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PRACTICE GUIDANCE

AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease

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PREAMBLE

The study of NAFLD has intensified significantly, with more than 1400 publications since 2018, when the last American Association for the Study of Liver Diseases (AASLD) Guidance document was published.[1] This new AASLD Guidance document reflects many advances in the field pertinent to any practitioner caring for patients with NAFLD and emphasizes advances in noninvasive risk stratification and therapeutics. A separate guideline focused on the management of patients with NAFLD in the context of diabetes has been written jointly by the American Association of Clinical Endocrinology and AASLD.[2] Given the significant growth in pediatric NAFLD, it will not be covered here to allow for a more robust discussion of the diagnosis and management of pediatric NAFLD in the upcoming AASLD Pediatric NAFLD Guidance. A "Guidance" differs from a "Guideline" in that it is not bound by the Grading of Recommendations, Assessment Development and Evaluation system. Thus, actionable statements rather than formal recommendations are provided herein. The highest available level of evidence was used to develop these statements, and, where high-level evidence was not available, expert opinion was used to develop guidance statements to inform clinical practice. Key points highlight important concepts relevant to understanding the disease and its management.

The most profound advances in NAFLD relevant to clinical practice are in biomarkers and therapeutics. Biomarkers and noninvasive tests (NITs) can be used

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AI, artificial intelligence; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic curve; BMI, body mass index; CAP, controlled attenuation parameter; CKD, chronic kidney disease; cT1, corrected T1; CVD, cardiovascular disease; DM, diabetes mellitus; DNL, de novo lipogenesis; DPP-4, dipeptidyl peptidase-4; ELF, Enhanced Liver Fibrosis; FAST, FibroScan-AST; FDA, US Food and Drug Administration; FIB-4, fibrosis-4 index; GH, growth hormone; GLP-1RA, glucagon-like peptide-1 receptor agonist; LDL-C, LDL cholesterol; LSM, liver stiffness measurement; MAST, score derived from MRI-PDFF, MRE, and serum AST; MEFIB, MRE combined with FIB-4; MRE, magnetic resonance elastography; NIT, noninvasive test; OSA, obstructive sleep apnea; PCOS, polycystic ovarian syndrome; PDFF, proton density fat fraction; PIVENS, Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with NASH; RCT, randomized controlled trial; SGLT-2, sodium glucose cotransporter-2; T2DM, type 2 diabetes mellitus; *TM6SF2*, transmembrane 6 superfamily member 2; UDCA, ursodeoxycholic acid; VCTE, vibration-controlled elastography

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clinically to either exclude advanced diseases or identify those with a high probability of cirrhosis.[3,4] NIT "cut points" vary with the populations studied, underlying disease severity, and clinical setting. Those proposed in this guidance are meant to aid decision-making in the clinic and are not meant to be interpreted in isolation. Identifying patients with "at-risk" NASH (biopsy-proven NASH with stage 2 or higher fibrosis) is a more recent area of interest. Although the definitive diagnosis and staging of NASH remain linked to histology, noninvasive tools can now be used to assess the likelihood of significant fibrosis, predict risk of disease progression and decompensation, make management decisions, and, to some degree, assess response to treatment.

There is an ongoing debate over the nomenclature of fatty liver disease, which had not been finalized at the time this guidance was published. At the culmination of a rigorous consensus process, it is intended that any formal change in nomenclature will advance the field without a negative impact on disease awareness, clinical trial endpoints, or the drug development/approval process. Furthermore, it should allow for the emergence of newly recognized disease subtypes to address the impact of disease heterogeneity, including the role of alcohol, on disease progression and response to therapy. Input from patients has been central to all stages of the consensus process to ensure the minimization of nomenclature-related stigma.

DEFINITIONS

NAFLD is an overarching term that includes all disease grades and stages and refers to a population in which $\geq 5\%$ of hepatocytes display macrovesicular steatosis in the absence of a readily identified alternative cause of steatosis (eg, medications, starvation, monogenic disorders) in individuals who drink little or no alcohol (defined as < 20 g/d for women and <30 g/d for men). The spectrum of disease includes NAFL, characterized by macrovesicular hepatic steatosis that may be accompanied by mild inflammation, and NASH, which is additionally characterized by the presence of inflammation and cellular injury (ballooning), with or without fibrosis, and finally cirrhosis, which is characterized by bands of fibrous septa leading to the formation of cirrhotic nodules, in which the earlier features of NASH may no longer be fully appreciated on a liver biopsy.

UPDATE ON EPIDEMIOLOGY AND NATURAL HISTORY

The prevalence of NAFLD and NASH is rising worldwide in parallel with increases in the prevalence of obesity and metabolic comorbid disease (insulin resistance, dyslipidemia, central obesity, and hypertension).[5,6] The prevalence of NAFLD in adults is estimated to be 25%–30% in the general population[7–9] and varies with the clinical setting, race/ethnicity, and geographic region studied but often remains undiagnosed.[10–14] The associated economic burden attributable to NASH is substantial.[15–17] The prevalence of NASH in the general population is challenging to determine with certainty; however, NASH was identified in 14% of asymptomatic patients undergoing colon cancer screening.[14] This study also highlights that since the publication of a prior prospective prevalence study,[18] the prevalence of clinically significant fibrosis (stage 2 or higher fibrosis) has increased >2-fold. This is supported by the projected rise in NAFLD prevalence by 2030, when patients with advanced hepatic fibrosis, defined as bridging fibrosis (F3) or compensated cirrhosis (F4), will increase disproportionately, mirroring the projected doubling of NASH.[5,19] As such, the incidence of hepatic decompensation, HCC, and death related to NASH cirrhosis are likewise expected to increase 2- to 3-fold by 2030.[5] Although expected to increase further, NASH-related cirrhosis is already the leading indication for liver transplantation in women and those >65 years of age and is on par with alcohol as the leading indication overall.[20–22]

Natural history of disease progression

Data from meta-analyses and pooled studies demonstrate that fibrosis and the presence of steatohepatitis are the primary predictors of disease progression.[23–25] The collinearity between NASH and the fibrosis it induces makes it challenging to demonstrate the independent contribution of NASH to fibrosis and adverse outcomes in multivariable analyses.[26,27] Although fibrosis is the primary determinant of adverse outcomes, increased liver-related morbidity and mortality and nonhepatic malignancy are observed in patients with NAFLD even in the absence of fibrosis on initial biopsy.[25] Nevertheless, patients with NASH and at least stage 2 fibrosis (F2), referred to as "at-risk" NASH, have a demonstrably higher risk of liver-related morbidity and mortality.[24,28]

Fibrosis progression is influenced by many factors such as the presence and severity of comorbid disease, genomic profile, and environmental factors. A meta-analysis of placebo-treated patients in 35 NASH trials found minimal progression, suggesting that nonpharmacologic factors (frequent visits/monitoring, dietary or lifestyle counseling, or changes) may reduce progression.[29] An earlier meta-analysis of cohorts with longitudinal paired biopsies[30] demonstrated a NAFLD fibrosis progression rate of one stage per 7 years in those with NASH versus 14 years for those with NAFL.[30]

The diagnosis of cirrhosis, determined by biopsy or noninvasively, is important because it changes clinical

management. Those with cirrhosis require biannual screening for HCC as well as screening for varices and monitoring for signs or symptoms of decompensation.[31,32] Among patients with cirrhosis, progression to clinical decompensation ranges from 3% to 20% per year.[12,33–35]

Association between disease stage and adverse outcomes

The most common causes of death in patients with NAFLD overall are cardiovascular disease (CVD) and nonhepatic malignancy, followed by liver disease. The amount of liver fibrosis identified histologically in patients with NAFLD has been strongly linked to the development of liver-related outcomes and death.[24,26,36,37] Bridging fibrosis and cirrhosis are associated with an exponentially greater risk of liver-related morbidity and mortality than earlier stages of fibrosis.[23,24,35] In a prospective study of 1773 patients, all-cause mortality in those with fibrosis stages 0–2 was 0.32 per 100 person-years, compared with 0.89 per 100 person-years in those with bridging fibrosis and 1.76 per 100 person-years in those with cirrhosis. After correcting for multiple factors, hepatic decompensation was associated with all-cause mortality (HR, 6.8; 95% CI, 2.2–21.3).[35] Cirrhosis regression has been associated with a 6-fold reduction in liver-related events in clinical trials.[38]

Key points:

- *Patients with NASH and F2–4 fibrosis are at higher risk for liver-related events and mortality and are considered to have "at-risk" NASH.*
- *The rates of fibrosis progression and hepatic decompensation vary depending on baseline disease severity, genetic, individual environmental, and comorbid disease determinants.*
- *CVD and nonhepatic malignancies are the most common causes of mortality in patients with NAFLD without advanced fibrosis; death from liver disease predominates in patients with advanced fibrosis.*

MOLECULAR AND CELLULAR PATHOGENESIS

The presence and severity of NAFL and NASH are substantially determined by factors that govern the supply and disposition of fatty acids, diacylglycerols, ceramides, cholesterol, phospholipids, and other intrahepatic lipids. Energy oversupply and limited adipose tissue expansion contribute to insulin resistance and metabolic disease.[39] When energy intake exceeds metabolic needs and disposal capacity, carbohydrates, in the form of dietary sugars (eg, fructose, sucrose, and glucose), drive the formation and accumulation of intrahepatic fat from de novo lipogenesis (DNL).[40,41] There is substantial inter-individual heterogeneity in the role of DNL among patients with NAFLD.[42,43] In addition, the type of fat consumed plays a role in the development of NASH, with a higher risk associated with saturated versus unsaturated fat consumption (Figure 1).[44–46]

Insulin resistance is nearly universal in patients with NAFLD and is present in the liver, adipose tissue, and muscle.[47] Adipose tissue insulin resistance is characterized by increased release of free fatty acids from adipocytes (lipolysis) in the fasting state[48] and worsens with the progression of NAFLD to NASH.[39,47,49]

Important factors that govern energy disposal include the frequency and intensity of exercise, the activation of brown adipose tissue to an energy-consuming thermogenic phenotype, and counterregulatory mechanisms that diminish energy disposal in response to reductions in calorie intake.[39,50] The ability and desire to engage in regular exercise can be strongly influenced by personal, community, corporate, societal, and legislative decisions, all of which thus have roles in the development of NASH.

