



Nonalcoholic Fatty Liver Disease: Review of Management for Primary Care Providers

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease in the United States and worldwide. The progressive form of NAFLD, nonalcoholic steatohepatitis (NASH), is a leading indication for liver transplant. Comorbidities associated with NAFLD development and NASH include type 2 diabetes, obesity, metabolic syndrome, and dyslipidemia. Extrahepatic morbidity and mortality are considerable as NAFLD is associated with an increased risk of cardiovascular disease and chronic kidney disease. Once NAFLD is diagnosed, the presence of liver fibrosis is the central determinant of hepatic prognosis. Severe liver fibrosis requires aggressive clinical management. No pharmacologic agents have regulatory approval in the United States for the treatment of NAFLD or NASH. Management is centered on efforts to reduce underlying obesity (lifestyle, medications, surgical or endoscopic interventions) and metabolic derangements (prediabetes, type 2 diabetes, hypertension, hyperlipidemia, and others). Current pharmacologic therapy for NAFLD is limited mainly to the use of vitamin E and pioglitazone, although other agents are being investigated in clinical trials. Cardiovascular and metabolic risk factors must also be assessed and managed. Here, NAFLD evaluation, diagnosis, and management are considered in the primary care setting and endocrinology clinics.

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Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease globally and in the United States.^{1,2} It is characterized by the development of hepatic steatosis (triglyceride accumulation in hepatocytes) in the absence of secondary causes, including significant alcohol consumption (US standard drink, 14 g of alcohol: >2 drinks/day for men, >1 drink/day for women).^{3,4} Nonalcoholic fatty liver disease encompasses the full spectrum of histopathologic changes (simple steatosis to extensive fibrosis to cirrhosis),^{4,5} whereas nonalcoholic steatohepatitis (NASH) is characterized by inflammation and hepatocyte injury (ballooning) with or without fibrosis.³ Disease progression from steatosis to cirrhosis may not be linear, and periods of stability or regression can occur.⁶ Liver fibrosis may progress to cirrhosis with all of its resulting complications, including end-stage liver disease, risk of hepatocellular

cancer, and possible need for liver transplant.³ Fibrosis progression occurs in approximately 40% of individuals with NASH.¹ The severity of liver fibrosis is a key predictor of the long-term outcomes in people with NASH, including overall mortality.⁷ The main features of NAFLD are presented in [Figure 1](#).^{1,3,4,8}

Nonalcoholic fatty liver disease is strongly associated with metabolic syndrome (MetS), obesity, type 2 diabetes (T2D), and dyslipidemia.³ Unsurprisingly, cardiovascular disease (CVD) is the most common cause of death in people with NAFLD³ (as it is overall in those with MetS⁹); NAFLD is associated with disease progression in cardiovascular disease (CVD) and chronic kidney disease (CKD)^{3,4} and with increased cancer-related mortality.¹⁰⁻¹³ Approximately 20% of people with NAFLD are classified as having NASH,¹ and 20% of those with NASH have advanced liver disease (category F3/F4 fibrosis).⁸ An estimated 18.2 million

American adults have T2D and NAFLD, of whom 6.4 million have NASH; 20-year costs for NAFLD in these patients are almost \$56 billion and are projected to increase significantly during the coming 20 years.¹⁴ The global epidemic of metabolic disorders related to obesity and diabetes will result in a considerable increase in the clinical and economic burden of NAFLD and NASH.

The aim of this review is to present current information on the evaluation, diagnosis, and management of NAFLD and NASH in adults in the primary care setting and endocrinology clinics.

METHODS

Literature was retrieved using Boolean searches for English-language articles in PubMed and Google Scholar and included terms related to NAFLD and NASH. The reference lists from retrieved articles were also considered.

PRAGMATIC APPROACH TO MANAGEMENT

Scientific societies from different regions of the world have developed guidelines for the management of patients with NAFLD. In the United States, the American Association for the Study of Liver Diseases (AASLD) published practice guidance in 2018,³ and combined guidance from 3 European societies was published in 2016 (European Association for the Study of the Liver [EASL], European Association for the Study of Diabetes [EASD], and European Association for the Study of Obesity [EASO]).⁴ In addition, guidelines have been published by the Asia-Pacific Working Party on Non-Alcoholic Fatty Liver Disease (2017),^{15,16} the Italian Association for the Study of the Liver (2017),¹⁷ and the United Kingdom's National Institute for Health and Care Excellence (2016).¹⁸ A comparison of all 5 sets of guidelines was reported by Leoni et al,¹⁹ and guidelines from the AASLD, the EASL-EASD-EASO, and the National Institute for Health and Care Excellence are summarized in Table 1.^{3,4,19} Whereas we expect more harmonized guidelines in the future, herein we attempt to provide a pragmatic approach to the management of patients with NAFLD.

ARTICLE HIGHLIGHTS

- Primary care providers can expect to see growing numbers of patients with nonalcoholic fatty liver disease (NAFLD), given its increasing prevalence—fueled by the global epidemics of obesity and type 2 diabetes.
- A significant risk of cardiovascular morbidity and mortality is associated with NAFLD. The progressive form of NAFLD, nonalcoholic steatohepatitis (NASH), is a leading indication for liver transplant.
- The presence of liver fibrosis (NASH fibrosis) is the central determinant of liver-related mortality; the presence of advanced fibrosis (stage \geq F3) requires aggressive clinical management.
- Clinical action is necessary if NAFLD is suspected, even with normal liver biochemistry or an absence of symptoms. Prompt diagnosis of NAFLD and determination of liver fibrosis risk are critical to improve patient outcomes.
- Liver biopsy is the “gold standard” for diagnosis of NASH but has several disadvantages; thus, noninvasive biomarkers (serum and imaging) are used more frequently.

