblast growth factor 21 analog. Bristol-Myers Squibb has launched the FALCON phase 2b program, which includes FALCON 1 (MB130-068), a randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of BMS-986036 in adults with NASH and stage 3 liver fibrosis,⁶⁶ and FALCON 2 (MB130-069),⁶⁷ a randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of BMS-986036 in adults with NASH and compensated cirrhosis. Both studies will be conducted in the United States and Japan.⁶⁸

Earlier studies have indicated that pegbelfermin improves NAS and fibrosis, increases adiponectin (higher levels are associated with reductions in steatosis, inflammation, and fibrosis), decreases Pro-C3 (an emerging biomarker of fibrosis), and improves insulin sensitivity and lipids, among other findings.⁶⁹⁻⁷¹

MK-3655 (NGM313)

Finally, Merck is entering the NASH arena with NGM313, now known as MK-3655, a once-monthly humanized monoclonal antibody activator of beta-Klotho/fibroblast growth factor receptor 1c. Following positive findings from a phase 1b trial of 25 patients with NAFLD and insulin resistance that compared a single 240-mg dose of NGM313 with daily pioglitazone 45 mg, Merck hopes to start a phase 2b trial to assess the effect of the drug on liver histology and glucose control in patients with NASH with or without diabetes.^{72,73}

The goals of therapy for patients with NAFLD/NASH include:

- Stabilization of histology
- Improvement of fibrosis
- Prevention of liver-related poor outcomes
- Improvement of comorbidities (ie, obesity, hyperlipidemia, insulin resistance, T2D)
- Long-term safety

Lifestyle Changes – The Sine Qua Non of Management

Lifestyle measures are important for all patients with NAFLD/NASH, beginning with the avoidance of alcohol because it can increase fibrinogenesis. Clinicians should convey to patients that a high-calorie diet, excess (saturated) fats, refined carbohydrates, sugar-sweetened beverages, and high fructose intake are all associated with weight gain, obesity, and NAFLD/NASH. Therefore, lifestyle modifications (ie, diet, exercise, and weight loss) are the first steps for preventing the development and progression of NAFLD/NASH.⁶ Clinicians need to be prepared to counsel patients aggressively about losing weight and maintaining weight loss. Weight-loss surgery may be needed in severe cases. Despite this, 25% of respondents in a survey of US gastroenterologists and hepatologists do not refer patients with NAFLD for bariatric surgery.²⁷

Although large randomized controlled trials (RCTs) assessing the effect of exercise on histopathology in NASH are needed, and although the optimal duration and intensity of exercise remain unknown, some studies indicate that even small amounts

of exercise—even without dietary changes—can make a significant difference. One study, which followed approximately 43,000 patients with fatty liver for 5 years, found that exercise ≥ 5 times per week (with each session lasting at least 10 minutes) decreased diagnoses of new NAFLD (hazard ratio [HR], 0.86; 95% CI, 0.80-0.92; $P < 0.001$) and improved existing NAFLD compared with no exercise (HR, 1.40; 95% CI, 1.25-1.55; $P = 0.001$).⁷⁴

The bottom line: A 3% to 5% body weight loss improves steatosis, whereas a 7% to 10% body weight loss improves histology and possibly fibrosis.⁵ And $>10\%$ weight loss has been associated with improvement in all features of NASH, including portal inflammation and fibrosis.⁷⁵ Despite these documented benefits, only about half of the participants in one trial were able to achieve $\geq 7\%$ weight loss at 1 year.⁷⁵

Pharmacologic Agents

To date there is no approved pharmacotherapy for treating steatohepatitis or fibrosis associated with NAFLD, although several agents (including some currently used in the management of T2D and MetS) are under study that target various pathways. Development of pharmacologic therapy is crucial because patients with NAFLD often have difficulty making—and maintaining—lifestyle changes.