The heterogeneity of factors contributing to the pathophysiology of NASH among patients has impeded the development of diagnostic tests and therapeutics.[51] Although in some patients, the development and progression of NASH are driven by substrate overload and insulin resistance, in other patients, disease progression is heavily influenced by genetic factors impacting hepatocyte lipid handling.[43] Genetic polymorphisms have been associated with more advanced liver disease and the development of HCC in NASH. The I148M polymorphism of PNPLA3 impairs lipolysis of triglyceride in lipid droplets,[52] and polymorphisms in other proteins that play a role in hepatocyte fat metabolism have also been linked to the prevalence and severity of NAFLD, including transmembrane 6 superfamily member 2 (*TM6SF2*), which may play a role in cholesterol metabolism,[53] and *MBOAT7*, which influences phospholipid metabolism.[54] Recently, loss-of-function variants in *HSD17B13*, a gene that encodes an enzyme that also localizes to lipid droplets in hepatocytes, have been linked to protection against NASH, progressive fibrosis, and HCC.[55] Rare loss-of-function mutations in *CIDEB*, a protein needed for activation of DNL,[56] have also been shown to be protective.[57]

A host of additional factors, the review of which is beyond the scope of this guidance, contribute to heterogeneity in disease activity and progression.[49,58–63] Additional factors such as hepatocyte uric acid production, exposure to products derived from the gut microbiome, and perhaps low hepatic magnesium levels, may also contribute to the NASH phenotype.[64–69] Transcriptomic

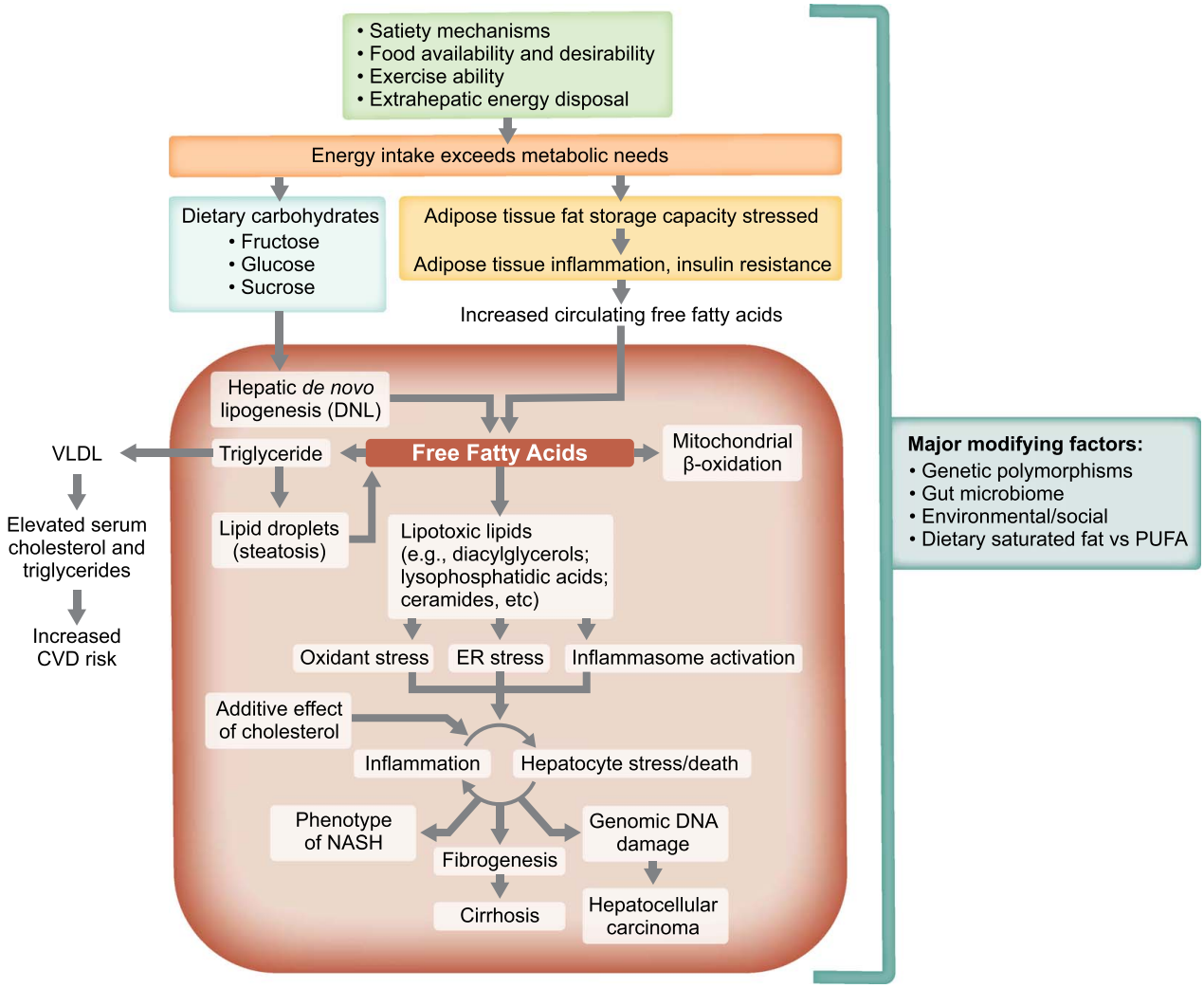

FIGURE 1 Pathogenic drivers of NAFLD as therapeutic targets. Overview of the major mechanisms that lead to the phenotype of NASH and its consequences, many of which can be leveraged therapeutically. Not shown are the many areas where genetic polymorphisms may play a role and where important modifying factors such as cholesterol, types of dietary fats consumed [saturated vs. polyunsaturated fatty acid (PUFA)], the gut microbiome, uric acid, and periodic hypoxia (sleep apnea) may also influence these pathways. A primary disease driver may be an oversupply of fat to adipocytes such that their ability to store triglyceride without inducing cell stress is exceeded, which activates inflammatory pathways and causes insulin resistance. Understanding the major drivers of NASH facilitates the rational development of therapies for patients with NASH. Specific sites of intervention that might prevent or resolve NASH include interventions that modulate food intake (eg, portion sizes, bariatric surgery, satiety regulators), increase energy disposal (eg, exercise, thermogenesis), improve adipocyte insulin sensitivity [eg, peroxisome proliferator-activated receptor (PPAR)γ ligands], impair de novo lipogenesis (eg, acetyl-coenzyme A carboxylase and fatty acid synthase inhibitors), increase hepatic oxidative metabolism (PPARα ligands and thyroid hormone receptor beta agonists), and attenuate inflammation, cell death, and fibrogenesis. Therapeutic agents affecting multiple metabolic pathways throughout the body with potential beneficial effects on the liver include peptide hormone analogs (eg, analogs of fibroblast growth factor-19, fibroblast growth factor-21, glucagon-like peptide-1, gastric inhibitory peptide, glucagon) and nuclear receptor ligands such as drugs that target PPARα, PPARδ, PPARγ, thyroid hormone receptor β, and farnesoid X receptor. Abbreviations: ER, endoplasmic reticulum; CVD, cardiovascular disease.

profiling of large cohorts of patients is further contributing to our understanding of this disease heterogeneity and its progression.[70,71] The response of the liver to lipotoxic injury includes activation and recruitment of resident macrophages, which further contributes to hepatocellular injury and stellate cell activation as part of a complex interplay among hepatic cell types.[60,72,73] Although markers of oxidative stress have been a consistent finding in NASH, its role in the pathogenesis of NASH in humans remains uncertain.[74]

Key points:

- *Fundamental elements of NASH pathogenesis include an imbalance between nutrient delivery to the liver and their utilization and disposal coupled with adipose tissue dysfunction. Interindividual differences in genetic,*

dietary, behavioral, and environmental factors influence disease course.
- *Systemic inflammation, particularly stemming from dysfunctional adipose tissue, contributes to disease progression.*
- *Insulin resistance contributes to the development of NAFLD and promotes disease progression.*

COMORBID CONDITIONS ASSOCIATED WITH NAFLD

NAFLD is closely linked to and often precedes the development of metabolic abnormalities (insulin resistance, dyslipidemia, central obesity, and hypertension).[47,61,75–77] Having several metabolic abnormalities confers an even greater risk of histological progression of NASH and all-cause mortality.[8,47,78–81] The association between NAFLD and metabolic comorbidities may also reflect bidirectional interactions between the liver and other endocrine organs (eg, pancreas, adipose tissue, muscle) through the secretion of hepatokines that regulate fatty acid metabolism, insulin action, and glucose metabolism,[82–88] adipokines, and myokines.[39,89,90]

Obesity

The presence and severity of obesity are associated with NAFLD and disease progression.[91–93] Body fat distribution is an important determinant of the contributory role of obesity in NAFLD (Table 1). Android body fat distribution, characterized by increased truncal subcutaneous fat and visceral fat confers a higher risk of insulin resistance, CVD, and hepatic fibrosis, irrespective of body mass index (BMI).[94–99] In contrast, gynoid body fat distribution, characterized by increased subcutaneous body fat predominantly in the hips or buttocks, appears to be protective against NAFLD.[39,100] Visceral fat, which is more metabolically active and inflammatory than subcutaneous fat, mediates the majority of this risk.[101–105] As adipose tissue becomes more metabolically stressed, dysfunctional, and inflamed, insulin signaling is progressively impaired, promoting the inappropriate release of fatty acids leading to intrahepatic lipid accumulation and inflammation.[47,106,107]

Type 2 diabetes mellitus (T2DM)

T2DM is the most impactful risk factor for the development of NAFLD, fibrosis progression, and HCC.[108–111] Given the central pathogenic role that insulin resistance plays in the pathogenesis of both T2DM and NAFLD, it is not surprising that patients with T2DM have a higher prevalence of NAFLD (ranging from 30% to 75%)[10,112,113] and a higher risk of developing NASH with fibrosis.[93,114–117] Furthermore, the probability of advanced fibrosis increases with the duration of T2DM. Although there is potential for lead time and length time biases, these studies underscore the strong relationship between T2DM and NAFLD.

The relationship between NAFLD and T2DM is bidirectional in epidemiological studies. Early in its course, NAFLD is associated with a reduction in insulin sensitivity,[47] even in the absence of overt diabetes. The presence of NAFLD is associated with a 2- to 5-fold risk of incident diabetes,[75,118–121] and therefore, patients with NAFLD should be screened for the presence of T2DM (Table 1). Furthermore, as liver disease progresses, so does insulin resistance and beta cell failure, making diabetes more challenging to manage.[107] The role of glycemic control in the progression of NAFLD/NASH remains controversial, with 2 small studies showing an association between poor glycemic control and hepatocellular injury and liver fibrosis,[68,122] whereas other studies have not corroborated this finding.[116,117,123] Although NAFLD has also been described in patients with type 1 diabetes, its prevalence is much lower than in T2DM, and it is closely related to coexistent metabolic risk factors (eg, higher BMI).[124,125]

TABLE 1 Initial evaluation of a patient with NAFLD

History	Weight history; medical comorbidities; recent and current medications; family history of T2DM, NAFLD, or cirrhosis; screening for OSA; alcohol use, including amount, pattern of use, and duration
Physical examination	Body fat distribution (eg, android vs. gynoid, lipodystrophic), features of insulin resistance (eg, dorsal-cervical fat pad, acanthosis nigricans), features of advanced liver disease (eg, firm liver, splenomegaly, prominent abdominal veins, ascites, gynecomastia, spider angiomata, palmar erythema)
Laboratory tests	Hepatic panel, CBC with platelets, fasting plasma glucose and glycated hemoglobin (A1c), fasting lipid profile, creatinine and urine microalbumin or protein to creatinine ratio, hepatitis C if not previously screened. Consider as appropriate other causes of steatosis/steatohepatitis (Table 2). Additional evaluation if elevated liver chemistries present: autoimmune serologies, transferrin saturation, ceruloplasmin, alpha-1 antitrypsin genotype, or phenotype

Abbreviations: CBC, complete blood count; OSA, obstructive sleep apnea; T2DM, type 2 diabetes mellitus.

