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CLINICAL PRACTICE UPDATE

AGA Clinical Practice Update: Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Lean Individuals: Expert Review

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DESCRIPTION: Nonalcoholic fatty liver disease (NAFLD) is well recognized as a leading etiology for chronic liver disease, affecting >25% of the US and global populations. Up to 1 in 4 individuals with NAFLD have nonalcoholic steatohepatitis, which is associated with significant morbidity and mortality due to complications of liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma. Although NAFLD is observed predominantly in persons with obesity and/or type 2 diabetes mellitus, an estimated 7%–20% of individuals with NAFLD have lean body habitus. Limited guidance is available to clinicians on appropriate clinical evaluation in lean individuals with NAFLD, such as for inherited/genetic disorders, lipodystrophy, drug-induced NAFLD, and inflammatory disorders. Emerging data now provide more robust evidence to define the epidemiology, natural history, prognosis, and mortality of lean individuals with NAFLD. Multiple studies have found that NAFLD among lean individuals is associated with increased cardiovascular, liver, and all-cause mortality relative to those without NAFLD. This American Gastroenterological Association Clinical Practice Update provides Best Practice Advice to assist clinicians in evidence-based approaches to the diagnosis, staging, and management of NAFLD in lean individuals. **METHODS:** This expert review was commissioned and approved by the American Gastroenterological Association (AGA) Institute Clinical Practice Updates Committee and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership and underwent internal peer review by the Clinical Practice Updates Committee and external peer review through standard procedures of *Gastroenterology*.

BEST PRACTICE ADVICE STATEMENTS

BEST PRACTICE ADVICE 1: Lean NAFLD should be diagnosed in individuals with NAFLD and body mass index <25 kg/m^2 (non-Asian race) or body mass index <23 kg/m^2 (Asian race). **BEST PRACTICE ADVICE 2:** Lean individuals with NAFLD should be evaluated routinely for comorbid conditions, such as type 2 diabetes mellitus, dyslipidemia, and hypertension. **BEST PRACTICE ADVICE 3:** Lean individuals with NAFLD should be risk stratified for hepatic fibrosis to identify those with advanced fibrosis or cirrhosis. **BEST PRACTICE ADVICE 4:** Lean individuals in the general population should not undergo routine screening for NAFLD; however, screening should be considered for individuals older than 40 years with type 2 diabetes mellitus. **BEST PRACTICE ADVICE 5:** NAFLD should be considered in lean individuals with metabolic diseases (such as type 2 diabetes mellitus, dyslipidemia, and hypertension), elevated liver biochemical tests, or incidentally noted hepatic steatosis. **BEST PRACTICE ADVICE 6:** Clinicians should query patients routinely regarding alcohol consumption patterns in all patients with lean NAFLD. **BEST PRACTICE ADVICE 7:** In patients with lean NAFLD, other causes of liver disease should be ruled out, including other causes of fatty liver, such as HIV, lipodystrophy, lysosomal acid lipase deficiency, familial hypobetalipoproteinemia, and medication-induced hepatic steatosis (methotrexate, amiodarone, tamoxifen, and steroids). **BEST PRACTICE ADVICE 8:** Current evidence is inadequate to support routine testing for genetic variants in patients with lean NAFLD. **BEST PRACTICE ADVICE 9:** Liver biopsy, as the reference standard, should be considered if there is uncertainty regarding contributing causes of liver injury and/or the stage of liver fibrosis. **BEST PRACTICE ADVICE 10:** Serum indices (NAFLD fibrosis score and Fibrosis-4 score) and imaging techniques (transient elastography and magnetic resonance elastography) may be used as alternatives to liver biopsy for fibrosis staging and patient follow-up. These tests can be performed at the time of diagnosis and repeated at intervals of 6 months to 2 years, depending on fibrosis stage and the patient's response to intervention. **BEST PRACTICE ADVICE 11:** If noninvasive tests (eg, Fibrosis-4 and NAFLD fibrosis score) are indeterminate, a second noninvasive test (eg, transient elastography or magnetic resonance elastography) should be performed to confirm the stage and prognosis of NAFLD. **BEST PRACTICE ADVICE 12:** In lean patients with NAFLD, lifestyle intervention, including exercise, diet modification, and avoidance of fructose- and sugar-sweetened drinks, to target a modest weight loss of 3%–5% is suggested. **BEST PRACTICE ADVICE 13:** Administration of vitamin E may be considered in lean persons with biopsy-confirmed nonalcoholic steatohepatitis, but without type 2 diabetes mellitus or cirrhosis. Oral pioglitazone 30 mg daily may be considered in lean persons with biopsy-confirmed nonalcoholic steatohepatitis without cirrhosis. **BEST PRACTICE ADVICE 14:** The therapeutic role of glucagon-like peptide-1 agonists and sodium-glucose cotransporter-2 inhibitors in the management of lean NAFLD is not fully defined and requires further investigation. **BEST PRACTICE ADVICE 15:** Hepatocellular carcinoma surveillance with abdominal ultrasound with or without serum

α-fetoprotein twice per year is suggested in patients with lean NAFLD and clinical markers compatible with liver cirrhosis.