Risk Factors, Comorbidities, and Complications

The pathogenesis of NAFLD is multifactorial and not yet fully understood (comprehensive reviews have been published²⁰⁻²³). Nonalcoholic fatty liver disease is often referred to as the hepatic manifestation of MetS.^{24,25} Briefly, the presence of excess lipid is the primary insult and is followed by the effects of pathogenic drivers, including insulin resistance, lipotoxicity, and immune system activation; these are combined with other modifying factors, such as adverse nutritional intake (eg, foods rich in fructose or saturated fats)^{26,27} and proinflammatory changes to the gut microbiome.²⁰ There are also known genetic predispositions to hepatic fat accumulation (eg, polymorphisms in the *PNPLA3* gene and variants of the *TM6SF2* gene)²⁸ as well as the newly discovered protective genetic polymorphism in the 17 β -hydroxysteroid dehydrogenase 13 gene, in which loss of function variants were associated with a reduced risk of chronic liver disease and

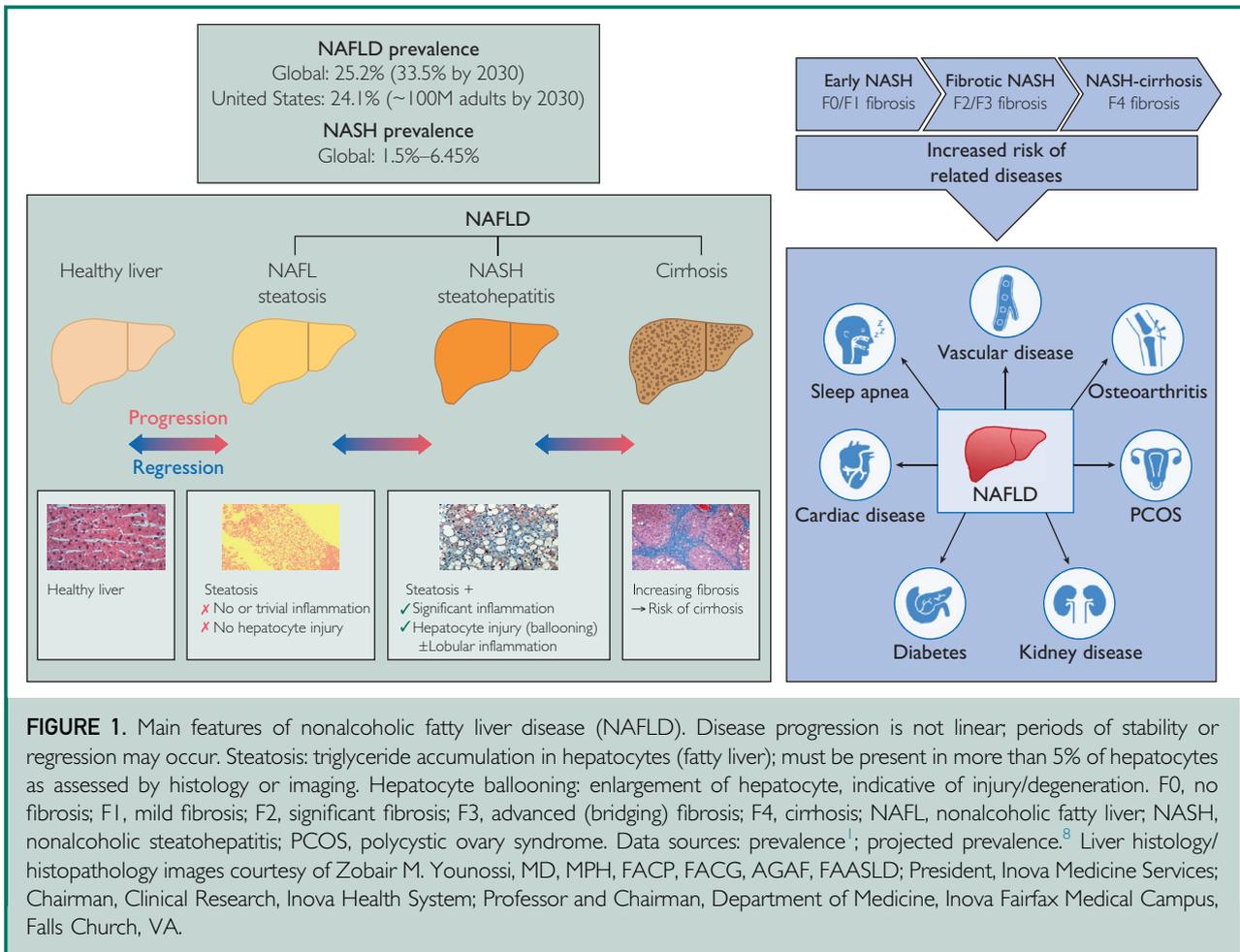


FIGURE 1. Main features of nonalcoholic fatty liver disease (NAFLD). Disease progression is not linear; periods of stability or regression may occur. Steatosis: triglyceride accumulation in hepatocytes (fatty liver); must be present in more than 5% of hepatocytes as assessed by histology or imaging. Hepatocyte ballooning: enlargement of hepatocyte, indicative of injury/degeneration. F0, no fibrosis; F1, mild fibrosis; F2, significant fibrosis; F3, advanced (bridging) fibrosis; F4, cirrhosis; NAFL, nonalcoholic fatty liver; NASH, nonalcoholic steatohepatitis; PCOS, polycystic ovary syndrome. Data sources: prevalence¹; projected prevalence.⁸ Liver histology/histopathology images courtesy of Zobair M. Younossi, MD, MPH, FACP, FACG, AGAF, FAASLD; President, Inova Medicine Services; Chairman, Clinical Research, Inova Health System; Professor and Chairman, Department of Medicine, Inova Fairfax Medical Campus, Falls Church, VA.