Hypertension

Hypertension is commonly associated with NAFLD. There is a higher incidence of hypertension in those with NAFLD across the disease spectrum, with incidence rates of 6.5 per 100 person-years in early disease to 14.5 per 100 person-years in those with cirrhosis.[35] The presence of hypertension is clearly additive to other metabolic comorbidities with respect to the epidemiological risk of NASH[126,127] and has been associated with fibrosis progression.[30] Whether hypertension mechanistically promotes the development of NAFLD/NASH or the inverse, or both are manifestations of underlying metabolic disease drivers, has not been established.[128,129]

Dyslipidemia

Patients with NAFLD are twice as likely to exhibit plasma lipid abnormalities as those without NAFLD,[120] and the serum lipid subfractions are more atherogenic in patients with NAFLD.[130,131] NASH resolution can lead to improved plasma HDL cholesterol and triglyceride levels and favorably impact lipoprotein subfractions, although it is unclear to what extent this is driven by the mechanism of the therapeutic intervention.[132–134] As patients progress to cirrhosis, they continue to remain at high risk for coronary artery disease[135] despite the normalization of serum lipids and lipoproteins due to hepatic synthetic failure.[130,136]

Management of dyslipidemia in NAFLD should include the use of moderate-intensity to high-intensity statins as first-line therapy based on lipid risk levels and atherosclerotic CVD risk scores. Combination therapies of statins with other hypolipemic agents, such as ezetimibe, PCSK-9 inhibitors, inclisiran, bempedoic acid, fibrates, omega 3 fatty acids, or icosapent ethyl, should be considered when monotherapy with a statin does not achieve therapeutic goals.

Statins are safe in patients with NAFLD across the disease spectrum, including advanced liver disease, and lead to a demonstrable reduction in cardiovascular morbidity and mortality.[137–140] However, in clinical practice, they are often underused despite extensive data demonstrating safety, even among patients with cirrhosis.[141–144] Statins are also considered safe in the context of compensated cirrhosis and may have beneficial effects on future decompensation and HCC risk, although additional confirmatory data are needed.[138] Although statins have been safely used in patients with decompensated cirrhosis, the risk of statin-induced adverse events might be higher in this population,[144] and thus more caution is warranted. In patients with decompensated cirrhosis and high CVD risk undergoing evaluation for liver transplantation, statin use can be considered with careful monitoring.[136]

In patients with NAFLD and severely elevated triglycerides levels (eg, >500 mg/dL), fibrates, or a combination of fibrates with prescription grade omega-3 fatty acids or icosapent ethyl, should be used to reduce the risk of pancreatitis. Fibrates may also improve atherosclerotic CVD outcomes when triglyceride concentrations are ≥ 200 mg/dL and HDL-C concentrations are <40 mg/dL. In high-risk individuals, icosapent ethyl is indicated as an adjunct to statin therapy to reduce atherosclerotic CVD risk. Pioglitazone can be considered for optimization of glycemic control due to its concomitant benefits on lipid profile. Caution should be taken when statins are used in combination with fibrates due to a higher risk of statin-induced myopathy.

Obstructive sleep apnea (OSA)

OSA is associated with NAFLD,[145] and several studies suggest OSA is also associated with more advanced NAFLD/NASH histology.[146–151] Intermittent hypoxia, a critical consequence of OSA, has been linked to mitochondrial dysfunction,[145] dysregulation of glucose and lipid metabolism,[152,153] worse insulin resistance,[154–156] and increased hepatic DNL.[157] Given the strong association between NAFLD and OSA, patients with NAFLD who are overweight or obese should be screened for OSA, and polysomnography or other sleep studies should be considered for those at high risk.

CVD

CVD is an important cause of death in patients with NAFLD[158]; however, the extent to which NAFLD independently drives CVD is unclear. A strong association exists between NAFLD and atherosclerotic heart disease, heart failure, and arrhythmias, particularly atrial fibrillation.[159–167] Perturbed lipoprotein metabolism, endothelial function, increased presence and higher-risk nature of atherosclerotic lesions, and impaired ischemic compensatory mechanisms support the link between NAFLD and CVD.[130,168–170] Furthermore, in a large prospectively studied observational cohort, the incidence of cardiac events was the same across all fibrosis stages; however, the number of cardiac events was relatively low.[35] Optimizing the management of CVD risk factors with the goal of reducing CVD morbidity and mortality is critical to improving outcomes in patients with NAFLD.[36,171,172] Aggressively treating comorbid conditions such as hypertension, dyslipidemia, and hyperglycemia and promoting smoking cessation is recommended to decrease CVD in those at risk.[173]

Chronic kidney disease (CKD)

A meta-analysis of 20 cross-sectional studies ($n=28{,}000$ individuals) found that NAFLD was

associated with a 2-fold increased prevalence of CKD.[174] NAFLD overall, and NASH specifically, are also associated with microvascular diabetic complications, especially CKD.[175,176] Recently published data from the NASH CRN demonstrate a higher prevalence of CKD in patients with advanced fibrosis compared with lower fibrosis stages.[35] The extent to which the liver mechanistically contributes to the development of CKD independent of associated metabolic disease remains to be determined.

Guidance statements:

1. Statins are safe and recommended for CVD risk reduction in patients with NAFLD across the disease spectrum, including compensated cirrhosis.

2. Limited data exist on the safety and efficacy of statins in patients with decompensated cirrhosis, although statin use with careful monitoring could be considered in patients with high CVD risk.

3. Hypertriglyceridemia can be managed through lifestyle changes and supplementation with omega-3 fatty acids, icosapent ethyl, or fibrates.

4. Patients with diabetes are at higher risk for NASH and advanced fibrosis and should be screened for advanced fibrosis.

5. Patients with NAFLD should be screened for the presence of T2DM.

Key points:

- *Prevalence and incidence of CKD is higher among patients with NASH and advanced fibrosis.*
- *Death from nonhepatic malignancies is a common cause of death in patients with NAFLD, and thus, adherence to age-appropriate cancer screening has the potential to improve survival.*

INITIAL EVALUATION OF A PATIENT WITH NAFLD

Patients with NAFLD are most commonly referred with incidentally noted hepatic steatosis on imaging or elevated liver chemistries. It is important to note that normal values provided by most laboratories are higher than what should be considered normal in NAFLD, in which a true normal alanine aminotransferase (ALT) ranges from 29 to 33 U/L in men and from 19 to 25 U/L in women.[177] Initial evaluation of such patients should include screening for metabolic comorbidities, assessment of alcohol intake, and exclusion of other causes of liver disease as well as physical examination to identify signs of insulin resistance and advanced liver disease (Table 1). When the clinical profile is atypical (eg, not associated with metabolic comorbidities) or accompanied by additional signs or symptoms suggesting additional/alternate etiologies, less common causes of steatosis or steatohepatitis should be excluded (Table 2). Rare causes of steatosis or fibrosing steatohepatitis can present in isolation or explain an exaggerated NASH phenotype and should be considered in specific clinical

TABLE 2 When to consider testing for less common causes of hepatic steatosis and steatohepatitis

Condition	Clinical scenario	Diagnostic test	Treatment
Hypobetalipoproteinemia	Low LDL, low triglycerides, fat malabsorption	ApoB level, genetic testing (MTTP, PCSK-9)	Low-fat diet, fat-soluble vitamin supplementation
LAL deficiency	Markedly elevated LDL-C and low HDL-C, elevated triglycerides, xanthelasma, hypersplenism, advanced fibrosis in young age, predominately microvesicular steatosis on liver biopsy	Enzyme assay, genetic testing	LAL replacement
Nutrient deficiency (eg, carnitine, choline)	Anorexia, short bowel, bypass surgeries	Nutrient levels	Supplementation
Wilson disease	Younger age, neuropsychiatric symptoms, low alkaline phosphatase, low ceruloplasmin	24-h urine copper; quantitative copper on liver biopsy	Chelation
Celiac disease	Iron deficiency, abdominal pain, bloating, vitamin D deficiency, bone loss, diarrhea, dermatitis herpetiformis	Tissue transglutaminase IgA, duodenal biopsy	Gluten-free diet

Abbreviations: ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; IgA, immunoglobulin A; LAL, lysosomal acid lipase; LDL-C, LDL cholesterol.

contexts (Table 2).[178] Several drugs can also lead to hepatic steatosis or steatohepatitis or exacerbate disease in those with underlying NAFLD and should be identified during initial evaluation (Table 3). Although gene-based risk stratification is currently not recommended in clinical practice, familial aggregation of insulin resistance and NAFLD supports gene-environment interactions in the risk for NAFLD, NASH, and advanced fibrosis.[209,210]

Role of alcohol consumption

Alcohol use can be an important contributor to fatty liver disease progression and should be quantified in all patients.[211] Alcohol intake can be broadly classified as mild [up to 20 g (women) and 30 g (men) per day], moderate [21–39 g (women) and 31–59 g (men) per day], or heavy [≥40 g (women) and ≥60 g (men) per day]. Moderate alcohol use increases the probability of advanced fibrosis,[212] particularly in patients with obesity or T2DM, indicating potential synergistic effects of insulin resistance and alcohol on liver disease progression. Obesity and alcohol use synergistically increase the risk of liver injury, cirrhosis, HCC, and death from liver disease.[213–215] Heavy alcohol consumption accelerates liver injury and fibrosis progression and should be avoided in patients with NAFLD/NASH.[211] Earlier epidemiological studies suggested a protective effect of mild alcohol consumption on the development of NAFLD,[216] but in a subsequent study, moderate alcohol use (defined broadly as >20 g/d) was associated with less improvement in steatosis and aspartate aminotransferase (AST) and lower odds of NASH resolution, compared with patients who did not consume alcohol.[217] In addition, daily alcohol may increase the risk for extrahepatic malignancies[218] and HCC.[219,220] Importantly, there is substantial variability in individual susceptibility to alcohol-induced liver injury, with an attendant lack of clarity on the dose required to impact disease course at an individual patient level. The impact of alcohol use (type, pattern, frequency, duration, and quantity) on the natural history of NAFLD/NASH requires further investigation.

Guidance statements:

6. In patients with NAFLD, alcohol can be a cofactor for liver disease progression, and intake should be assessed on a regular basis.

7. Patients with clinically significant hepatic fibrosis (≥F2) should abstain from alcohol use completely.

Key points:

- *Abstinence, particularly for those patients with moderate-to-heavy alcohol intake, may lower the risks of fibrosis progression and hepatic and extrahepatic malignancies in patients with NAFLD.*

ASSOCIATED ENDOCRINE DISORDERS

In addition to its strong association with obesity and other metabolic risk factors, higher rates of NAFLD have been reported in patients with hypothyroidism, hypogonadism, growth hormone (GH) deficiency, and polycystic ovarian syndrome (PCOS).

TABLE 3 Drugs with potential mechanistic links to macrovesicular steatosis or steatohepatitis

Drug	Mechanism	Histological pattern	References
Amiodarone	Promotion of DNL, impairment of β-oxidation	Hepatic steatosis and steatohepatitis, phospholipidosis, cirrhosis	[179–184]
5-FU	Accumulation of 5-FU catabolites reduce hepatic capacity to metabolize lipids	Hepatic steatosis	[185–188]
Irinotecan	Induces mitochondrial dysfunction, impaired autophagy	Steatohepatitis	[189–194]
Tamoxifen	Estrogen receptor modulator, promotion of DNL, impairment of β-oxidation. *May or may not be independent of concomitant metabolic risk factors	Steatosis and steatohepatitis	[195–203]
Methotrexate	Mitochondrial injury (inhibits mitochondrial electron transport chain), injury to canals of Hering	Steatosis, steatohepatitis, cirrhosis	[204–206]
Corticosteroids	Exacerbation of metabolic comorbidities, impairment of β-oxidation, impairment of hepatic triglyceride secretion, lipid peroxidation	Steatosis	[207,208]

Abbreviations: 5-FU, 5-fluorouracil; DNL, de novo lipogenesis.