Nonalcoholic fatty liver disease (NAFLD) is well recognized as a leading etiology for chronic liver disease with a global public health impact, affecting >25% of the US and global populations.[1] Up to 1 in 4 patients with NAFLD may have nonalcoholic steatohepatitis (NASH), which is associated with considerable morbidity and mortality due to complications of liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC).[1] In the context of rising incidence and prevalence of NAFLD in tandem with obesity and the metabolic syndrome, NAFLD-associated cirrhosis and HCC now represent a leading indication for liver transplantation in the United States.[2,3]

Although NAFLD is observed predominantly in persons with obesity and/or type 2 diabetes mellitus (T2DM), an estimated 7%–20% of individuals with NAFLD have lean body habitus.[1,4–7] Although similar NASH pathogenesis may be observed in lean patients with NAFLD, rates of disease progression, associated conditions, and diagnostic and management approaches differ for lean vs nonlean patients with NAFLD. There is a major unmet need to provide clear guidance to clinicians regarding the evaluation and management of NAFLD among lean patients.

This review is designed to provide best practice advice on several key clinical issues pertaining to the diagnosis, risk stratification, and treatment of NAFLD in lean individuals. We developed 15 Best Practice Advice statements to address key issues with high clinical relevance.

Best Practice Advice 1: Lean NAFLD should be diagnosed in individuals with NAFLD and a body mass index (BMI) <25 kg/m^2 (non-Asian race) or a BMI <23 kg/m^2 (Asian race).

Lean NAFLD is generally defined by the presence of NAFLD in an individual who does not have an overweight or obese BMI. For adults, the Centers for Disease Control and Prevention and the World Health Organization define a normal range BMI to be between 18.5 and 24.9 kg/m^2; BMI of 25–29.9 kg/m^2 is considered overweight and BMI of 30–34.9 kg/m^2 is grade 1 obesity.[8] The World Health Organization recommends a lower BMI cutoff for overweight and obesity (BMI 23–27.5 kg/m^2 for overweight and BMI >27.5 kg/m^2 for obesity) for those of Asian ancestry, recognizing that different populations may experience metabolic risk at a lower BMI.[8,9] We suggest using the term *lean NAFLD* when discussing NAFLD in the setting of a normal range BMI, while considering race-based cutoffs. Although the terms *nonobese NAFLD* and *lean NAFLD* are sometimes used interchangeably, this review will focus on lean patients, as defined by normal BMI. Recent findings from the Global NAFLD/NASH Registry revealed that approximately 6.8% of patients with confirmed NASH have lean body habitus and, relative to overweight/obese patients, this cohort appeared to be older, more often Asian, and had fewer components of the metabolic syndrome, while retaining a similar risk for advanced liver fibrosis.[10] Data from the National Health and Nutrition Epidemiology Survey III epidemiology survey revealed that 10.8% of lean individuals had evidence of NAFLD and were characterized as more likely to be older and were more frequently men.[11]

Best Practice Advice 2: Lean individuals with NAFLD should be evaluated routinely for comorbid conditions, such as T2DM, dyslipidemia, and hypertension.

Lean patients with NAFLD have been observed to have alterations in bile salt metabolism, which may contribute to pathologic changes in cholesterol metabolism and liver fat.[12] Various studies have also reported differences in genetic variants, including the *TM6SF2* rs58542926 (T) allele, which protect against diet-associated obesity compared with those with nonlean NAFLD.[12]

An individual's risk for cardiometabolic disease may differ in those with lean NAFLD compared with nonlean NAFLD. In several observational studies, patients with lean NAFLD had a lower proportion of cardiometabolic disease risk factors, including hypertension, T2DM, and metabolic syndrome, and less atherosclerotic disease compared with those with nonlean NAFLD.[6,13] Other studies have shown that, compared with lean subjects without NAFLD, lean individuals with NAFLD have a similar or higher prevalence of multiple cardiometabolic risk factors, risk scores,[14] and cardiovascular events than overweight and obese persons with NAFLD.[13,15–17] We suggest that lean persons with NAFLD be evaluated and treated for modifiable cardiovascular disease risk factors, including diabetes, dyslipidemia, and hypertension.

Best Practice Advice 3: Lean individuals with NAFLD should be risk stratified for hepatic fibrosis to identify those with advanced fibrosis or cirrhosis.