progression from steatosis to steatohepatitis.^{29,30}

The association between NAFLD and metabolic disorders is well documented, as is the occurrence of NAFLD with CVD or CKD (summarized later and reviewed in a number of publications^{22,31-36}). Obesity (excessive body mass index [BMI] and visceral obesity) is the most common risk factor for NAFLD and NASH (prevalence of 51% and 82%, respectively¹) and includes the range from overweight to severely obese.³ The increasing frequency of obesity in American adults—current prevalence of 42% (severe obesity 9%)³⁷ and anticipated to rise to 49% (severe obesity 24%) by 2030³⁸—can be expected to fuel an increase in NAFLD. Some normal-weight individuals (BMI <25 kg/m²) can exhibit NAFLD with or without exhibiting abnormal levels of

liver enzymes; this is so-called lean NAFLD.^{39,40} Although generally exhibiting a more favorable metabolic profile than obese individuals, lean NAFLD patients can develop the full spectrum of liver damage associated with “non-lean” NAFLD.⁴¹ This may be due to such individuals’ having dysfunctional adipose tissue or expressing genes associated with obese NAFLD patients (eg, *PNPLA3*).^{4,41} Notably, insulin resistance is also associated with NAFLD in individuals without diabetes or obesity, suggesting that it may play an intrinsic role in the pathogenesis of NAFLD independent of BMI.^{42,43} All components of MetS correlate with hepatic fat content independently of BMI.⁴ Metabolic syndrome is defined as the presence of 3 of the following 5 criteria: impaired fasting glucose level or T2D, hypertriglyceridemia, low high-density lipoprotein cholesterol

TABLE 1. Comparison of NAFLD Management Guidelines in Adults From the United States (AASLD), Europe (EASL-EASD-EASO), and United Kingdom (NICE)^{3,4,18,19}

Guidelines	Diagnostic criteria	Screening strategy; diagnostic tests and prognostic scores	Evaluation and monitoring of fibrosis; liver biopsy	Lifestyle interventions	Pharmacotherapy
AASLD 2018 ³	Evidence of HS ($\geq 5\%$) by imaging or histology Exclusion of secondary causes of HS (no significant alcohol consumption, no existing liver disease) Alcohol consumption threshold (weekly): >21 drinks in men or >14 drinks in women (United States standard drink, 14 g of alcohol)	No systematic screening No screening in high-risk groups; but "vigilance" for chronic liver disease in T2D HS imaging: US; MRI is better but routine availability limited Assess risk of CVD and T2D Presence of metabolic disease most potent predictor of adverse outcome	Serum biomarkers Clinical decision aids: NFS or FIB-4 Imaging: TE or MRE Monitoring: no information Liver biopsy with advanced liver fibrosis suggested by serum or noninvasive imaging tools Liver biopsy with MetS + risk liver inflammation	Structured programs: weight loss, healthy diet, regular physical activity 500-1000 kcal deficit; 3%-5% weight loss improves HS; 7%-10% weight loss improves NASH (including fibrosis) Moderate-intensity exercise Macronutrients/diet: no information	For NASH + fibrosis Metformin: not recommended Pioglitazone: may be used in adult T2D + biopsy-proven NASH GLP-1 RAs: insufficient data Vitamin E: may be used in nondiabetic adult + biopsy-proven NASH UCDA: not recommended Omega-3 fatty acids: may be used in adult hypertriglyceridemia + NAFLD Statins: may be used in adults + dyslipidemia + NAFLD or NASH
EASL-EASD-EASO 2016 ⁴	HS in $>5\%$ hepatocytes by imaging or histology Associated with insulin resistance Exclusion of secondary causes (no significant alcohol consumption) Alcohol consumption threshold (daily): >30 g in men or >20 g in women	No community screening Screening in high-risk groups by US or liver enzymes HS imaging: US; MRI is "gold standard," but availability and cost issues HS score: FLI (SteatoTest) or NAFLD liver fat score Assess risk of CVD and T2D	Serum biomarkers Clinical decision aids: NFS or FIB-4 Imaging: TE (in combination with biomarkers/scores, as less reliable with high BMI) Monitoring for progression: NASH \pm fibrosis, yearly; NASH cirrhosis, every 6 months Liver biopsy when medium/high risk of advanced liver fibrosis suggested by serum or noninvasive imaging tools	Structured programs: weight loss, healthy diet, regular physical activity 500-1000 kcal deficit; 7%-10% weight loss to improve HS and NASH 150-200 min/wk moderate-intensity aerobic and resistance training (split into shorter sessions) Diet: low to moderate fat + moderate to high carbohydrates; low-carbohydrate ketogenic or high protein	For NASH + fibrosis For early NASH + high risk of progression Metformin: insufficient evidence Pioglitazone: may be used in adult NASH with T2D (off-label outside T2D) GLP-1 RAs: initial data favorable; insufficient evidence Vitamin E: may be used in noncirrhotic nondiabetic adult + NASH; more data needed UCDA: no effect observed Omega-3 fatty acids: insufficient data to support use Statins: no benefit or harm to liver disease
NICE ¹⁸	Excessive fat in liver Exclusion of secondary causes (no significant alcohol consumption) Alcohol consumption threshold	No community screening Consider that NAFLD is common in T2D and MetS	ELF blood test Monitoring: ELF negative, reassess every 3 years; ELF positive, referral to hepatologist Liver biopsy is the gold standard	Consider NICE guidelines for obesity excessive weight gain	For NASH + fibrosis Metformin: not mentioned Pioglitazone: consider use regardless of diabetes status GLP-1 RAs: not mentioned

Continued on next page

TABLE 1. Continued

Guidelines	Diagnostic criteria	Screening strategy; diagnostic tests and prognostic scores	Evaluation and monitoring of fibrosis; liver biopsy	Lifestyle interventions	Pharmacotherapy
	(daily): >30 g in men or >20 g in women		for diagnosis but impractical to use widely in at-risk patients		UCDA: not mentioned Omega-3 fatty acids: not recommended Statins: continue use if already taking statins; stop if liver enzymes elevate ($\times 2$ within 3 months) Vitamin E: consider use regardless of diabetes status

AASLD, American Association for the Study of Liver Diseases; BMI, body mass index; CVD, cardiovascular disease; EASD, European Association for the Study of Diabetes; EASL, European Association for the Study of the Liver; EASO, European Association for the Study of Obesity; ELF, enhanced liver fibrosis; FIB-4, Fibrosis-4; FLI, fatty liver index; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HS, hepatic steatosis; MetS, metabolic syndrome; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NFS, NAFLD fibrosis score; NICE, National Institute for Health and Care Excellence; T2D, type 2 diabetes; TE, transient elastography; UCDA, ursodeoxycholic acid; US, ultrasound.