Hypothyroidism

Despite the known role of thyroid hormone in the regulation of hepatic lipid metabolism,[221,222] the association between NAFLD and systemic hypothyroidism in humans remains controversial.[223–225] No significant association between NAFLD and hypothyroidism (subclinical or overt) was observed in a large meta-analysis[226]; however, a cohort study of nearly 9500 patients followed for a mean of 10 years found hypothyroidism was associated with a 24% higher chance of NAFLD.[222–228]

GH deficiency

GH and the primary mediator of its metabolic effects, insulin-like growth factor-1, are important regulators of glucose and lipid metabolism, growth, body composition, and cellular regeneration.[229–232] GH deficiency is associated with body fat redistribution and increased visceral adipose tissue mass and can result in insulin resistance, hyperglycemia, hyperlipidemia, and NAFLD.[233] In a meta-analysis, insulin-like growth factor-1 levels were lower in patients with NAFLD and strongly associated with obesity and insulin resistance.[234] One cause of GH deficiency, panhypopituitarism, is associated with weight gain, insulin resistance, impaired glucose tolerance, and dyslipidemia, with a small case series demonstrating an increased risk for NASH and fibrosis.[235–237]

Studies evaluating effects of GH replacement in subjects with GH deficiency and NAFLD have been small and uncontrolled. In a study of adults with hypopituitarism (n = 69), GH replacement reduced AST (n = 11 with NAFLD) and improved liver histology in NASH (n = 5 with paired biopsies).[235,238] In another study, GH replacement (n = 12 subjects) reduced visceral fat and hepatic steatosis by magnetic resonance spectroscopy.[239] In patients with HIV, lipodystrophy, and NAFLD, tesamorelin, a GH-releasing hormone analog, which augments pulsatile GH secretion and increases insulin-like growth factor-1 without adversely affecting insulin sensitivity,[240] reduced liver fat.[241] Overall, the association between a disturbance in the GH axis and NAFLD is strongly linked to changes in visceral fat and insulin resistance, but screening is not recommended for all patients.

Hypogonadism

A number of studies report associations among hypogonadism, impaired glucose and lipid metabolism,[242] and NAFLD.[242–245] A meta-analysis found that NAFLD was associated with lower serum testosterone levels in men but higher levels in women,[246] a finding confirmed by others.[247] The association between hypogonadism and NAFLD is often confounded by the presence of obesity and insulin resistance, both of which are known to be associated with hypogonadotropic hypogonadism. In contrast, low testosterone levels can also negatively affect body composition, worsen insulin resistance, and thus contribute to the development of hepatic steatosis.[248]

One study in men suggested that a low serum total testosterone level was independently associated with NAFLD, and the association was unchanged even after controlling for visceral adipose tissue volume and insulin resistance.[249] In contrast, in another study including 175 men with T2DM evaluated by ^{1}H-magnetic resonance spectroscopy (MRS) and liver histology, the relationship between lower total testosterone and steatosis disappeared when adjusted for insulin resistance and obesity, with no relationship to the severity of liver necroinflammation or fibrosis.[250] Testosterone replacement in men improves insulin resistance, serum lipids, and visceral adiposity, indicating a more direct role of testosterone on metabolic risk factors for NAFLD in men,[195] but it should be reserved for carefully selected patients, particularly as it may exacerbate OSA.

The role of menopause and sex hormones in NAFLD

In women, hypogonadism is associated with increased liver enzymes as well as a higher prevalence of NAFLD and advanced fibrosis.[251–254] The prevalence of NAFLD is higher in postmenopausal compared with premenopausal women.[255] Limited data suggest that higher free testosterone levels in premenopausal women are associated with an increased risk of prevalent NAFLD after menopause. Furthermore, there is a 25% likelihood of NAFLD in higher quintiles of testosterone as well as an association between lower serum estradiol levels and NASH.[244,256] Limited studies demonstrate the benefit of hormone replacement therapy on NAFLD, although adverse hepatic effects were found in one study that were attributed to progesterone.[256] Apart from estrogen deficiency, relative androgen excess and decreased sex hormone-binding protein levels are observed in postmenopausal women. The associated increased abdominal adiposity closely relates to the severity and progression of NAFLD, although direct causality has not been established.

PCOS

In PCOS, hyperinsulinemia promotes hypothalamic luteinizing hormone stimulation of ovarian theca cells resulting in excessive androgen production.[257,258] Large meta-analyses and population studies have demonstrated a 2- to 4-fold increase in the prevalence

of NAFLD and an increased risk of T2DM among women with PCOS, suggesting that insulin resistance is the main driver of disease in PCOS.[257,259,260] In a retrospective study of women with biopsy-confirmed NAFLD ($n = 102$), PCOS was associated with the severity of steatohepatitis and advanced fibrosis after adjusting for age and BMI.[261] However, this study did not account for insulin resistance, which may have influenced the association.

Guidance statements:

8. NAFLD is more common in men with androgen deficiency, but current data do not support routine measurement of testosterone levels. If hypogonadism is present, as suggested by clinical signs or symptoms, this should be treated accordingly.

Key points:

- *Although GH deficiency and panhypopituitarism may be associated with hepatic steatosis, their independent role on the development and progression of steatohepatitis and fibrosis remains to be established.*
- *Androgen excess can worsen insulin resistance in women with PCOS, which together with obesity and T2DM can promote NAFLD and potentially more progressive disease in this population.*

NAFLD IN LEAN INDIVIDUALS

Although NAFLD is commonly associated with obesity, it can also occur in nonoverweight (BMI <25 kg/m^2 or <23 kg/m^2 in Asian individuals) patients.[262] Initial histological findings are typically milder compared with overweight or obese patients,[263,264] and the prevalence of NAFLD in lean individuals varies from 4.1% in the United States[265] to as high as 19% in Asia.[266–271] Compared with healthy controls, lean subjects with NAFLD have increased IR, metabolic comorbidities, visceral adiposity,[39,272] and decreased muscle mass. Alcohol use and alterations in the gut microbiome may also contribute to NAFLD in lean individuals.[178,273–277]

Genetic factors likely play a significant role in this population, but the overall genetic contribution to NAFLD requires further study.[39,178,272–274] Lean individuals with NAFLD are more commonly of Hispanic or Asian origin, which is likely in part driven by a higher prevalence of the PNPLA3 I148M polymorphism.[266,274,278] In addition, alterations in the *TM6SF2* gene, which confers susceptibility to NASH and fibrosis but protection against cardiovascular events, is more prevalent in lean individuals with NAFLD compared with patients who were overweight or had obesity,[279] but genetic testing is currently not recommended, as it does not alter management.[262] Uncommon genetic conditions can also play a role (e.g., lipodystrophy, lysosomal acid lipase deficiency, hypobetalipoproteinemia) and should be considered in selected patients (Table 2).[178,262,273,274]

Management of NAFLD in patients without obesity can be clinically challenging. Recommending weight loss may not be appropriate for lean patients with NAFLD, but dietary modifications and exercise in this group may be beneficial.[262,275–277]

WHICH PATIENTS SHOULD BE SCREENED FOR THE PRESENCE OF CLINICALLY SIGNIFICANT FIBROSIS?

Targeted screening of populations at increased risk for advanced liver disease is advised to identify and manage those with clinically significant fibrosis (stage ≥ 2).[36,172,280] Screening in high-risk populations, such as those with T2DM,[112,113,116,281–285] obesity with metabolic complications,[286–292] a family history of cirrhosis,[293,294] or significant alcohol use[211,295–297] (see also separate discussion on the contributory role of alcohol), may identify those with asymptomatic but clinically significant fibrosis. Early identification of such at-risk patients allows for interventions that may prevent

TABLE 4 Screening for advanced fibrosis in high-risk populations

Screening recommended[a]	Prevalence of advanced fibrosis, %	References
T2DM	6–19	[10,112,113,115,118,280–284]
Medically complicated obesity	4–33	[256–262,473–480]
NAFLD in context of moderate alcohol use	17	[285–291,300–307]
First-degree relative of a patient with cirrhosis due to NAFLD/NASH	18	[292,293]

Abbreviation: T2DM, type 2 diabetes mellitus.
[a]Prevalence of advanced fibrosis in background population 0.9%–2%.[14,302,303,305]

future hepatic complications.[298] Careful assessment of family history is important because first-degree relatives of probands with NASH cirrhosis have a 12-fold higher risk of advanced fibrosis.[293] Furthermore, the risk of NAFLD and advanced fibrosis may be increased, even among nonrelated household members, likely because of related similar environmental risk factors, lifestyle patterns, and gut microbiota.[299] Screening recommendations are summarized in Table 4.

How should NAFLD be managed in primary care and endocrinology practice settings?

In most patients, NAFLD is asymptomatic or associated with vague symptoms, often leaving patients undiagnosed. The prevalence of advanced disease is lower in primary care practices than in hepatology practices, and thus, the approach to evaluation is context dependent (Figure 2). Patients suspected to have NAFLD on the basis of metabolic risk factors or incidentally identified as having fatty liver by imaging in the absence of other etiologies of hepatic steatosis (ie, Wilson disease, celiac disease, HCV, alcohol use, etc.) should undergo primary risk assessment (Figure 2). The objective of this primary risk assessment is to identify patients who are not likely to have advanced fibrosis [low risk, eg, fibrosis-4 index (FIB-4) <1.3]. Due to the excellent negative predictive value of NITs (reviewed in detail below) in excluding advanced fibrosis, patients in low-risk categories can be managed in primary care. However, patients with ≥2 metabolic risk factors, particularly those with prediabetes mellitus (pre-DM) or T2DM, should undergo more frequent risk assessment with FIB-4 every 1–2 years (Figure 2).[2] Screening patients with T2DM and suspected NAFLD-related advanced hepatic fibrosis using FIB-4, a score derived from available clinical and laboratory data, may be cost-effective[281] and allow for the prediction of outcomes such as progression to cirrhosis or decompensation, although the performance of NITs may be less robust in patients with diabetes.[308,309] Once more data are available, it is possible that the recommended cutoffs for FIB-4 in patients with T2DM will change.[113]

Those who may have a moderate or high risk of advanced disease based on FIB-4 should undergo secondary risk assessment. In the primary care setting, vibration-controlled elastography (VCTE) or ultrasound-based methods such as acoustic radio force impulse (as available) are favored over magnetic resonance elastography (MRE), as initial secondary assessments due to cost considerations. The Enhanced Liver Fibrosis (ELF) test is approved for prognostication when advanced fibrosis is suspected, although it can be ordered for secondary risk assessment, particularly because the availability of elastography may be limited in some settings. If secondary risk assessment is still consistent with an intermediate or high risk of fibrosis, patients should be referred to specialty care for further evaluation and potential intervention. For those patients with advanced hepatic fibrosis or cirrhosis, primary or secondary prevention of complications of portal hypertension[310–312] or sarcopenia[313] may decrease the risks of liver-related outcomes (Figure 2).