Several cross-sectional studies have observed that lean participants with NAFLD have a lower prevalence of advanced fibrosis and cirrhosis compared with those that were overweight or obese with NAFLD.[6,13] In a small longitudinal study, lean participants with biopsy-confirmed NAFLD followed for a median of 8.4 years had a higher risk of liver-related death compared with overweight or obese participants with NAFLD, although those with lean NAFLD had a higher prevalence of advanced fibrosis at baseline in this study.[18] A larger longitudinal study of more than 1300 subjects with biopsy-confirmed NAFLD from Europe and Australia found that those with lean NAFLD had less severe histologic disease compared with those with nonlean NAFLD.[19] Despite these differences, over about 7.5 years of follow-up, nearly 5% of those with lean NAFLD

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Abbreviations used in this paper: AASLD, American Association for the Study of Liver Diseases; AUROC, area under receiver operating characteristic; BMI, body mass index; ELF, Enhanced Liver Fibrosis; FIB-4, Fibrosis-4; GLP-1, glucagon-like peptide-1; HCC, hepatocellular carcinoma; MRE, magnetic resonance elastography; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NFS, nonalcoholic fatty liver disease fibrosis score; NIT, noninvasive test; T2DM, type 2 diabetes mellitus; TE, transient elastography.

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reported liver-related events, even though the vast majority maintained a lean BMI.[19] Similarly, in a population-based Swedish registry study with nearly 20 years of follow-up, patients with lean NAFLD had lower stages of fibrosis at baseline, but a higher risk for developing severe liver disease compared with nonlean patients with NAFLD.[15] These findings highlight that individuals with lean NAFLD are at risk for progressive liver disease, independent of weight gain, and should not be classified as having a benign NAFLD phenotype. All patients with lean NAFLD should undergo risk stratification with noninvasive tests (NITs) to identify those at highest risk for progression (see Best Practice Advice 10).

Best Practice Advice 4: Lean individuals in the general population should not undergo routine screening for NAFLD; however, screening should be considered for individuals older than 40 years with T2DM.

If approximately 10%–20% of individuals with NAFLD are lean, this translates to 8–10 million adults in the United States with lean NAFLD.[20] There is a lack of consensus on who should be screened for NAFLD, regardless of BMI. The European Association for the Study of Liver and the European Diabetes and Obesity Societies recommend screening for NAFLD in all patients with obesity or metabolic syndrome.[21] The American Diabetes Association recommends evaluation for NASH and hepatic fibrosis in persons with T2DM and elevated liver biochemical tests or fatty liver on ultrasound.[22] The American Association for the Study of Liver Disease (AASLD) does not endorse NAFLD screening[23] and cites limited cost-effectiveness for screening for NAFLD in patients with T2DM.[24] However, emerging data suggest that screening and risk-stratification pathways are cost-effective when applied to those with T2DM.[25–27] This led to the recent adoption of screening in high-risk individuals by the American Gastroenterological Association.[27] Because the prevalence of NAFLD among lean individuals is relatively low, general screening for NAFLD among lean individuals is not advised. However, screening for NAFLD and subsequent risk stratification for advanced fibrosis should be performed in lean persons with T2DM.

Best Practice Advice 5: NAFLD should be considered in lean individuals with metabolic diseases (such as T2DM, dyslipidemia, and hypertension), elevated liver biochemical tests, or incidentally noted hepatic steatosis.

In individuals with multiple cardiometabolic disease risk factors, elevations in liver biochemical tests, or incidentally noted hepatic steatosis, NAFLD should be considered in the differential diagnosis across the BMI range.[28] We suggest that the initial diagnostic approach should be the same for lean or nonlean individuals with suspected NAFLD. In the case of elevated liver biochemical tests, patients should undergo standard evaluation, including for drug-induced liver injury and chronic liver diseases.[29]

Best Practice Advice 6: Clinicians should query patients routinely regarding alcohol consumption patterns in all patients with lean NAFLD.

When distinguishing between NAFLD and alcohol-related liver disease, many consider an average alcohol consumption of more than 14 drinks per week for women or 21 drinks per week for men to be consistent with alcohol-related liver disease rather than NAFLD.[23] However, alcohol use below this threshold likely contributes to liver fat. In a recent cohort study of participants who consumed alcohol within thresholds consistent with NAFLD, higher average weekly alcohol use was associated with a higher prevalence of computed tomography–defined NAFLD.[30] Moreover, alcohol use patterns, including the number of drinking days per week, the maximum number of drinks consumed in 24 hours, and binge drinking behavior, are all associated with increased odds of NAFLD.[30] We suggest that health care providers query patients on alcohol use and alcohol consumption patterns when considering possible contributions of alcohol to hepatic steatosis. In addition, underreported alcohol use likely contributes to the misdiagnosis of NAFLD in lean individuals. Sensitive biomarkers of alcohol use, including urine ethyl glucuronide (detection within 3–5 days) and blood phosphatidylethanol (detection within 1–2 weeks), can be considered to exclude alcohol overuse.

Best Practice Advice 7: In patients with lean NAFLD, other causes of liver disease should be ruled out, including other causes of fatty liver, such as HIV, lipodystrophy, lysosomal acid lipase deficiency, familial hypobetalipoproteinemia, and medication-induced hepatic steatosis (methotrexate, amiodarone, tamoxifen, and steroids).