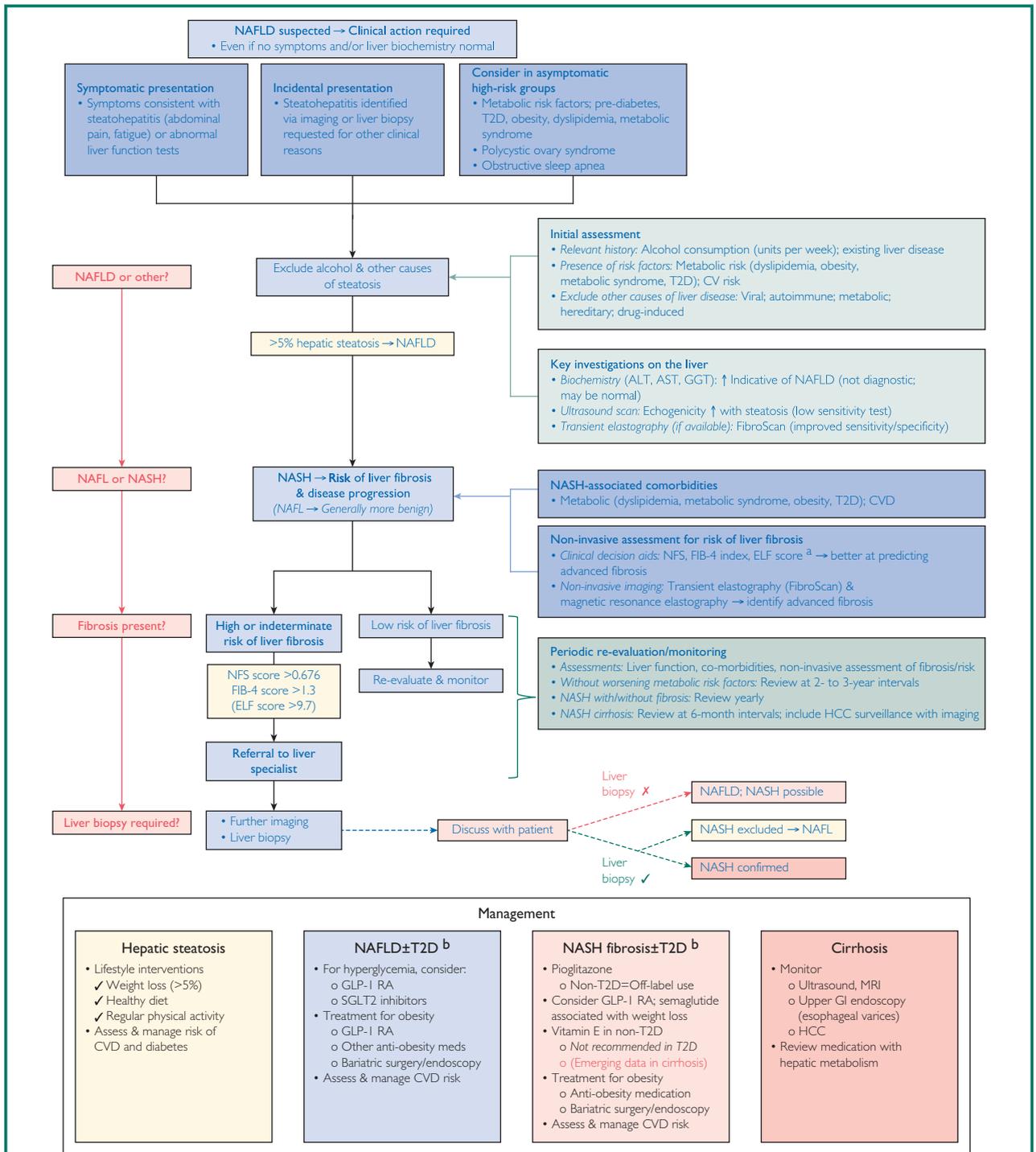


FIGURE 2. Management pathway for nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH).^{3,4,56-58} ALT, alanine aminotransferase; AST, aspartate aminotransferase; CV, cardiovascular; CVD, cardiovascular disease; ELF, enhanced liver fibrosis; FIB-4, Fibrosis-4; GGT, γ -glutamyltransferase; GI, gastrointestinal; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; NAFL, nonalcoholic fatty liver; NFS, NAFLD fibrosis score; SGLT2, sodium-glucose cotransporter 2; T2D, type 2 diabetes; US, ultrasound. ^aThe enhanced liver fibrosis (ELF) score is expected to be available in the United States in 2022. ^bBecause of the current lack of efficacy data, the following agents are not recommended to treat steatohepatitis, but their use may be continued as needed for the treatment of hyperglycemia in persons with T2D and NAFLD or NASH: metformin, acarbose, dipeptidyl peptidase IV inhibitors, and insulin.

concentration (sex adjusted), increased waist circumference, and hypertension.⁴⁴ A bidirectional association between MetS and NAFLD has been established, and the presence of MetS in an individual should prompt an evaluation for NAFLD risk and vice versa.^{3,4} The severity of NAFLD was shown to correlate with the number of MetS criteria present in an individual.⁴⁵ The relationship between NAFLD and T2D is also bidirectional, and the 2 conditions can develop concurrently in a patient.³ Both NAFLD and T2D are associated with insulin resistance, obesity, and inflammation, but the precise order of events is not understood.³⁶ A 60% prevalence of NAFLD in individuals with T2D was reported (meta-analysis of 24 studies involving T2D; >35,000 patients)⁴⁶; T2D is strongly associated with NAFLD progression to NASH^{47,48} and with the risk of advanced fibrosis.⁴⁹ Dyslipidemia (high serum triglyceride and low high-density lipoprotein levels) is also frequently observed in people with NAFLD (prevalence >50%)³ and often occurs secondary to insulin resistance.