Serum AST levels are often used clinically to identify patients with liver disease but can be normal in patients with diabetes, NASH, and advanced hepatic fibrosis.[118,283] Although AST levels are neither sensitive nor specific for the identification of NAFLD/NASH with advanced fibrosis, intermittently (i.e., fluctuating above and below normal thresholds) or chronically (≥6–12 mo) elevated ALT or AST above a threshold of 30 U/L may suggest the presence of chronic liver injury.[7,314,315] These thresholds are below the upper reference range values provided by most clinical laboratories, which is likely related to the lack of exclusion of patients with risks for NAFLD from reference populations.[316]

Further risk stratification in the gastroenterology and hepatology practice settings

The primary goal in the specialty care setting is the identification of patients with "at-risk" NASH or advanced fibrosis. Such patients require further assessment and may benefit from targeted interventions (Figure 2). MRI-based tools such as MRE or MRI corrected T1 (cT1) can be used to further risk stratify patients in whom other NITs have been indeterminate or not reflective of clinical suspicion. Liver biopsy should be considered when there is diagnostic uncertainty, as may occur with discordant or indeterminate NITs; discordance between NITs and clinical, radiographic, or laboratory features suggesting a diagnosis of advanced fibrosis; competing or concomitant possible diagnoses (eg, autoimmune hepatitis, DILI, iron overload); or when there is persistent elevation (>6 mo) in liver chemistries.

Guidance statements:

9. General population-based screening for NAFLD is not advised.

10. All patients with hepatic steatosis or clinically suspected NAFLD based on the presence of obesity and metabolic risk factors should undergo primary risk assessment with FIB-4.

11. High-risk individuals, such as those with T2DM, medically complicated obesity, family history of cirrhosis, or more than mild alcohol consumption, should be screened for advanced fibrosis.

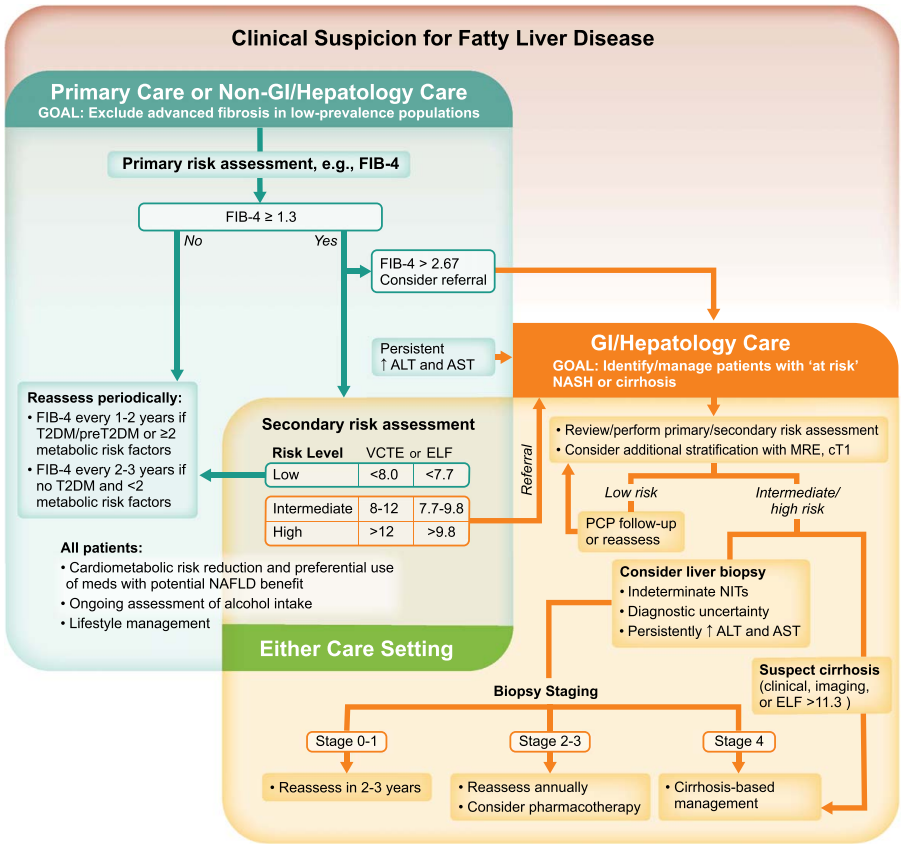

FIGURE 2 Algorithm for the evaluation of patients at risk for or with established NAFLD across practice settings. Patients with steatosis noted on imaging or for whom there is a clinical suspicion of NAFLD, such as those with metabolic risk factors or unexplained elevation in liver chemistries, should undergo further evaluation. In settings with a low prevalence of advanced fibrosis, such as in the primary care setting, the emphasis is on excluding advanced fibrosis using a test with a high negative predictive value. When the fibrosis-4 index (FIB-4) is <1.3, patients can be followed in the primary care setting and reassessed periodically. Patients without prediabetes/type 2 diabetes mellitus (T2DM) and 1–2 metabolic risk factors can be reassessed every 2–3 years. Patients with prediabetes/T2DM or 2 or more metabolic risk factors are at higher risk for disease progression, and more frequent FIB-4 monitoring (eg, every 1–2 y) should be considered. In patients older than age 65, a FIB-4 cutoff of >2.0 should be used. FIB-4 has low accuracy in those under age 35; thus, secondary assessment should be considered in those <35 with increased metabolic risk or elevated liver chemistries. FIB-4 should not be used in acutely ill patients. In patients with FIB4 ≥1.3, a secondary assessment should be done [preferentially vibration-controlled elastography (VCTE) or Enhanced Liver Fibrosis (ELF) initially] or the patient referred for further risk stratification (if being seen in a nongastroenterology/hepatology setting). Direct referral to gastroenterology/hepatology should be considered in those with aminotransferases persistently (>6 mo) above normal to exclude other causes of liver disease or when FIB4 > 2.67 due to the increased risk of clinically significant fibrosis. In higher prevalence settings, such as gastroenterology/hepatology clinics, additional risk assessment with magnetic resonance elastography (MRE) may be appropriate when noninvasive tests (NITs) are indeterminate or there is clinical suspicion of more advanced disease. Identification of cirrhosis should prompt screening for HCC and esophageal varices. In addition, MRE or corrected T1 (cT1) may help identify patients with "at-risk" NASH (NASH with NAFLD activity score ≥4 and fibrosis stage ≥2) who may benefit from a therapeutic intervention as they become available. If cirrhosis is suspected based on NITs, clinical data, or imaging findings, then cirrhosis-based management may be initiated without a liver biopsy. Liver biopsy should be considered when NITs suggest significant fibrosis (≥F2), especially if additional evaluation suggests the presence of "at-risk" NASH (eg, using FAST, MEFIB, MAST, or cT1), NIT assessment is indeterminate, aminotransferases are persistently elevated (>6 mo), or additional/alternate diagnoses are suspected. Note that in patients with confirmed or suspected advanced fibrosis, an ELF ≥11.3 is a predictor of future liver-related events and is approved for this purpose; use of other ELF cutoffs in secondary risk assessment is based on expert option. Patients at all stages of disease should be counseled on lifestyle modifications, and those with ≥F2 fibrosis targeted for pharmacological interventions as they become available. Specific threshold values of NITs are approximations supported by current evidence and are meant to guide clinical management through primary care to gastroenterology/hepatology practices rather than be interpreted in isolation. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; PCP, primary care provider.

12. In patients with pre-DM, T2DM, or 2 or more metabolic risk factors (or imaging evidence of hepatic steatosis), primary risk assessment with FIB-4 should be repeated every 1–2 years.

13. Patients with NASH cirrhosis are at the highest risk for liver-related outcomes and require routine surveillance for HCC, esophageal varices, and monitoring for decompensation.

14. Patients with suspected advanced NASH or discordant NITs should be referred to a specialist for evaluation, management, and/or further diagnostic evaluation.

15. Aminotransferase levels are frequently normal in patients with advanced liver disease due to NASH and should not be used in isolation to exclude the presence of NASH with clinically significant fibrosis.

16. First-degree relatives of patients with NASH cirrhosis should be counseled regarding their increased individual risk and offered screening for advanced hepatic fibrosis.

Key points:

- *Patients with "at-risk" NASH (NASH with* at least *stage 2 fibrosis) are at increased risk of developing cirrhosis and liver-related complications.*

BIOMARKERS/NITS FOR THE DIAGNOSIS AND ASSESSMENT OF NAFLD

Although liver biopsy assessment remains the reference standard for the grading and staging of NASH, it has important limitations related to risk, cost, and resource utilization. Therefore, liver biopsies for grading and staging of NASH are not consistently performed in clinical practice and should be reserved for specific clinical scenarios (Figure 2).[317] Noninvasive biomarkers are emerging as valuable tools for predicting adverse liver-related outcomes (see more below), hitherto an important function of liver biopsies. Validation of noninvasive biomarkers in accordance with the US Food and Drug Administration (FDA)–National Institutes of Health guidance[318] will facilitate the diagnosis of patients with clinically meaningful disease and evaluate their response to treatment without the need for liver biopsies.

Noninvasive identification and quantification of hepatic steatosis

Although commonly used in clinical practice, conventional B-mode ultrasound lacks sufficient sensitivity for lesser degrees of steatosis, particularly in those with concomitant obesity,[319,320] and provides only a subjective semiquantitative assessment of steatosis severity. The absence of detectable steatosis on ultrasound does not exclude the presence of NASH or the presence of fibrosis, although ultrasound can be helpful when cirrhotic liver morphology is identified or if it identifies evidence of portal hypertension (eg, ascites, splenomegaly, portosystemic collateral vessels). For the assessment of hepatic steatosis, the controlled attenuation parameter (CAP), typically measured in conjunction with VCTE, provides a point-of-care semi-quantitative assessment of hepatic steatosis but does not accurately quantify or monitor changes in liver fat[321] (Table 5).

MRI–proton density fat fraction (PDFF) is an accurate, reproducible, and precise MRI-based biomarker for liver fat quantification that is routinely used in clinical research. Its role in clinical practice is evolving, although it is being increasingly used in tertiary care centers. Although MRI-PDFF is superior to CAP in the diagnosis as well as the quantification of liver fat, this advantage is tempered by cost, patient acceptance, and the disadvantage of not being a point-of-care technique[321] (Table 5).