Causes of primary or secondary steatosis in lean persons should be considered. The causes of lean NAFLD include those related to diet (eg, high-fructose or high-fat intake); changes in fat distribution of the body (eg, visceral obesity); changes in body composition (eg, lipodystrophy in HIV and non-HIV persons); medications (methotrexate, amiodarone, tamoxifen, and corticosteroids); and rare congenital abnormalities, such as lysosomal acid lipase deficiency, familial hypobetalipoprotein B, and abetalipoproteinaemia.[31,32] Other conditions that should be considered are viruses (eg, hepatitis C genotype 3), nutritional and gastrointestinal tract–related factors (eg, total parenteral nutrition), endocrine disorders (eg, hypothyroidism), and toxin exposures (eg, vinyl chloride) (Table 1).[32]

We suggest a stepwise approach to ruling out alternative diagnoses for lean individuals with suspected NAFLD, particularly if cardiometabolic risk factors are absent and should be guided by clinical context, as outlined in Table 2.

Best Practice Advice 8: Current evidence is inadequate to support routine testing for genetic variants in patients with lean NAFLD.

NAFLD pathophysiology is complex and is likely the result of interactions between many factors, including the interplay between genetic variants and environmental factors. In up to 75% of cases,[33] variable hepatic fat accumulation has been found related to inherited factors. Genetic variants in *PNPLA3 I148M, TM6SF2 E167K, MBOAT7, GCKR,* and *HSD17B13* are the most common variants related to NAFLD and its severity.[34] These variants, especially the *PNPLA3* and *TM6SF2* variants,[35–37] have been associated with the severity of steatosis, steatohepatitis, fibrosis,

Table 1. Potential Secondary Causes of Fatty Liver in Lean Individuals

Liver-related	Systemic
Specific liver conditions	Endocrine
Chronic hepatitis C (especially genotype 3)	Hypothyroidism
Wilson's disease	Hypopituitarism
A1 antitrypsin	Polycystic ovary syndrome
Liver diseases of pregnancy	Growth hormone insufficiency
Acute fatty liver of pregnancy	Other genetic disorders
HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome	Lysosomal acid lipase deficiency
Drug-induced liver injury	Familial hypobetalipoprotein B
Methotrexate, amiodarone, corticosteroids, valproic acid, tetracycline, and amphetamines	Abetalipoproteinemia
HIV medications (cART: didanosine, stavudine, and zidovudine)	Urea cycle disorders
	Hereditary fructose intolerance
	Glycogen storage disease
	Fatty acid oxidation disorders
	Autosomal recessive carbamoyl phosphate synthetase I deficiency
	Environmental toxins
	Metal: Arsenic, cadmium, mercury, lead
	Chloroalkenes: (vinyl chloride, trichloroethylene, perchloroethylene)
	Herbicides, pesticide Nutritional effects
	Total parenteral nutrition
	Malnutrition/Kwashiorkor disease
	Acute weight loss (eg, bariatric surgery, prolonged fasting)
	Short bowel syndrome
	Celiac disease

cirrhosis, and risk of HCC and mortality.[38] However, *HSD17B13* has been linked to robust protection against liver inflammation, cirrhosis, HCC, and even to mortality.[39,40] Measurement of polygenic risk scores has evolved as a potential method to balance the genetic variants and achieve higher accuracy in correlating the disease and its severity. The risk scores are a weighted sum of disease-risk alleles that a person carries.[33,41–43] The polygenic or genetic risk scores are in early stages of investigation and are not advised for clinical use. Furthermore, given the paucity of data on genetic variants in lean NAFLD, routine genotyping in lean NAFLD patients is not advised.[44–47] Additional studies are needed to inform an evidence-based approach to the selection of patients for genetic testing, appropriate assays, test interpretation, and clinical management.

Best Practice Advice 9: Liver biopsy, as the reference standard, should be considered if there is uncertainty regarding contributing causes of liver injury and/or the stage of liver fibrosis.

Liver biopsy is considered the reference standard for identifying NASH and staging hepatic fibrosis.[23,48] However, liver biopsy is invasive and is associated with sampling errors and both intraobserver and interobserver variability.[23] Despite its drawbacks, liver biopsy is the definitive method for diagnosing NAFLD and NASH, especially in the lean NAFLD population, and excluding alternative etiologies (see Table 1). Liver biopsy should therefore be considered in lean patients with NAFLD if other causes cannot be excluded through routine testing. In addition, liver biopsy, along with other specific tests (see Table 2), may be helpful in the considerations of more rare causes of lean NAFLD. As a standard practice, a tissue sample of $\geq$2 cm in length is preferred to allow an accurate reading.[49] The Brunt criteria and Kleiner score can be used to assess those patients who have NASH to provide categorical assessment of disease activity and fibrosis.[50,51]

Best Practice Advice 10: Serum indices (NAFLD fibrosis score and Fibrosis-4 score [FIB-4]) and imaging techniques (transient elastography [TE] and magnetic resonance elastography [MRE]) may be used as alternatives to liver biopsy for fibrosis staging and patient follow-up. These tests can be performed at the time of diagnosis and repeated at intervals of 6 months to 2 years, depending on fibrosis stage and the patient's response to intervention.