Given the association between NAFLD and the metabolic disorders described, it is unsurprising that the risk of CVD is also increased in patients with NAFLD. Although it is not yet clear whether there is a causal relationship between the 2 conditions, NAFLD is at least a risk marker for CVD, and NAFLD has been linked with markers of subclinical atherosclerosis, including coronary artery calcification and increased coronary artery calcium score.³² Therefore, cardiovascular risk assessment should be undertaken in individuals with NAFLD.^{3,4,32} Evidence indicates that NAFLD increases the risk of hypertension, coronary heart disease, cardiomyopathy, and arrhythmias, resulting in increased cardiovascular morbidity and mortality in patients with NAFLD.³² The link between NAFLD and CKD has also been examined,^{31,34} and there is increasing epidemiologic evidence that NAFLD is an independent risk factor for CKD,^{34,50,51} although causality is not yet proven. As with CVD, the occurrence of CKD in NAFLD is not unexpected, given

the presence of multiple CKD risk factors in individuals with NAFLD. Individuals with NAFLD should undergo an assessment of kidney function, and a review of any medication that may affect kidney function should be undertaken. The possible mechanisms linking NAFLD with the development of CVD and CKD have been described^{27,32-34,52,53} (Supplemental Video, available online at <http://www.mayoclinicproceedings.org>).

Nonalcoholic steatohepatitis is now among the top causes of hepatocellular carcinoma (HCC) and the second most common indication for liver transplant in the United States.⁵⁴ The risk for HCC is highest among those with NAFLD cirrhosis, such that surveillance is warranted.⁵⁵ There is also a risk of HCC with lesser levels of liver fibrosis, but there is no observed increased risk for HCC in those assessed as “low risk” of liver fibrosis measured by noninvasive serum biomarkers (eg, Fibrosis-4 [FIB-4] index).⁵⁵

Clinical Pathway for Primary Care Providers

A clinical pathway for assessing individuals with NAFLD and NASH in the primary care setting is presented in Figure 2.^{3,4,56-58}

The key questions to be answered are the following: Does the patient have NAFLD or something else? If NAFLD is diagnosed, does the patient have NASH? If NASH is diagnosed, what is the patient’s risk for development of liver fibrosis? Is a liver biopsy necessary? There is no individual diagnostic test for NAFLD, and it is largely a diagnosis of exclusion. Patients with NAFLD may be identified incidentally during investigation for other conditions (eg, abdominal imaging, liver function tests). People with uncomplicated NAFLD are typically asymptomatic, or their symptoms are vague (eg, fatigue, abdominal discomfort). The presence of clinical features of obesity, T2D, MetS, or dyslipidemia increases the clinical suspicion of NAFLD. Clinicians should consider the following individuals to be “at risk” or “high risk”: those with obesity, T2D, or MetS; those with hepatic steatosis on any imaging study; and those with persistently elevated plasma aminotransferases (at least 2 abnormal values within 6 months). These

individuals should be screened for NAFLD and advanced fibrosis. Clinical action should be taken if NAFLD is suspected, even in the absence of symptoms or abnormal liver biochemistry. Secondary causes of hepatic steatosis and causes of concurrent liver diseases must be excluded to make a diagnosis of NAFLD, including alcohol and drug use, hepatitis C virus (genotype 3), autoimmune liver disease, Wilson disease, and hemochromatosis.^{3,4} Liver biochemistry is inadequate in assessing NAFLD (eg, transaminases were within the normal range in 43% of patients with NAFLD who were enrolled in the NASH Clinical Research Network studies⁵⁹) and is not predictive of liver fat content or fibrosis stage.⁶⁰

First-line identification of hepatic steatosis is done by abdominal ultrasound scan, on which increased echogenicity is indicative of steatosis. Ultrasound is an inexpensive and accessible tool. Although it has limitations, an ultrasound scan offers the convenience of enabling complete liver imaging and liver fibrosis assessment to be carried out in the same session. Other imaging techniques are available,⁶¹ including vibration-controlled transient elastography (VCTE), shear wave elastography,⁶² and magnetic resonance imaging (MRI). For example, FibroScan (Echosens North America) is a transient elastography device that measures liver fat and fibrosis,⁶³ and LiverMultiScan software (Perspectum Ltd) analyzes MRI data,^{64,65} including the generation of MRI proton density fat fraction maps.^{66,67} (Details of imaging modalities are presented in Supplemental Table 1, available online at <http://www.mayoclinicproceedings.org>.)

The initial finding of hepatic steatosis is important for the diagnosis of NAFLD, but it is the presence or absence of liver fibrosis (ie, NASH fibrosis) that is the crucial determinant of liver-related mortality. Importantly, if the stage of fibrosis is F3 (severe [bridging] fibrosis) or higher, the clinical action plan must shift from routine monitoring and lifestyle modification to aggressive management. Liver biopsy remains the “gold standard” for the diagnosis of NASH,³ but it is impractical to perform routinely on

every patient with NAFLD. Furthermore, the procedure has well-documented limitations; it is invasive, there is a risk of procedural complications and sampling errors, and it has cost implications.³ Nevertheless, liver biopsy should be considered in any individual with NAFLD in whom there is a high suspicion of NASH or if other causes of hepatic steatosis or chronic liver disease need to be excluded.^{3,68} A range of noninvasive assessments of liver disease in NAFLD are also available to identify individuals at risk of NASH and liver fibrosis⁶⁹⁻⁷¹; they are broadly divided into risk indices that use serum biomarkers associated with various types of liver disease and imaging techniques to measure liver steatosis or fibrosis (Supplemental Figure, available online at <http://www.mayoclinicproceedings.org>). Anthropometric assessments (eg, BMI) and noninvasive biomarkers (eg, liver fibrosis scores) can be used to make an initial assessment of the patient's risk of NAFLD with liver fibrosis. The preferred noninvasive test is the FIB-4 index^{72,73}; it is validated and free of charge. Other patented scoring systems are available, such as the enhanced liver fibrosis (ELF) score (available in the United States in 2022).⁶⁹ Most of these noninvasive risk indices are better at identifying advanced stages of fibrosis (\geq F3) rather than less advanced stages.⁴ Liver imaging by VCTE, shear wave elastography, or magnetic resonance elastography (where available) may be used to further identify persons who need referral to a hepatologist for consideration of a liver biopsy.^{71,74}