Estimation of liver fibrosis in patients with suspected or confirmed NAFLD

Clinical and laboratory-based fibrosis biomarkers

NITs derived from clinical variables can estimate of the presence of advanced fibrosis (Table 5). Several have been developed (eg, FIB-4, NAFLD Fibrosis Score, AST Platelet Ratio Index); however, FIB-4 is the most validated. FIB-4 is calculated using a simple algorithm based upon age, ALT, AST, and platelet count[337] and outperforms other calculations in its ability to identify patients with a low probability of advanced fibrosis. High values of FIB-4 and other NITs have also been associated with all-cause and liver-related outcomes in population-based studies.[338] In addition, a change in FIB-4 status category from low risk (<1.3) to intermediate risk (1.3–2.67) to high risk (>2.67) may be used to assess clinical progression.[339] Although FIB-4 is statistically inferior to other serum-based fibrosis markers such as the ELF panel, FIBROSpect II, and imaging-based elastography methods to detect advanced fibrosis, FIB-4 is still recommended as a first-line assessment for general practitioners and endocrinologists based on its simplicity and minimal, if any, added cost.[332,340,341] The ELF panel is a proprietary blood test consisting of three elements involved in matrix turnover: hyaluronic acid, tissue inhibitor of metalloproteinase-1, and *N*-terminal procollagen III peptide. An ELF score of ≥ 9.8 reliably identifies patients with NAFLD at increased risk of progression to cirrhosis and liver-related clinical events.[342,343] The

TABLE 5 Parameters for the noninvasive assessment of NAFLD according to clinical context of use

Modality type	Cut point: Likely	Cut point: Unlikely	Strengths/limitations, references/caveats
Identification of hepatic steatosis			
Imaging			
Ultrasound	"Detected"	NA	Semiquantitative assessment: mild/moderate/severe; low sensitivity with less severe steatosis[322]; steatosis can have similar echo characteristics as advanced fibrosis
FibroScan: CAP	≥ 288 dB/min		Limited accuracy for quantification[323]
MRI-PDFF	≥ 5%	< 5%	Most sensitive across spectrum of steatosis; accurate to assess dynamic change[324]
Identification of "at-risk" NASH			
FAST	≥ 0.67	< 0.35	≤ 0.35 (sensitivity 90%), ≥ 0.67 (specificity 90%); in validation cohorts, the PPV of FAST ranged between 0.33 and 0.81[28,325]
MAST	≥ 0.242	≤ 0.165	0.242 (specificity 90%),[326] 0.165 (sensitivity 90%)[326]
MEFIB	FIB-4 ≥ 1.6 plus MRE ≥ 3.3 kPa	FIB-4 <1.6 plus MRE <3.3 kPa	Sequential approach identifies patients with at least stage 2 fibrosis with > 90% PPV[327]
cT1	≥ 875 ms	< 825 ms	Requires further validation[328]
Detection of advanced fibrosis			
Serum			
FIB-4	≥ 2.67	< 1.3	No added cost[117,329,330]; not accurate in age <35 y and lower rule-out threshold among high-risk individuals who have high pretest probability
NFS	≥ 0.672	< −1.44	No added cost; not accurate in age <35 y, people with obesity and/or type 2 diabetes[117,329,330]
ELF	≥ 9.8	< 7.7	Blood test sent to a reference laboratory[331]; cost
FIBROSpect II	≥ 17	< 17	Blood test sent to a reference laboratory[332]; cost
Imaging			
VCTE	≥ 12 kPa	< 8 kPa	Point of care[4]
ARFI	≥ 1.34	< 1.3	Cut points not well validated[333]
SWE	≥ 12 kPa	< 8 kPa	Cut points not well validated[488]
MRE	≥ 3.63 kPa	< 2.55 kPa	MRE LSM ≥ 3.63 kPa (associated with advanced fibrosis, AUROC of 0.93)[334]
Diagnosis of cirrhosis (rule-in or rule-out)	Rule-in	Rule-out	
CPR			
FIB-4	≥ 3.48	< 1.67	90% specificity cut point for ruling-in and 90% sensitivity for ruling out cirrhosis, respectively[4,335]
ELF	≥ 11.3	< 7.7	ELF ≥ 11.3 is associated with increased risk of hepatic decompensation among patients with cirrhosis[331]
Imaging			
VCTE	≥ 20 kPa	< 8 kPa	LSM by VCTE ≥ 20 kPa is associated with cirrhosis, but for ruling out, cirrhosis optimal cut point is <8 kPa[4]
MRE	≥ 5 kPa	< 3 kPa	LSM by MRE ≥ 5 kPa has a very good (approaches 95%) specificity for diagnosis of cirrhosis and is also associated with increased risk of incident hepatic decompensation[334,336]

Note: "at-risk" NASH is defined as NASH with stage ≥ 2 fibrosis

Abbreviations: AUROC, area under the receiver operating characteristic curve; CAP, controlled attenuation parameter; CPR, clinical prediction rule; cT1, corrected T1; ELF, Enhanced Liver Fibrosis; FAST, FibroScan assessed liver stiffness measurement in kPa, CAP, and serum aspartate aminotransferase; FIB-4, fibrosis-4 index; LSM, liver stiffness measurement; MAST: score from MRI-PDFF, MRE, and serum aspartate aminotransferase; MEFIB, FIB-4 ≥ 1.6 plus MRE ≥ 3.3 kPa; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging–proton density fat fraction; NFS, NAFLD Fibrosis Score; PPV, positive predictive value; SWE, shear wave elastography; VCTE, vibration-controlled elastography.

ELF test is approved for clinical use as a prognostic biomarker in the US and several other countries. Such serum-based fibrosis tests may be good options as secondary risk assessments when elastography is not available (Figure 2).

Elastography

Liver stiffness is a physical characteristic of the liver that increases with fibrosis severity as well as other processes such as passive congestion, marked inflammation, and infiltrative diseases. VCTE (eg, FibroScan®) is the most commonly used method to assess liver stiffness and can be used to exclude significant hepatic fibrosis. A recent meta-analysis suggested that a VCTE-derived liver stiffness measurement (LSM) <8 kPa can be used to rule out advanced fibrosis, especially if used sequentially after FIB-4.[4] LSMs by VCTE between 8 and 12 kPa may be associated with fibrotic NASH, and LSM >12 kPa is associated with a high likelihood of advanced fibrosis, although the positive predictive value is low (range: 0.34–0.71).[336,344] Changes in liver stiffness may also be useful in identifying disease progression, such that an increase in liver stiffness of 20% on either VCTE or MRE may be associated with disease progression and long-term clinical outcomes.[345,346]

In identifying patients with cirrhosis, a sequential approach with a FIB-4 >3.48 and LSM by VCTE ≥20 kPa had a specificity of 90%.[4] However, such an approach will likely miss some patients with cirrhosis due to low sensitivity of these cut points. Sequential combination of low cut points to exclude advanced fibrosis and high cut points to identify advanced fibrosis may be used until more precise methods become available. Similar cut points for shear wave elastography, point shear wave elastography, and other ultrasound-based elastography methods are emerging options but have not been well validated compared with the more extensive data on VCTE (Table 5).

MRE is more sensitive than VCTE in the detection of fibrosis stage ≥2[347] and is considered to be the most accurate noninvasive, imaging-based biomarker of fibrosis in NAFLD.[321,336,348,349] Although MRE is not a first-line approach to risk stratification in a patient with NAFLD, it can be an important tool if clinical uncertainty exists, if there is a need for concomitant cross-sectional imaging, or when other elastography techniques are unavailable. Among patients with cirrhosis, baseline LSM by MRE predicts future risk of incident hepatic decompensation and death.[350] The range of LSM values that correlate with the stage of fibrosis is technique-dependent (Table 5). An LSM by MRE ≥5 kPa is suggestive of cirrhosis (area under the receiver operating characteristic curve range: 0.89–0.94).[334,336] Liver stiffness assessed by MRE may also be useful to assess the risk of decompensation. In one study, MRE LSMs of 5 and 8 kPa were associated with 9% versus 20% risk of incident hepatic decompensation or death, respectively.[350] Note that the units for LSM by VCTE and MRE are both kilopascals, but the scales are different. An individual patient meta-analysis provided further validation of these findings with a baseline MRE LSM stratified into three categories of <5 kPa, 5–8 kPa, and >8 kPa that were associated with 1.6%, 17%, and 19% risk of decompensation over 3 years of follow-up, respectively.[351] In addition, a 1 kPa increase in MRE liver stiffness is associated with a higher risk of liver-related as well as CVD outcomes.[350,352] Although more data are needed, NIT improvements in patients with cirrhosis regression suggest they may be reliable as surrogates for histological improvement in response to therapeutic intervention once properly validated.

Methods under study for the identification of "at-risk" NASH

Several serum and imaging biomarkers are under study for the detection of NASH, but these have not reached the level of clinical evidence needed for use in routine clinical practice. NIS-4 (a panel of 4 biomarkers including microRNA-34a, alpha-2 macroglobulin, YKL-40, and glycated hemoglobin)[353] and other serum and plasma-based lipidomic, metabolomic, and proteomic biomarkers are in development for "at-risk" NASH. Imaging techniques such as cT1 may also be considered for the identification of "at-risk" NASH,[354] In an individual patient meta-analysis of 543 patients, cT1 performed well (area under the receiver operating characteristic curve: 0.78),[328] although this requires further validation in large independent cohorts. Precise cutoffs have not been validated, and superiority over less expensive, point-of-care techniques remains to be demonstrated.[355]

Techniques that combine clinical parameters with liver stiffness assessment that may be predictive of outcomes are emerging. The FibroScan-AST (FAST) score is a composite score calculated from liver stiffness and CAP determined by VCTE and serum AST for the detection of "at-risk" NASH,[28] with one study showing performance differences based on race and BMI across different populations.[325] In a head-to-head comparative study, MRE combined with FIB-4 (FIB-4 ≥1.6 plus MRE ≥3.3 kPa) has been shown to be superior to FAST.[347] A positive MRE combined with FIB-4 has been linked to increased risk of hepatic decompensation, and a negative MRE combined with FIB-4 has a 99% negative predictive value for a 5-year risk of hepatic decompensation.[351] A score derived from MRI-PDFF, MRE, and serum AST is also able to identify "at-risk" NASH.[326] Other emerging combinations, such as a score based on cT1, AST, and fasting glucose (cTAG), may be effective but require further validation.[356] Clear superiority of

one approach over the over needs to be determined and the relative importance of point-of-care access weighed in depending on the context of use (Table 5).

Guidance statements:

17. Although standard ultrasound can detect hepatic steatosis, it is not recommended as a tool to identify hepatic steatosis due to low sensitivity across the NAFLD spectrum.

18. CAP as a point-of-care technique may be used to identify steatosis. MRI-PDFF can additionally quantify steatosis.

19. If FIB-4 is $\geq$1.3, VCTE, MRE, or ELF may be used to exclude advanced fibrosis.

Key points:

- *Highly elevated liver stiffness, FIB-4, and ELF scores can predict an increased risk of hepatic decompensation and mortality.*

THE ROLE AND INTERPRETATION OF LIVER BIOPSY

Histological evaluation of NAFLD should provide three basic pieces of information: diagnosis, grading of necroinflammatory activity, and staging of fibrosis severity.[357] To adequately assess these features, biopsies obtained with a 16-G needle should be at least 1.5 cm in length but preferably 2–2.5 cm in length.[358] Good-quality sectioning and staining are also important. Within the spectrum of NAFLD there are several distinct patterns: the common zone 3 injury pattern of adult steatohepatitis, the zone 1 steatosis-fibrosis pattern observed most often in young children, and steatosis with or without mild inflammation that does not meet criteria for steatohepatitis. Reporting of severity includes description of the pattern and degree of steatosis, inflammation, ballooning changes, and fibrosis.[357] Although fibrosis stage is the best predictor of long-term outcome in multivariable analyses,[30,36] ballooning injury and portal inflammation are short-term predictors of fibrosis progression or regression and are commonly combined as measures of disease grade[359,360] (Figure 3). Composite histological scores such as the NAFLD activity score (NAS) and the steatosis, activity, fibrosis score combine histological features and are used in clinical studies to offer a structured overall assessment of severity.[361,362] Biopsy remains the best method for providing information on the architectural distortion and the complex anatomic interrelationships of cellular injury, inflammation, and fibrosis.