Metformin

Metformin, an insulin-sensitizing agent that is considered first-line treatment for T2D, seems to at least temporarily improve insulin sensitivity and liver enzyme levels, but it does not improve histology or fibrosis.^{76,77} Although some early studies suggested histologic benefit, the benefit was more likely related to concomitant weight loss than to the agent itself.^{78,79} More recent meta-analyses have confirmed that metformin is not effective for the treatment of NAFLD or NASH.^{80,81}

Rosiglitazone

In a key study (the Fatty Liver Improvement With Rosiglitazone Therapy [FLIRT] trial), published in 2008 and involving 63 patients with histologically proven NASH, 32 patients received rosiglitazone 4 mg/d for the first month and 8 mg/d thereafter, while 31 patients received placebo, for 1 year.⁸² The researchers found that rosiglitazone improved transaminase levels and steatosis, despite weight gain, but did not improve other parameters of liver injury.

The FLIRT 2 extension trial found that, although rosiglitazone has a substantial antisteatogenic effect in the first year of treatment, longer therapy does not produce additional benefit, despite a maintained effect on insulin sensitivity and transaminase levels, suggesting that improving insulin sensitivity is not sufficient in NASH and that additional targets of therapy for liver injury are needed.⁸³

Caffeine: A Possible Protector?

- A few cups of caffeinated coffee per day may help keep NAFLD away.
- In one study evaluating National Health and Nutrition Examination Survey (NHANES) data collected between 2001 and 2008, the authors assessed intake of 62 nutrients in a group with NAFLD and a control group. Caffeine intake was significantly higher in the group without liver disease. In fact, caffeine ranked in the top 2 of the items studied in terms of statistical significance, and remained highly significant even after adjusting for race, gender, and MetS components.

Reference: 1. Binerdinc A, Stepanova M, Pawloski L, Younossi ZM. Caffeine is protective in patients with non-alcoholic fatty liver disease. *Aliment Pharmacol Ther.* 2012;35:76-82.

“Once a patient starts developing scar tissue in the liver, you need to refer the patient to a hepatologist so that they receive optimal care that includes the option to participate in clinical trials. Without an appropriate referral mechanism, researchers cannot locate sufficient numbers of patients who are suitable for participation in clinical trials.”

– Nikolaos Pyrsopoulos, MD

Pioglitazone

Initial studies showed a benefit of pioglitazone in patients with NASH with and without diabetes.⁸⁴⁻⁸⁶

The PIVENS Study included 247 adults with NASH but without T2D, cirrhosis, hepatitis C, or heart failure and with limited alcohol intake over the previous 5 years. The study compared treatment with pioglitazone 30 mg/d (n=80), vitamin E 800 IU/d (n=84), or placebo (n=83) for 96 weeks.⁸⁷ The authors found that vitamin E was superior to placebo at the primary outcome (improving histologic features of NASH, as assessed with a composite of standardized scores for steatosis, lobular inflammation, hepatocellular ballooning, and fibrosis). The researchers also found that, although there was no benefit of pioglitazone over placebo for the primary outcome, benefit was observed for some of the secondary outcomes, such as reducing serum ALT and AST levels, hepatic steatosis, and lobular inflammation. A meta-analysis published in 2012 also demonstrated that pioglitazone improves steatosis, inflammation, and, to a lesser degree, fibrosis in patients with NASH.⁸⁸

On the downside, in addition to causing weight gain, pioglitazone has been associated with increased risk for congestive heart failure, bladder cancer, and reduced bone density.⁸⁹⁻⁹¹ But a meta-analysis of more than 16,000 patients with T2D demonstrated an 18% reduction in death, myocardial infarction, and stroke.⁹² AASLD practice guidelines for NAFLD state that pioglitazone may be considered for patients with and without T2D with biopsy-proven NASH, but the authors caution that the risks and benefits should be discussed with each patient before starting therapy.⁶

Vitamin E

Because it acts as an antioxidant, vitamin E could theoretically mitigate the effects of inflammation and thus has been studied for the treatment of NASH. Summarizing recent research findings, AASLD practice guidelines state that vitamin E is associated with a decrease in aminotransferase levels and that it seems to improve steatosis, inflammation, ballooning, and resolution of steatohepatitis in nondiabetic adults with NASH, but that it has no effect on hepatic fibrosis.⁶

Vitamin E is clearly not a panacea, and the use of this compound is not beneficial for all patients. Associations between vitamin E and a small overall increase in all-cause mortality at doses >400 IU/d and increased risks for hemorrhagic stroke and prostate cancer have been reported, although a meta-analysis found this not to be true.^{27,93-97}