Given the limitations of liver biopsy, numerous NITs have been developed and have shown accuracy in the assessment of NAFLD-related fibrosis in lean individuals (Supplementary Table 1).[52] NITs can be categorized into the following: those that use routinely performed laboratory and clinical tests to calculate a risk score, such as the FIB-4 and NAFLD fibrosis score (NFS); imaging tools that quantify liver stiffness, the most frequently used method being TE, but 2-dimensional shear wave elastography and MRE are also used; and blood-based biomarkers of liver fibrosis, such as the Enhanced Liver Fibrosis (ELF) test.[52–58] Because fibrosis is the histologic feature most associated with poor outcomes, many NITs are focused on identifying NAFLD-related fibrosis and/or fibrotic NASH. Few studies have specifically evaluated NITs in lean individuals with NAFLD. In a multicenter study of 709 participants with NAFLD, of whom 11% were lean, the area under the receiver operating characteristic (AUROC) curves for identifying advanced fibrosis were generally higher for most NITs among lean

Table 2. Stepwise Approach for Ruling Out Alternative Causes of Lean Nonalcoholic Fatty Liver Disease

Diagnosis	Diagnostic tool	Clinical management
Consider more common alternative diagnoses in most lean patients with suspected NAFLD		
Covert alcohol use	Alcohol Use Disorders Identification Test Carbohydrate-deficient transferrin Phosphatidylethanol	Alcohol cessation counseling
Hepatitis C	Hepatitis C antibody/RNA	Direct-acting antiviral therapy
Celiac disease	Tissue transglutaminase/IgA level	Gluten-free diet
Hypothyroidism	Thyroid-stimulating hormone level	Levothyroxine
Drug-induced liver injury	Review medications: methotrexate, amiodarone, corticosteroids, valproic acid, tetracycline, and amphetamines HIV medications (cART: didanosine, stavudine, and zidovudine)	Consider alternative medications, if possible

Clinical scenario	Diagnosis	Diagnostic tool	Clinical management
Consider additional alternative diagnoses depending on clinical suspicion			
Muscle weakness and/or neurologic symptoms Low alkaline phosphatase level	Wilson's disease	Ceruloplasmin (low) 24-h urinary copper level	Copper chelation therapy
Chronic obstructive pulmonary disease Family history	α-1 antitrypsin deficiency	Genetic testing	α-1 antitrypsin protein infusions Lung/liver transplantation
Pregnancy	Acute fatty liver of pregnancy HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome	Liver biochemical tests Hepatic ultrasound Platelet count	Delivery
Irregular menses Hirsutism Acne Male-pattern baldness Infertility	Polycystic ovary syndrome	Testosterone Luteinizing hormone Follicle-stimulating hormone	Hormonal birth control
Reduced muscle strength Short stature Dyslipidemia	Hypopituitarism/growth hormone deficiency	Low growth hormone	Referral to endocrinologist
Lipid abnormalities	Hypobetalipoproteinemia	Low triglycerides, apoB, LDL levels Genetic testing	Vitamin E supplementation
Lipid abnormalities	*ABHD5* insufficiency	Elevated triglycerides and LDL levels	Family counseling
Hepatomegaly Microvesicular steatosis Splenomegaly Malabsorption Steatorrhea Lipid abnormalities	Lysosomal acid lipase deficiency	High LDL Low high-density lipoprotein level Lysosomal acid lipase enzyme activity	Sebelipase alfa treatment
Lipodystrophy	Familial partial lipodystrophy syndromes Secondary lipodystrophy from HIV	Low leptin	Leptin replacement therapy
Muscle weakness and fatigue	Mitochondrial disorders	Elevated lactate	Dietary restriction/ supplementation
Mental status changes	Urea cycle disorders (eg, ornithine transcarbamylase deficiency or cabamoyl phosphate synthetase I deficiency)	High blood ammonia	Prevent excess ammonia formation

LDL, low-density lipoprotein.

compared with obese participants.[59] In a study of patients with lean NAFLD, FIB-4 and NFS performed similarly in lean and obese patients, which is important, as BMI is a part of the NFS calculation.[59] Importantly, NITs had high negative predictive values, which demonstrates the usefulness at ruling out advanced fibrosis. Finally, this study found that vibration-controlled TE (or TE) has similar performance in lean and obese patients.