Image analysis by artificial intelligence (AI) can provide more granular detail of histological findings as well as quantification of features on a continuous scale rather than the semiquantitative scoring system available to human observers.[363,364] Evaluation of steatosis and fibrosis are the most developed of the AI algorithms because the physicochemical properties of lipid droplets and collagen allow for easier identification by machines. The inherent variability in the composition and character of lobular and portal inflammation as well as the spectrum of hepatocyte injury that is identified as ballooning presents more challenges in correct classification and quantification by AI algorithms but is under development.

TREATMENT

A healthy diet and regular exercise form the foundation of treatment for the vast majority of those with NAFLD.[365] Even if weight loss is not needed, improved diet composition and increased exercise promote cardiovascular health in addition to improved liver health and metabolic comorbidities. For optimization of associated metabolic comorbid disease, a multidisciplinary team of clinicians provides the best chance for success in reducing liver and cardiovascular morbidity and mortality in patients with NAFLD (Figure 4).[173,366] Some of the medications approved for commonly associated comorbidities such as T2DM and obesity have been studied in the context of NAFLD and may reduce liver enzymes or steatosis or improve liver histology. Therefore, medications with possible liver-related benefits should be considered when managing comorbidities (Table 5).[2]

Liver protective healthy behaviors (lifestyle intervention)

Weight loss

Even modest amounts of weight loss can be impactful, especially in those with milder disease. Weight loss of 3%–5% improves steatosis, but greater weight loss ($>$10%) is generally required to improve NASH and fibrosis.[262,367–370]

Achieving and sustaining weight loss is challenging. Sustained weight loss reduces adipose tissue stress and improves peripheral insulin sensitivity,[39] which can reduce the drive for liver injury in NASH (Figure 1). Few patients ($\leq$10%) achieve effective weight loss despite structured interventions at 1 year, and fewer than half of these maintain the weight lost 5 years after intervention,[367,371] highlighting the need for ongoing nutrition support through multidisciplinary care

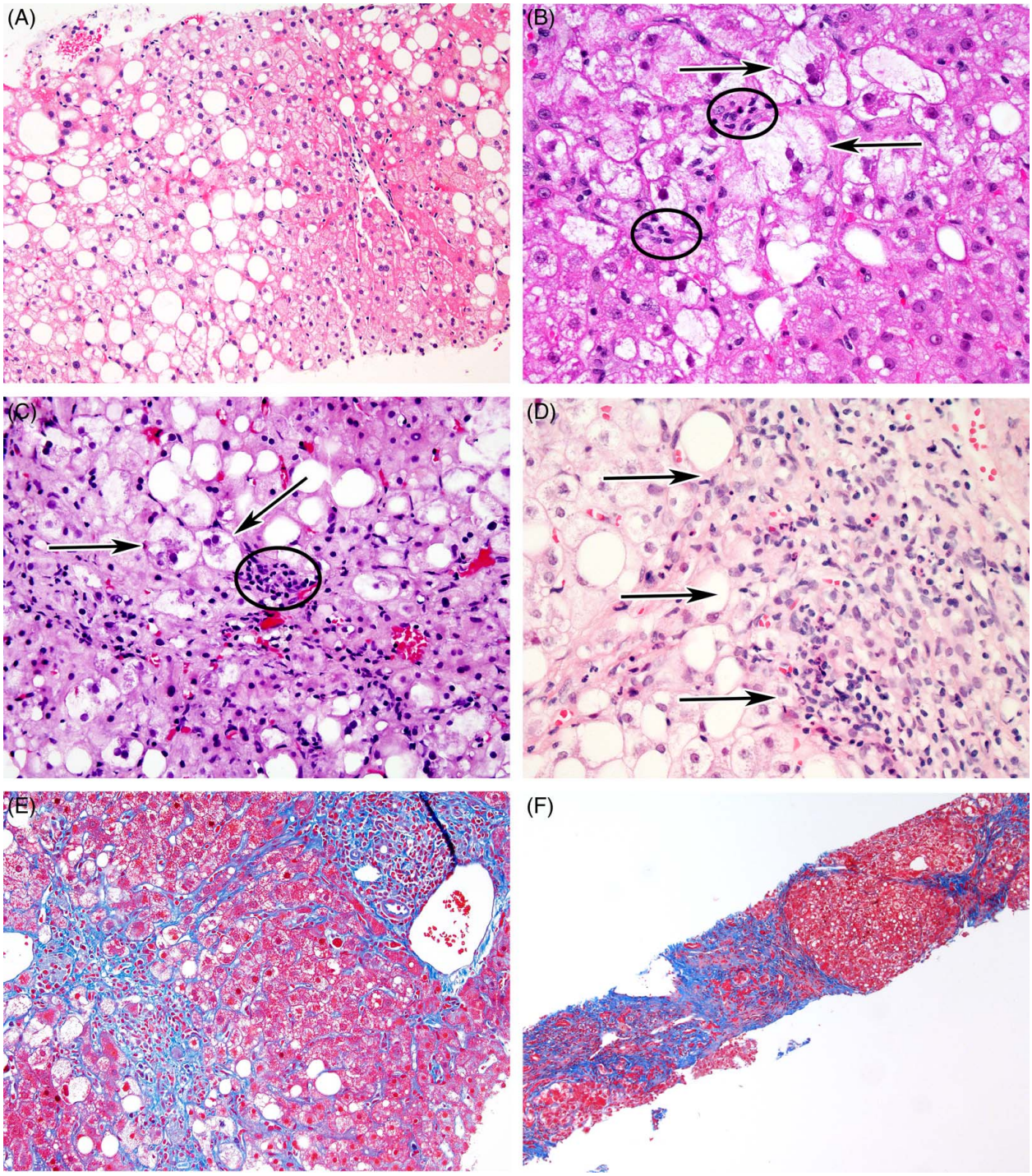

FIGURE 3 Histology of NAFLD. Liver biopsy shows characteristic features of the spectrum of NAFLD. (A) Hepatic steatosis (typically zone 3) without ballooned hepatocytes or fibrosis [hematoxylin and eosin (H&E), ×200]. (B) Multiple ballooned hepatocytes with Mallory-Denk bodies (arrows) and mild lobular inflammation (circles) (H&E, ×400). (C) Ballooned hepatocytes (arrows) with moderate lobular inflammation (circle) (H&E, ×200). (D) Some cases of steatohepatitis may show significant portal inflammation and interface hepatitis (arrows) (H&E, ×200). (E) Dense perisinusoidal and periportal fibrosis (blue stain), with a thin connecting fibrotic bridge (Masson trichrome, ×200). (F) Cirrhosis (nodule formation) due to steatohepatitis (Masson trichrome, ×100).

(Figure 4). Unfortunately, reducing caloric intake can also be associated with counterproductive reductions in metabolic energy disposal.[372] Psychological barriers can impede the implementation of a successful dietary and exercise plan; therefore, engagement with a health psychologist can be an invaluable tool for selected patients.[373,374] A multidisciplinary approach, inclusive of patient support systems and family engagement, with behavioral medicine specialists, dieticians, and/or nutritionists, can optimize success over provider

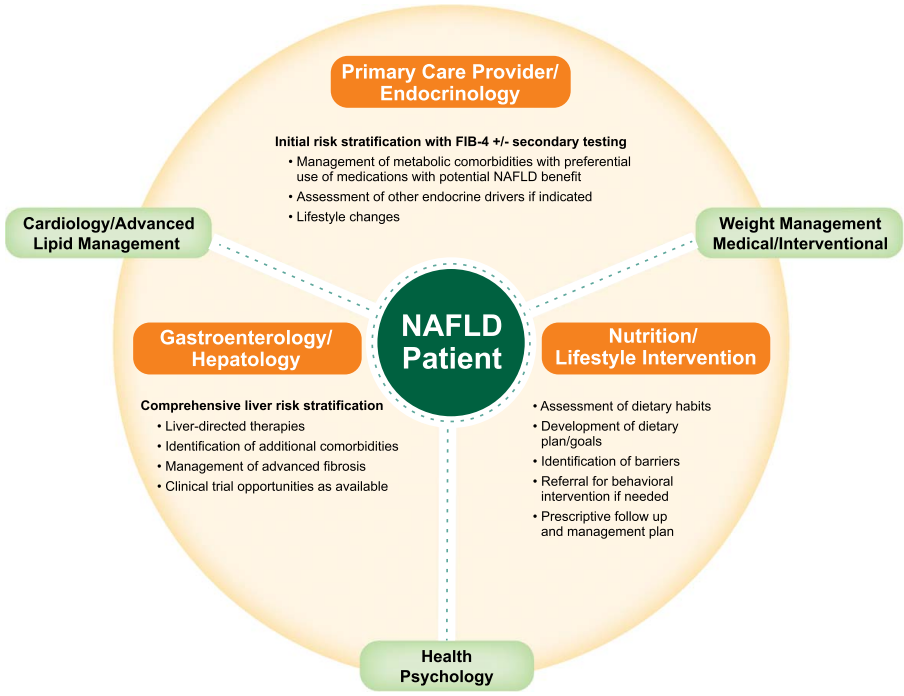

FIGURE 4 A multidisciplinary approach to the management of NAFLD. Optimal care of the patient with NAFLD requires a multidisciplinary approach. The majority of patients are in the primary care/endocrine setting, in which management of medical comorbidities should be optimized, with preference given to treatments for type 2 diabetes mellitus, hypertension, or obesity that likely also have beneficial effects on NAFLD. In this setting, at-risk patients should be identified and initial risk stratification performed [ie, fibrosis-4 index (FIB-4) ± vibration controlled elastography or Enhanced Liver Fibrosis]. The role of the gastroenterologist/hepatologist includes more comprehensive liver risk stratification, exclusion of other liver diseases, and a focus on liver-directed therapy. Close communication between gastroenterology/hepatology and primary care or endocrinology facilitates multidisciplinary management of metabolic comorbidities as well as the prioritization of medications or interventions that may also offer liver benefits (see the Treatment section). All patients should undergo dietary/nutritional assessment and a plan established for regular follow-up independent of gastroenterology/hepatology visits. The need for more specialized obesity management, including bariatric surgery referral, health psychology, and additional cardiology or lipid metabolic support, should be assessed on an individual basis (dotted arrows).

counseling alone in addressing the social, economic, and psychological challenges of lifestyle change (Figure 4).[375,376]

Role of macronutrient composition

A diet containing excess calories, particularly excess saturated fats, refined carbohydrates, and sugar-sweetened beverages, is associated with obesity and NAFLD.[377–379] Excessive fructose consumption in particular increases the risk of NAFLD, NASH, and advanced fibrosis independent of calorie intake.[380–382] Changes in dietary composition (eg, low-carbohydrate vs. low-fat diets, saturated vs. unsaturated fat diets, intermittent fasting, Mediterranean diet, etc.) and different intensities of caloric restriction appear comparable in their ability to improve NAFLD/NASH.[383,384] Some data suggest that the benefits of dietary intervention may be amplified in patients with certain genetic polymorphisms.[385,386] The Mediterranean diet is often recommended to patients with NAFLD based on its associated improvement in cardiovascular health[387] and reduction in liver fat.[388,389] Although the benefits of the Mediterranean diet over other dietary approaches in small randomized trials is debated,[47,390,391] it is sustainable and has cardiovascular benefit.[387] Although it may not be directly applicable across cultures and ethnicities, similar dietary modifications tailored to a patient's cultural and personal preferences may promote long-term adherence and compliance.