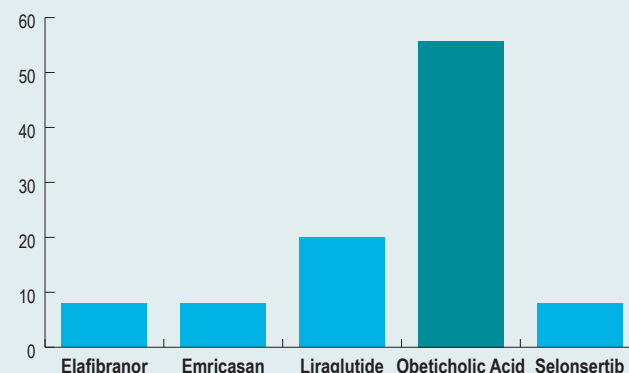
A 2016 survey of US hepatologists and gastroenterologists indicated that about 45% of specialists prescribed vitamin E to all their patients with NASH.²⁷ Only about 34% appropriately excluded patients with diabetes, about 21% appropriately excluded patients with cirrhosis, and about 9% appropriately excluded patients with both conditions.²⁷

In addition, the survey indicated that a broad awareness of the potential adverse effects of vitamin E has led a subset of respondents to avoid using the agent unnecessarily.²⁷ According to AASLD guidelines, vitamin E 800 IU/d may be considered for nondiabetic adults with biopsy-proven NASH. However, vitamin E is not recommended to treat NASH in patients with diabetes, NAFLD in patients who have not had a liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis.⁶

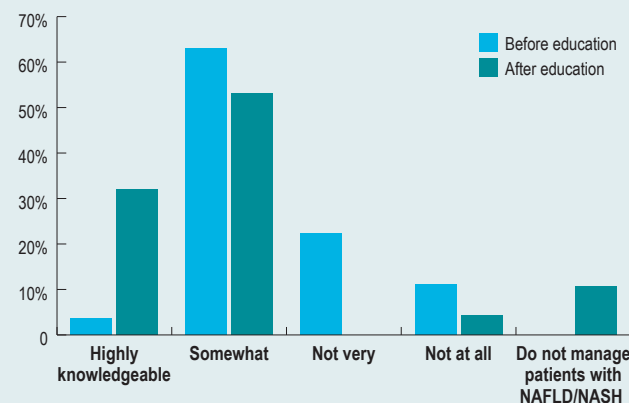
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Just over half of learners were aware that obeticholic acid, an emerging potential therapy for NASH, is a farnesoid X receptor agonist.

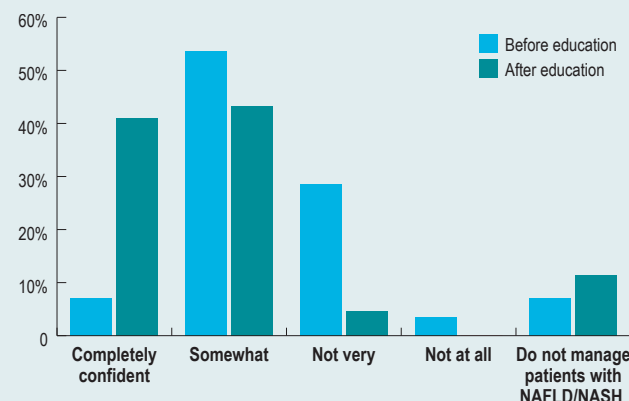
Q. Farnesoid X receptor (FXR) is a nuclear key regulator controlling several processes of the hepatic metabolism. Which of the following agents for NASH acts as an FXR agonist?



Before the symposium, only 4% of learners reported that they were highly knowledgeable about NAFLD/NASH, and 63% reported they were somewhat knowledgeable. After the symposium, self-reported knowledge increased dramatically; 32% reported that they were now highly knowledgeable and 53% were somewhat knowledgeable.



Confidence in the ability to evaluate and manage patients with NAFLD/NASH also improved significantly. Before the symposium, only 7% of learners reported that they were completely confident, and 54% said they were somewhat confident. After the symposium, 41% said they were completely confident and 43% were somewhat confident.