MRE, with 2-dimensional MRE, has been accurate in assessing fibrosis in patients with NAFLD.[60] Although studies with MRE in lean NAFLD have not been conducted, MRE is thought to be less affected by BMI or body habitus.[60] MRE should be considered, when available, as a confirmatory test for fibrosis assessment (Figure 1). The ELF test consists of measurements of N-terminal propeptide of type III procollagen, hyaluronic acid, and tissue inhibitor of metalloproteinase-1. ELF test has been used to assess hepatic fibrosis in addition to predicting liver outcomes. A systematic review and meta-analysis found that an ELF low cutoff value of 7.7 has a sensitivity of 0.93 (95% CI, 0.82–0.98) for excluding fibrosis and ELF at a high cutoff at 9.80 had a high specificity of 0.86 (95% CI, 0.77–0.92) for diagnosing fibrosis.[55] ELF has not been tested in patients with lean NAFLD and further studies are needed. We concluded that ELF test may be used as a confirmatory prognostic test in patients with lean NAFLD until further data are available.

We have proposed an algorithm for assessing and staging patients with lean NAFLD (Figure 1). Longitudinal NIT assessment of fibrosis should be considered every 6 months to 1 year in patients who have F2 or greater fibrosis and every 1–2 years in those who have F0 or F1 fibrosis.

Best Practice Advice 11: If noninvasive tests (eg, FIB-4 and NFS) are indeterminate, a second noninvasive test (eg, TE or MRE) should be performed to confirm the stage and prognosis of NAFLD.

Sequential testing, with 2 serologic tests or a serologic test combined with an imaging test, is likely to minimize the frequency of indeterminate cases and improve diagnostic accuracy. A study from primary care clinics in England assessed sequential testing of FIB-4 followed by TE among patients with T2DM.[61] That strategy led to a nearly 7-fold increased diagnostic rate for identifying advanced fibrosis, and the data were supported by a meta-analysis that assessed more than 5700 patients in whom sequential testing with FIB-4 and TE improved the sensitivity and specificity to rule in or rule out advanced fibrosis.[62] Data from the United Kingdom demonstrated that a FIB-4+ELF care pathway reduced the referral of patients with mild disease.[63] Limited data specific to lean patients with NAFLD are available. However, sequential testing with serum tests and elastography may increase the accuracy of NITs in fibrosis staging in this population (Figure 1).

Finally, given that patients with NASH and F2 or greater fibrosis are the targeted population for clinical therapy trials and future NASH-directed pharmacotherapy, recent studies have focused on combining biomarkers to identify NASH and F2 or greater fibrosis or "at-risk NASH" more accurately. The MRE FIB-4 scores combine MRE with FIB-4 in diagnosing F2 or greater fibrosis with high accuracy and excellent positive predictive value.[64] The FibroScan–aspartate aminotransferase score combines the steatosis values measured via controlled attenuation parameter on TE, liver stiffness measurement on TE, and aspartate aminotransferase values to diagnose at-risk NASH, with an AUROC between 0.8 and 0.85.[65] The MR imaging–aspartate aminotransferase score combines the steatosis values measured via MR imaging proton density fat fraction, liver stiffness measurement on MRE, and aspartate aminotransferase to diagnose patients with at-risk NASH; MR imaging–aspartate aminotransferase had an AUROC of 0.93 in the derivation cohort and an AUROC of 0.86 in the validation cohort.[66] Finally, NIS-4 is a blood-based biomarker panel that consists of miR-34a-5p, α-2 macroglobulin, YKL-40, and glycated hemoglobin.[67] The NIS-4 test assesses at-risk NASH[67] and it had an AUROC of 0.80 (95% CI, 0.73–0.85) in the discovery cohort. These tests have not been evaluated in lean NAFLD, but they may be used in identifying patients with at-risk NASH (Figure 1). The advantage of these tests is that they measure steatohepatitis combined with fibrosis, thus examining the entire spectrum of the disease pathobiology.

Best Practice Advice 12: In lean patients with NAFLD, lifestyle intervention, including exercise, diet modification, and avoidance of fructose- and sugar-sweetened drinks, to target a modest weight loss of 3%–5% is suggested.

Lifestyle modification and medical weight loss through hypocaloric diet and exercise is advised as a first-line intervention for treatment of NAFLD. However, specific guidance on how best to operationalize recommendations in obese and lean individuals is currently limited and does not address variability in clinical phenotype based on host and liver disease factors. The 2017 Guidelines of the AASLD address the role of lifestyle modification as follows: "Weight loss generally reduces hepatic steatosis, achieved either by hypocaloric diet alone or in conjunction with increased physical activity."[23] In a large longitudinal study that included more than 2000 lean adults with NAFLD, weight reduction over a median follow-up of 3 years was associated with NAFLD resolution in a dose-dependent manner.[68] A randomized controlled trial from Asia investigated the effects of a 12-month lifestyle intervention on weight reduction and MR spectroscopy liver fat fraction in nonobese and obese patients.[69,70] As expected, more patients in the intervention group had improvement in MR liver fat, regardless of their obesity status. Interestingly, almost one-half of nonobese individuals achieved NAFLD remission with 3%–5% weight loss, and the same was reached in obese individuals with 7%–10% weight loss. After up to 6 years of follow-up, nonobese patients in the lifestyle intervention group were more likely to maintain weight loss and alanine aminotransferase normalization compared with the reference group.