Clinicians should consider doing further work-up if an individual has obesity or T2D and intermediate or high noninvasive liver fibrosis scores. Patients with T2D and a FIB-4 score above 1.3 should be screened by VCTE (if available). In the absence of VCTE, shear wave elastography, or magnetic resonance elastography, clinicians should use risk indices such as the ELF score⁷⁵ or other proprietary biomarkers that establish or exclude advanced fibrosis. Similarly, patients with type 1 diabetes should be screened if they have additional risk factors

TABLE 2. Follow-up Interval and Need for Referral to Hepatologist for Patients With Various Stages of Liver Fibrosis

Liver fibrosis stage	Follow-up interval	Referral to hepatologist
F0-F1 without comorbidities or risk factors	2 to 3 years	No
F0-F1 with comorbidities or risk factors	12 months	No
F2 without comorbidities or risk factors	12 months	Possibly
F2 with comorbidities or risk factors	12 months	Yes
≥F3	6 months	Yes

F0, no fibrosis; F1, mild fibrosis; F2, significant fibrosis; F3, advanced (bridging) fibrosis; F4, cirrhosis.

for NAFLD, such as obesity, MetS, elevated alanine aminotransferase or aspartate aminotransferase (≥ 30 U/L) or FIB-4 score (> 1.3), or hepatic steatosis on imaging.

For an NAFLD patient with liver fibrosis at stage F2 (significant fibrosis) based on biomarkers and the presence of comorbidities, liver imaging (eg, FibroScan) should be carried out with a subsequent referral to a hepatology specialist, and the primary care provider should continue to manage patient care. Patients with liver fibrosis at stage F3 or higher (advanced [bridging] fibrosis) require the involvement of a hepatology specialist. Wherever possible, patients should be encouraged to return to their primary care provider for regular monitoring visits, help with adherence to diets and weight loss programs, and metabolic control (discussed later). If appropriate, patients should be encouraged to consider participating in NAFLD or NASH clinical trials. Ideally, the primary care provider and hepatology specialist should work together closely to manage risk factors and to mitigate disease progression to cirrhosis.

Optimal follow-up in NAFLD is currently undetermined, but EASL-EASD-EASO guidelines recommend the following: patients who have nonalcoholic fatty liver without worsening metabolic risk factors should be monitored at 2- to 3-year intervals; patients with NASH or fibrosis should be monitored annually; and those with NASH cirrhosis should be monitored at 6-month intervals.⁴ Follow-up intervals and criteria for referral to a hepatologist for patients with various stages of liver fibrosis are shown in Table 2. In all cases, monitoring

should include routine biochemistry, assessment of metabolic and CVD risk factors (including blood pressure, lipids, and T2D), and noninvasive assessment of fibrosis.⁴ For patients with cirrhosis, surveillance for HCC with imaging should be carried out every 6 months.⁷⁶ Referral to additional specialists (eg, diabetologist, cardiologist, nephrologist, obesity or nutritional specialist) should also be considered, depending on the clinical profile of an individual patient and the comfort level and experience of the primary care provider in managing these conditions.

Management of Patients With NAFLD

Standard treatment for NAFLD centers on lifestyle modification leading to weight loss, including calorie reduction, exercise, and healthy food intake.^{77,78} The EASL-EASD-EASO guidelines recommend using macronutrients per the Mediterranean diet, in which a large fraction of dietary lipid is provided as monounsaturated fatty acids.⁴ A diet high in monounsaturated fatty acids was shown to lower liver fat and to improve hepatic and total insulin sensitivity.⁷⁹ Data from clinical trials (randomized and non-randomized) have shown an association between weight loss interventions and improved biomarkers of liver disease in NAFLD^{80,81} and NASH.⁸¹ Loss of at least 5% of body weight improved steatosis, and weight loss of 7% to 9% improved most histopathologic changes, but improvement in fibrosis was observed only with weight loss of more than 10%.^{3,77} However, these levels of weight loss are extremely difficult to achieve, let alone to sustain.⁸² Intensive

behavior-based interventions can induce clinically meaningful weight loss and are recommended by the US Preventive Services Task Force⁸³; measures include counseling, self-monitoring, peer support, and relapse prevention. The involvement of primary care practitioners plus other specialists (such as psychologists, dietitians, fitness coaches) is central in supporting an individual through long-term weight loss management.⁸⁴ In individuals in whom these measures are not sufficient, pharmacotherapy is recommended as an adjunct to lifestyle modifications in patients with a BMI above 30 kg/m² or in patients with a BMI above 27 kg/m² in the presence of weight-related comorbidities, such as diabetes, hypertension, and dyslipidemia.⁸⁵ Five medications are currently approved by the US Food and Drug Administration (FDA) for chronic weight management: orlistat (lipase inhibitor), phentermine/topiramate extended release (sympathomimetic plus anticonvulsant), naltrexone extended release/bupropion extended release (opioid antagonist plus aminoketone antidepressant), and liraglutide and semaglutide (glucagon-like peptide 1 receptor agonists [GLP-1 RAs]).⁸⁶ In addition to significant weight loss, semaglutide has been shown to improve NASH, although not fibrosis,⁸⁷ and it is also associated with significant cardioprotective and nephroprotective effects. Bariatric surgery (discussed later) could also be considered in the treatment of persons with NAFLD or NASH and a BMI of 35 kg/m² or higher (≥ 32.5 kg/m² in Asian populations), particularly if T2D is present, when medical therapy has failed to achieve durable weight loss and improvement of comorbidities.