Sodium-Glucose Cotransporter 2 (SGLT-2) Inhibitors

Empagliflozin was recently studied in an RCT involving 50 patients with T2D and NAFLD.⁹⁸ Patients received either their standard medication for T2D plus empagliflozin 10 mg/d or their standard treatment without empagliflozin. Those taking empagliflozin had significantly reduced liver fat content and improved serum ALT levels.⁹⁸

Small studies have also been conducted using canagliflozin and dapagliflozin with some positive findings, but it is still too early to tell whether these agents will become useful in the treatment of NAFLD or NASH.^{99,100}

Glucagon-Like Peptide-1 (GLP-1) Analogs

Similarly, it is too early to consider GLP-1 analogs for the treatment of NAFLD/NASH. However, the LEAN (Liraglutide Efficacy and Action in Nonalcoholic steatohepatitis) trial, an RCT conducted at four medical centers in the United Kingdom and involving 52 overweight patients with biopsy-proven NASH, found that subcutaneous once-daily liraglutide (1.8 mg/d) for 48 weeks produced greater resolution of steatohepatitis and less progression of fibrosis than placebo.¹⁰¹ Nine of 23 (39%) patients who received liraglutide and two of 22 (9%) patients receiving placebo had resolution of NASH (relative risk, 4.3; 95% CI, 1-17.7; $P=0.019$). Two of 23 (9%) patients in the liraglutide group and eight of 22 (36%) patients in the placebo group had progression of fibrosis. The liraglutide group also had greater weight loss and more gastrointestinal adverse effects (81% of the liraglutide group vs 65% of the placebo group).⁶⁶

The GLP-1 analog semaglutide has also entered the NASH arena. One phase 2 randomized trial involving 320 patients with NASH is investigating the safety and efficacy of three different doses of subcutaneous semaglutide once daily vs placebo. Top-line results are expected by the end of 2019.¹⁰²

In addition, the phase 2 NAFLD HEROES (Non-Alcoholic Fatty Liver Disease, the Hepatic Response to Oral Glucose, and the Effect of Semaglutide) trial hopes to recruit about 84 patients and explore whether semaglutide once weekly is associated with either: A) a ≥ 2 -point decrease in NAFLD activity score, or B) a reduction of liver fat content by $\geq 25\%$ and a reduction by $\geq 25\%$ or normalization of ALT by 30 weeks.¹⁰³

Lastly, Gilead and Novo Nordisk plan to collaborate on a clinical trial involving patients with NASH using compounds from each of their pipelines, including Novo Nordisk's semaglutide (a glucagon-like peptide-1 receptor agonist [GLP-1 RA]) and Gilead Sciences' cilofexor (a nonsteroidal farnesoid X receptor [FXR] agonist) and firsoostat (an acetyl-CoA carboxylase [ACC] inhibitor).¹⁰⁴

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors.

The role of DPP-4 inhibitors in the treatment of NAFLD/NASH has been limited to testing in small, short-term clinical trials. Some of these trials have demonstrated an association between DPP-4 inhibitors and reduced plasma aminotransferase levels and/or reduced intrahepatic triglyceride content, but generally effects appear modest.¹⁰⁵

Is Bariatric Surgery a Viable Option?

Although bariatric surgery is not a treatment for NASH, patients with a body mass index ≥ 35 might consider either laparoscopic sleeve gastrectomy or minimally endoscopic endosuturing. (Roux-en-Y is considered obsolete.) Evidence suggests that such surgery in those who are severely obese decreases steatosis grade, hepatic inflammation, and fibrosis.

Reference: Sasaki A, Nitta H, Otsuka K, et al. Bariatric surgery and non-alcoholic fatty liver disease: current and potential future treatments. *Front Endocrinol (Lausanne)*. 2014;5:164.

Summary

Given the rapidly growing incidence of NAFLD/NASH, the inextricable links between these diseases and concomitantly rising metabolic conditions, the significant burden of comorbidities and outcomes, and the lack of available treatments, NAFLD/NASH clearly warrants continued attention from the medical community. Although research on the pathophysiology of these entities and on potential therapies has come a long way, additional investigative efforts are needed to bring long-awaited therapies for these conditions to market so that patients have more than just lifestyle changes to rely on. Clinicians should be prepared to identify, evaluate, and manage patients at greatest risk using a combination of lifestyle changes and treatment for associated comorbidities, and they should remain informed of developments in the field that could result in important changes in the clinical landscape.

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