Other studies have shown that physical activity and aerobic and anaerobic exercise were associated with reduction in liver fat and other metabolic benefits independent of weight loss.[71–73] Finally, high fructose consumption is a well-known risk factor for NAFLD and NASH,

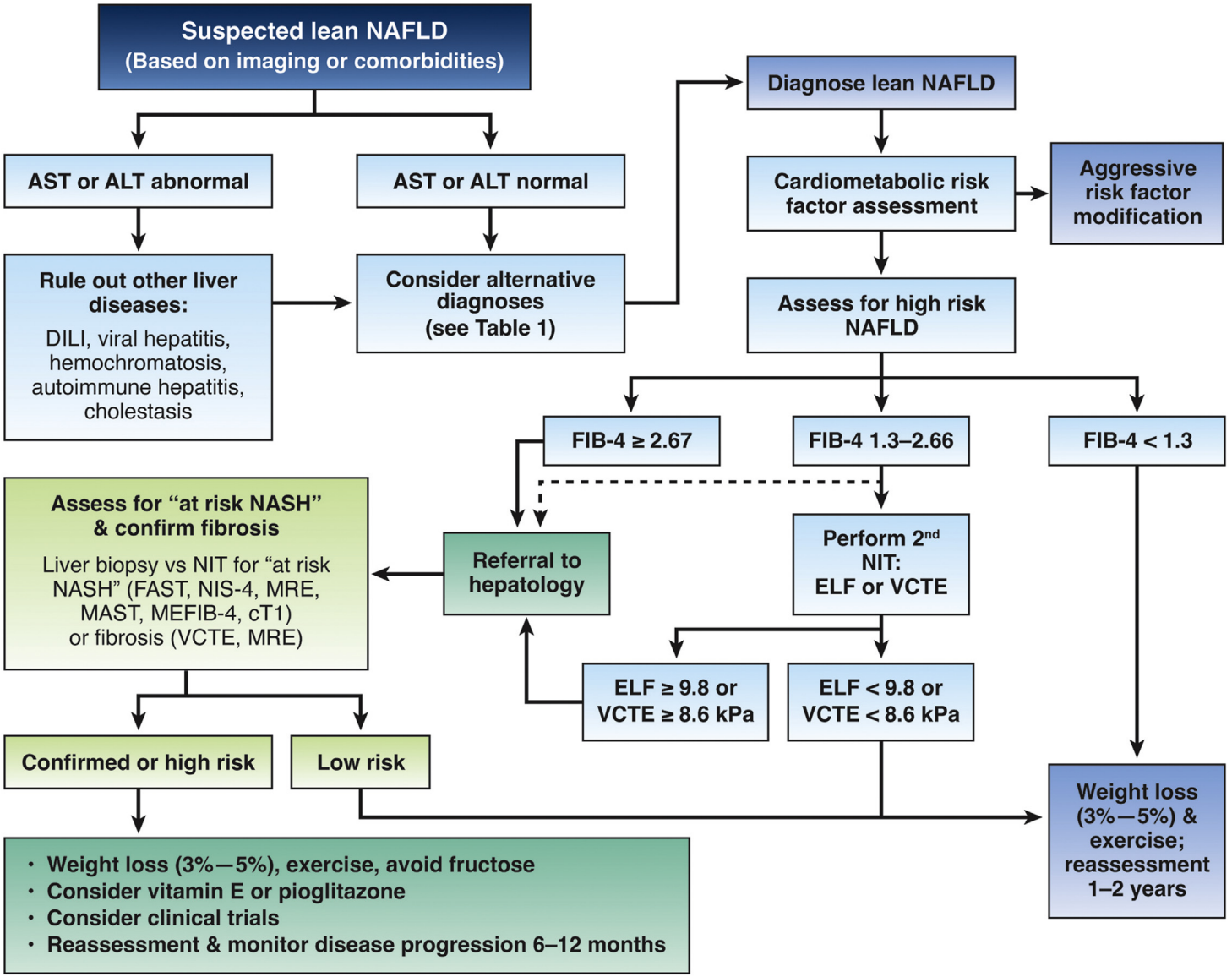

Figure 1. Management and treatment algorithm in patients with suspected lean NAFLD.

especially in children and adolescents. In a study of young, nonobese individuals without metabolic risk factors, the single independent factor for the detection of NAFLD was higher juice and soft drink intake contributing up to a 4-fold increased risk of NAFLD compared with individuals consuming fewer sugar-sweetened beverages.[74] Therefore, limiting fructose intake is suggested, particularly in younger, lean patients with NAFLD.

On the basis of these data, we advise modest weight loss of 3%–5% in lean persons with NAFLD, as it has been found to be beneficial. Although, the type of diet in lean NAFLD should be studied further, patients may benefit from limiting fructose- and sugar-sweetened beverages. Exercise, increasing physical activity, and decreasing visceral fat are beneficial as well.