Pharmacologic treatments are intended primarily to improve liver disease and should be offered to patients with progressive NASH (biopsy-proven with fibrosis and cirrhosis).^{3,4} The aim is to interrupt the pathophysiologic processes of NASH, and it is likely that combination drug therapies with different mechanisms of action will be required. Pharmacotherapy may also be used in patients with less severe liver disease but at

high risk of disease progression (MetS, diabetes, persistently elevated alanine aminotransferase, high necroinflammatory activity).⁴ At the time of writing, no pharmacologic agents have completed phase 3 clinical trials or gained regulatory approval for use in the management of NASH in the United States or Europe.^{3,88,89} Adjunctive treatment options for NAFLD and NASH are presented in Table 3.^{3,4,90-101} Treatment recommendations from the NAFLD guidelines are mainly confined to the use of vitamin E (in confirmed NASH; non-diabetes, non-cirrhosis) or pioglitazone (in biopsy-confirmed NASH; off-label use in non-T2D).^{3,4,18} However, both of these treatments come with additional risks and contraindications. Pioglitazone is associated with weight gain, bone loss in women, and increased risk of bladder cancer and heart failure.¹⁰² Long-term vitamin E treatment is associated with an increase in all-cause mortality, hemorrhagic stroke risk, and increased risk of prostate cancer in men.¹⁰³ Limited clinical trials data indicate that GLP-1 RAs and sodium-glucose cotransporter 2 (SGLT2) inhibitors may contribute to improvements in NAFLD and NASH.¹⁰⁴ The results of longer term randomized controlled trials are awaited with interest, particularly as these agents are associated with risk reduction in cardiovascular events,¹⁰⁵ which is the leading cause of NAFLD mortality. Tirzepatide, a dual glucose-dependent insulinotropic polypeptide and GLP-1 RA,¹⁰⁶ is under FDA consideration for use in T2D, but no recommendation can be given for its use in NAFLD or NASH at this time. Several other pharmacologic therapies for NAFLD and NASH are in clinical development¹⁰⁷⁻¹¹⁶ (Supplemental Table 2, available online at <http://www.mayoclinicproceedings.org>). The main agents being evaluated are obeticholic acid (Ocaliva),¹¹⁷ a farnesoid X receptor agonist; arachidyl amido cholanoic acid (Aramchol),¹¹⁸ a stearyl-coenzyme A desaturase modulator; and resmetirom,¹¹⁹ a thyroid hormone receptor β agonist. Following the submission of a New Drug Application to the FDA for obeticholic acid in the treatment of NASH, an Incomplete Response letter was issued in

TABLE 3. Adjunctive Treatment Options in NAFLD and NASH

Drug class	Details
Antioxidants	
Vitamin E	<ul style="list-style-type: none"> • Can be used in patients with biopsy-proven NASH^{3,4,90,91} • Not to be used in NASH patients with <ul style="list-style-type: none"> ○ Diabetes ○ Cirrhosis (because of lack of supporting efficacy data)
Insulin sensitizers	
Metformin	<ul style="list-style-type: none"> • Insufficient data for evidence-based recommendations in NAFLD or NASH treatment^{3,4} <ul style="list-style-type: none"> ○ Rodent study data suggest that metformin reduces liver fat accumulation, but this is not consistently supported by clinical trials data.^{92,93}
Pioglitazone	<ul style="list-style-type: none"> • Can be used in patients with biopsy-proven NASH <ul style="list-style-type: none"> ○ With or without T2D^{3,4,92,94-96} (Use is off-label in the absence of T2D.) • Consider adverse effects associated with glitazones: <ul style="list-style-type: none"> ○ Weight gain, bone fractures (women), heart failure (rare)
Lipid-lowering agents	
Statins	<ul style="list-style-type: none"> • Can be used to treat dyslipidemia in patients with NAFLD or NASH^{3,4,97} • Not to be used in patients with decompensated cirrhosis
Newer glycemic control agents	
GLP-1 RAs	<ul style="list-style-type: none"> • Insufficient data for evidence-based recommendations in NAFLD or NASH treatment³ <ul style="list-style-type: none"> ○ Meta-analysis (24 trials, >6300 participants) reported efficacy in reducing hepatic steatosis and inflammation⁹⁸ and the potential to reverse fibrosis.^{87,98,99} ○ Further clinical trials are needed to make a full assessment (ie, longer duration, use of histologic end points). • Potentially relevant cardiorenal benefits in large randomized clinical trials enrolling patients with T2D¹⁰⁰
SGLT2 inhibitors	<ul style="list-style-type: none"> • Not mentioned in NAFLD/NASH guidelines <ul style="list-style-type: none"> ○ Limited clinical trials data indicate potential beneficial effects in NAFLD (improvement in liver enzymes and liver fat; no evidence of liver fibrosis improvement has been reported).¹⁰¹ ○ Further clinical trials are needed to make a full assessment (ie, longer duration, use of histologic end points). • Potentially relevant cardiorenal benefits in large randomized clinical trials enrolling patients with and without T2D¹⁰⁰

GLP-1 RA, glucagon-like peptide 1 receptor agonist; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; SGLT2, sodium-glucose cotransporter 2; T2D, type 2 diabetes.

June 2020. An FDA re-review based on longer term safety data from the clinical trial is expected in the first half of 2022.¹²⁰

Comorbidities present in patients with NAFLD should be managed according to current standards of care (obesity, prediabetes, and T2D¹²¹; CVD¹²²; hypertension¹²³⁻¹²⁵; dyslipidemia^{126,127}; renal disease^{128,129}). For patients with hypercholesterolemia, statins

should be continued where possible as the leading nonliver cause of mortality in patients with NAFLD is cardiovascular death. For patients with prediabetes, referral to a Centers for Disease Control and Prevention–certified diabetes prevention program or use of metformin is recommended. For patients with T2D, preference should be given to treatments that address insulin resistance (eg, metformin) or

to newer agents such as the GLP-1 RAs that have shown promising data for NASH.