Best Practice Advice 13: Administration of vitamin E may be considered in lean persons with biopsy-confirmed NASH but without T2DM or cirrhosis. Oral pioglitazone 30 mg daily may be considered in lean persons with biopsy-confirmed NASH without cirrhosis.

The current drug development efforts are focused predominantly on patients with NASH who are overweight and obese; indeed, many trials exclude lean patients. Therefore, evidence on effective pharmacotherapy in lean patients with NASH remains inadequate. Treatment options for individuals with NASH include vitamin E (limited to patients without T2DM) or pioglitazone, both endorsed as first-line treatment options by the AASLD and European Association for the Study of the Liver.[23] The PIVENS (Pioglitazone vs Vitamin E vs Placebo for Treatment of Non-Diabetic Patients with Nonalcoholic Steatohepatitis) trial, which compared pioglitazone, vitamin E, and placebo in patients with NASH but without T2DM, reported improvement in liver biochemistry, inflammation, and fibrosis in the vitamin E and pioglitazone treatment arms.[75] Subsequent studies have confirmed the role of pioglitazone in improving NASH histology in persons with or without T2DM.[76,77] Vitamin E, at its recommended dose of 800 IU daily, has shown potent antioxidant properties and improved histology in patients with NASH.[78,79] However, some concerns have been raised about its potential increase in all-cause mortality, hemorrhagic shock, and prostate cancer.[78,79] Pioglitazone has been associated with adverse reactions, including weight gain, peripheral edema, heart failure, and fractures; therefore, the use of peroxisome proliferator–activated receptor–γ agonists requires individualized assessment in patients with NASH.[78,79] The use of either vitamin E or pioglitazone should be restricted to patients with biopsy-confirmed NASH.

Best Practice Advice 14: The therapeutic role of glucagon-like peptide-1 (GLP-1) agonists and sodium-glucose cotransporter-2 inhibitors in the management of lean NAFLD is not fully defined and requires further investigation.

GLP-1 receptor agonists and sodium-glucose transport protein-2 inhibitors are promising agents for the treatment of NASH.[80–83] Ongoing trials with GLP-1 receptor agonists in NASH patients are mostly enriched with overweight and obese patients. Until further data are available, the use of GLP-1 receptor agonists or sodium-glucose transport protein-2 inhibitors is premature for the treatment of lean NASH, but may be considered in the management of comorbid metabolic conditions, such as T2DM.

Best Practice Advice 15: HCC surveillance with abdominal ultrasound with or without serum α-fetoprotein twice per year is suggested in patients with lean NAFLD and clinical markers compatible with liver cirrhosis.

Cirrhosis, whether secondary to NAFLD or other causes, is a well-established risk factor for incident HCC.[84,85] AASLD Guidelines, along with most experts, recommend considering screening for HCC in all patients with cirrhosis.[86] Health care providers should consider patient age, overall health status and comorbidities, functional status, and personal preferences for screening and willingness to undergo treatment should HCC be diagnosed during screening. Abdominal ultrasound with or without serum α-fetoprotein should be offered to all patients with cirrhosis, including lean patients with NAFLD-related cirrhosis.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://dx.doi.org/10.1053/j.gastro.2022.06.023.

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Conflicts of interest
The authors disclose the following: Michelle T. Long is on the advisory board for Novo Nordisk and receives research grant support from Echosens Corporation and Gilead Sciences. Mazen Noureddin has been on the advisory board/consultant for 89BIO, Altimmune, Gilead, cohBar, Cytodyn, Intercept, Pfizer, Novo Nordisk, Blade, EchoSens, Fractyl, Madrgial, NorthSea, Prespecturm, Terns, Siemens, and Roche diagnostic; has received research support from Allergan, BMS, Gilead, Galmed, Galectin, Genfit, Conatus, Enanta, Madrigal, Novartis, Pfizer, Shire, Viking, and Zydus; and is a shareholder or has stocks in Anaetos, Chrownwell, Ciema, Rivus Pharma, and Viking. Joseph K. Lim has received research contracts (to Yale University) from Allergan, Celgene, Genfit, Gilead, Intercept, Pfizer, and Viking.

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Supplementary Table 1. Performance of Select Noninvasive Tests in the Assessment of Advanced Fibrosis in Lean Nonalcoholic Fatty Liver Disease

Test	Cutoff	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %	AUROC for advanced fibrosis (95% CI)
FIB-4[59]	<1.3	75	77	43	93	0.86 (0.75–0.98)
	≥2.67	42	98	83	88	
NFS[59]	< –1.455	67	85	50	92	0.85 (0.73–0.96)
	>0.676	8	98	50	82	
VCTE[59]	<7.9 kPa	88	80	52	96	0.93 (0.87–0.98)
	>9.6 kPa	69	92	69	92	

VCTE, vibration-controlled transient elastography.