For otherwise eligible obese individuals with NAFLD or NASH, bariatric surgery may be considered if lifestyle measures are unsuccessful or insufficient.^{3,4} However, the potential benefits should be balanced against the risks from perisurgical and postsurgical complications. Data from randomized controlled trials are needed, but observational study data indicate that bariatric surgery may reverse the pathologic liver changes associated with NAFLD^{130,131} in addition to inducing weight loss and improving the features of MetS and T2D.¹³⁰ A prospective study by Lassailly et al¹³² demonstrated a durable and sustained resolution of NASH in 84% of patients at 1 year after bariatric surgery, with progressive reduction in fibrosis observed during 5 years. Recent data on the use of endoscopic bariatric procedures, including the intragastric balloon and endoscopic sleeve gastrectomy, also suggest that other treatment options will be available in the near future.¹³³⁻¹³⁶

CONCLUSION

Primary care providers are frequently at the front line in identifying and assessing individuals with suspected NAFLD. They can expect to see increasing numbers of patients with this disease, given that the prevalence of NAFLD is increasing—fueled by the global epidemic of obesity and T2D. In addition to the hepatic consequences, NAFLD and NASH are associated with an increased risk of CVD morbidity and mortality as well as CKD and cancer-related mortality. Prompt diagnosis of NAFLD, determination of NASH status, and assessment of liver fibrosis risk are critical to improve patient outcomes. Liver biopsy is the gold standard for diagnosis of NASH but has disadvantages; thus, noninvasive biomarkers are being used more frequently. Current clinical guidelines for the management of NAFLD have many points in common but also diverge in several areas. In the United States, patients with NAFLD or NASH should be treated according to AASLD guidelines.

Importantly, comorbid conditions including obesity, prediabetes and T2D, dyslipidemia, and CVD should be treated aggressively, especially in patients with NASH or fibrosis. As new data from clinical trials investigating potential NAFLD and NASH treatments become available, it is anticipated that a greater consensus in clinical practice will occur.

ACKNOWLEDGMENTS

Medical writing assistance, supported financially by Boehringer Ingelheim Pharmaceuticals, Inc, was provided by Debra Brocksmith, MB ChB, PhD, of Elevate Scientific Solutions during the preparation of this manuscript. Boehringer Ingelheim Pharmaceuticals, Inc was given the opportunity to check the data in this manuscript for factual accuracy only.

Rajia Arbab, MSc, DO candidate at Lake Erie College of Osteopathic Medicine (Erie, Pennsylvania), research assistant to Dr Basu, provided assistance in developing Figure 1.

USEFUL RESOURCES

Fibrosis Risk Calculators (Serum Biomarkers)

- MD Calc, Fibrosis-4 (FIB-4) Index for Liver Fibrosis: <https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis>
- MD Calc, AST to Platelet Ratio Index (APRI): <https://www.mdcalc.com/ast-platelet-ratio-index-apri>
- MD Calc, NAFLD Fibrosis Score (NFS): <https://www.mdcalc.com/naflid-non-alcoholic-fatty-liver-disease-fibrosis-score>

NAFLD/NASH Resources

- American Association for the Study of Liver Diseases: <https://www.aasld.org/>
- American College of Gastroenterology: <https://gi.org/topics/fatty-liver-disease-naflid/>
- American Liver Foundation: <https://liverfoundation.org/for-patients/about-the->

[liver/diseases-of-the-liver/non-alcoholic-fatty-liver-disease/](https://www.mayoclinic.org/diseases-conditions/liver/diseases-of-the-liver/non-alcoholic-fatty-liver-disease/)

- European Association for the Study of the Liver: <https://easl.eu/>
- LiverScreen: <https://www.liverscreen.eu/>
 - Population-based screening study for liver fibrosis across European countries; study started in January 2020
- Medscape: <https://emedicine.medscape.com/gastroenterology>

Patient and Caregiver Resources

- Fatty Liver Foundation (fatty liver, NAFLD, NASH, and cirrhosis): <https://www.fattyliverfoundation.org/>
- National Institute of Diabetes and Digestive and Kidney Diseases (NAFLD, NASH): <https://www.niddk.nih.gov/health-information/liver-disease/nafl-d-nash>
- The NASH Education Program: <https://www.the-nash-education-program.com/what-is-nash/>

POTENTIAL COMPETING INTERESTS

R.B. has received research support from AstraZeneca and Abbott Diabetes Care. M.N. has been on the advisory board for 89BIO, Gilead, Intercept, Pfizer, Novartis, Novo Nordisk, Allergan, Blade, Echosens, Fractyl, Terns, OWL, Siemens, Roche Diagnostic, and Abbott; M.N. has received research support from Allergan, BMS, Gilead, Galmed, Galectin, Genfit, Conatus, Enanta, Madrigal, Novartis, Shire, Viking, and Zydus; M.N. is a minor shareholder or has stocks in Anaetos and Viking. J.M.C. has served on a scientific advisory board for Boehringer Ingelheim Pharmaceuticals, Inc, and Novo Nordisk.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://www.mayoclinicproceedings.org>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **AASLD**, American Association for the Study of Liver Diseases; **BMI**, body mass index; **CKD**, chronic kidney disease; **CVD**, cardiovascular disease; **EASD**, European Association for the Study of Diabetes; **EASL**, European Association for the Study of the Liver; **EASO**, European Association for the Study of Obesity; **FIB-4**, Fibrosis-4 index; **GLP-1 RA**, glucagon-like peptide 1 receptor agonist; **HCC**, hepatocellular carcinoma; **MetS**, metabolic syndrome; **MRI**, magnetic resonance imaging; **NAFLD**, nonalcoholic fatty liver disease; **NASH**, nonalcoholic steatohepatitis; **T2D**, type 2 diabetes; **VCTE**, vibration-controlled transient elastography

Grant Support: The work was supported by NIH grant DK R01 029953 (R.B.). Medical writing support was funded by Boehringer Ingelheim Pharmaceuticals, Inc (Ridgefield, Connecticut). The authors received no direct compensation related to the development of the manuscript.

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