Coffee consumption, independent of caffeine content, may also be beneficial. Drinking 3 or more cups per day could be recommended in the absence of contraindications based on the reduced risk for NAFLD and liver fibrosis demonstrated in epidemiological studies and meta-analyses.[392–394]

Impact of exercise

Exercise, independent of weight loss, has hepatic and cardiometabolic benefit and should be routinely recommended and tailored to the patient's preferences and physical abilities.[50,395–400] Some studies demonstrate that regular moderate exercise at least 5 times per week for a total of 150 minutes per week or an increase in activity level by more than 60 minutes per week can prevent or improve NAFLD.[365,398,401,402] Others suggest that more vigorous exercise is needed to improve

NASH histology, with even higher intensity exercise needed to reduce fibrosis.[403] Studies combining diet with exercise consistently demonstrate reductions in liver fat proportional to the intensity of the intervention.[47,404–407] Therefore, although the optimal duration and intensity of exercise need to be individualized, patients should be encouraged to exercise as much as possible.[397,398,402]

Patients with cirrhosis require a slightly different approach that prioritizes protein intake and recognizes potential physical limitations.[313] In one study of patients with obesity and cirrhosis, weight loss and regular physical activity reduced portal pressure.[408] Exercise can also improve frailty, sarcopenia, and quality of life in patients with chronic liver disease.[409]

Guidance statements:
20. Patients with NAFLD who are overweight or obese should be prescribed a diet that leads to a caloric deficit. When possible, diets with limited carbohydrates and saturated fat and enriched with high fiber and unsaturated fats (e.g., Mediterranean diet) should be encouraged due to their additional cardiovascular benefits.

21. Patients with NAFLD should be strongly encouraged to increase their activity level to the extent possible. Individualized prescriptive exercise recommendations may increase sustainability and have benefits independent of weight loss.

Key points:

- *Weight loss improves hepatic steatosis, NASH, and hepatic fibrosis in a dose-dependent manner.*
- *The necessary support to manage comorbid disease and foster the adoption of liver protective health behaviors is best achieved using a multidisciplinary approach.*
- *Coffee consumption (caffeinated or not) of at least 3 cups daily is associated with less advanced liver disease.*

Bariatric surgery

Although currently accepted criteria for bariatric surgery are BMI $\geq$40 kg/m^2 irrespective of metabolic comorbid disease or BMI $\geq$35 kg/m^2 with comorbidities (T2DM or pre-DM, uncontrolled hypertension, osteoarthritis of hip or knee, urinary incontinence), NAFLD/NASH is increasingly accepted as a comorbid condition benefitting from bariatric surgery.[410,411] The overwhelming majority of patients undergoing bariatric surgery have NAFLD and many have NASH; however, the prevalence of advanced hepatic fibrosis and cirrhosis is low in published series,[412] in part due to presurgical screening that often excludes those with evidence of chronic liver disease or cirrhosis.

Bariatric surgery can resolve NASH, improve hepatic fibrosis, induce sustained weight loss of up to 30%, cure diabetes, and decrease all-cause morbidity and mortality.[413–421] In a prospective long-term follow-up study with consecutive liver biopsies, resolution of NASH without worsening of fibrosis occurred in 80% of patients 1 year following bariatric surgery,[422] which was maintained at 5 years.[423] Failure to achieve substantial weight loss following bariatric surgery is associated with persistent NASH. Restrictive surgical procedures result in substantially less weight loss than malabsorptive procedures and are more likely to be associated with persistent NASH.[420,422] Endoscopic bariatric and metabolic surgery procedures are promising less-invasive options; however, long-term safety and efficacy data are needed.[424–426]

In the setting of cirrhosis, data regarding hepatic benefits are limited, and the choice of bariatric intervention should be focused on striking a balance between desired weight loss and the risk of complications, including hepatic decompensation.[424–426] In general, bariatric surgery currently cannot be considered a primary therapy for the treatment of compensated NASH cirrhosis; however, it seems to be safe in carefully selected patients. Bariatric surgery in the setting of decompensated cirrhosis or clinically significant portal hypertension is associated with an increased risk of postoperative mortality and should only be considered at high volume centers under special circumstances such as when combined with liver transplant or as part of a research protocol.

Guidance statements:
22. Bariatric surgery should be considered as a therapeutic option in patients who meet criteria for metabolic weight loss surgery, as it effectively resolves NAFLD or NASH in the majority of patients without cirrhosis and reduces mortality from CVD and malignancy.

Key points:

- *The type, safety, and efficacy of bariatric surgery in patients with well-compensated NASH cirrhosis is not established and requires a careful benefit–risk assessment by a*

multidisciplinary team of experts that includes a hepatologist.

- *Decompensated cirrhosis should be considered an absolute contraindication for bariatric surgery due to increased risk and unproven liver-related benefit, unless performed in conjunction with liver transplantation at experienced centers.*

Use of available medications

Although there are currently no FDA-approved drugs for the treatment of NASH at any disease stage, there are medications approved for other indications that have shown benefits for NASH in clinical trials and should be considered under specific circumstances (Table 6).

Vitamin E

In a multicenter, randomized controlled trial (RCT), Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with NASH (PIVENS), treatment with rrr α-tocopherol (the natural form of vitamin E) 800 IU daily for 96 weeks improved histology ($\geq$2-point reduction in NAS) compared with placebo.[427] These findings were supported by a meta-analysis showing that vitamin E improved serum aminotransferases in addition to steatosis, inflammation, and cellular ballooning on biopsy.[439,440] A reduction in serum ALT to $\leq$40 U/L and by $\geq$30% of baseline value after initiation of vitamin E is associated with improvement in histological parameters.[441] Although no study has demonstrated that vitamin E meaningfully reduces fibrosis, a retrospective study of 236 patients with NASH and advanced fibrosis showed that vitamin E use was associated with lower rates of hepatic decompensation (37% vs. 62%, $p = 0.04$) and higher transplant free survival (78% vs. 49%, $p < 0.01$).[442] The reduction in morbidity and mortality was independent of underlying diabetes status. Concern about the risks of vitamin E on bleeding and specifically hemorrhagic stroke has been raised, but prospective data are needed to confirm this observation. In addition, data demonstrating a relationship between vitamin E and prostate cancer are conflicting.[443,444] Such potential risks should be discussed with patients before initiation of long-term high-dose (eg, 800 IU daily) vitamin E therapy.

Thiazolidinediones

Thiazolidinediones are ligands for peroxisome proliferator-activated receptor γ approved for the treatment of T2DM.[445] In patients with NASH with or without pre-DM or T2DM, treatment with pioglitazone improves histology and insulin resistance.[429,446] Pioglitazone use also improves serum lipids profiles.[447] In the PIVENS trial, pioglitazone treatment did not meet the a priori primary endpoint of a $\geq$2-point reduction NAS without worsening of fibrosis, although 47% had NASH resolution compared with 21% of participants receiving placebo ($p < 0.001$).[427] Subsequently, in an 18-month study of patients with either preDM or T2DM and NASH, pioglitazone treatment led to a $\geq$2-point reduction in NAS and a trend toward fibrosis improvement.[430] A pooled network meta-analysis demonstrated that pioglitazone was better than placebo in achieving NASH resolution as well as fibrosis improvement.[448] Potential side effects associated with pioglitazone include weight gain, osteoporosis in postmenopausal women, a debated risk of bladder cancer, and potential risk for worsening heart failure in those with preexisting cardiac dysfunction.[449–451] Although pioglitazone may improve CVD,[452–454] its use in clinical practice has been overtaken by the increasing use of newer antidiabetic agents such as glucagon-like peptide-1 receptor agonist (GLP-1RA) and sodium glucose cotransporter-2 (SGLT-2) inhibitors (SGLT-2i) with pleiotropic metabolic benefits, most notably weight loss and reduction in cardiovascular mortality.[455,456]

GLP-1RAs

The biological effects of GLP-1RAs on lipids, glucose metabolism, weight loss, and cardiovascular outcomes make them attractive agents for treatment of NASH.[456–459] Some in this class are approved for the treatment of diabetes, and two have been approved for the treatment of obesity.[460] Although several GLP-1RAs are approved for treatment of T2DM, none has been approved for treatment of NASH. In a small study of patients with NASH, liraglutide improved steatosis, resolved NASH, and reduced fibrosis progression compared with placebo.[432] In an adequately powered phase 2b RCT of daily s.c. semaglutide, 320 patients with NASH (F1–3) were randomized to 0.1, 0.2, or 0.4 mg or placebo daily for 72 weeks (primary endpoint, resolution of NASH without worsening fibrosis).[433] NASH resolution was dose dependent and occurred in 59% in the treatment group versus 17% in the placebo group ($p < 0.001$). Despite evidence of fibrosis improvement in the treatment groups, there was no statistically significant reduction in fibrosis compared with placebo; however, a dose-dependent decrease in progression was observed. A larger, phase 3 trial of semaglutide in the treatment of NASH-related fibrosis is currently underway. Tirzepatide, a recently approved glucagon-like peptide-1/glucose-dependent insulinotropic polypeptide receptor agonist for the treatment of T2DM, demonstrates weight loss as high as 20.9% in nondiabetics compared with 3.1% in the placebo group and an absolute reduction in liver fat content

TABLE 6 Potential impact of available medications on patients with NAFLD

Medication	FDA indication	Patient population	Clinical benefits	Potential side effects	Cardiac benefit
Vitamin E (rrr-alpha) 800 IU daily[427,428]	NA	NASH without T2DM or cirrhosis	Liver related: improves steatosis, NASH resolution? No proven benefit on fibrosis	Hemorrhagic stroke, risk of prostate cancer?	No
Pioglitazone 30–45 mg po daily[429–431]	T2DM	NASH with and without T2DM	Liver related: improves steatosis, activity and NASH resolution, fibrosis improvement? Nonliver related: improves insulin sensitivity, prevention of diabetes, CV risk reduction and stroke prevention	Weight gain, risk of heart failure exacerbation, bone loss	Yes
Liraglutide[a] 1.8 mg s.c. daily (T2DM) 0.6–3 mg s.c. daily (obesity)[432]	T2DM, obesity	NASH without cirrhosis	Liver: improves steatosis, no proven impact on fibrosis. Nonliver related: improvement in insulin sensitivity, weight loss, CV risk reduction, may slow progression of renal disease	Gastrointestinal, gallstones (related to weight loss), pancreatitis	Yes
Semaglutide[b] 0.4 mg s.c. daily, 0.25–2.4 mg SQ weekly[433]	T2DM, obesity	NASH without cirrhosis	Liver related: improves steatosis, activity, and NASH resolution, no proven benefit on fibrosis, but may slow fibrosis progression. Nonliver related: improvement in insulin sensitivity, weight loss, improves CV and renal outcomes, stroke prevention	Gastrointestinal, gallstones (related to weight loss), pancreatitis	Yes
Tirzepatide[434,435]	T2DM	T2DM or obesity with NAFLD	Liver related: reduces steatosis on imaging. Nonliver related: improvement in insulin sensitivity, significant weight loss	Gastrointestinal, gallstones related to weight loss, pancreatitis	Unknown
SGLT-2i[436–438]	T2DM	T2DM and NAFLD	Liver related: reduction in steatosis by imaging. Nonliver related: may improve insulin sensitivity, improves CV and renal outcomes; benefit in heart failure, modest weight loss	Risk of genitourinary yeast infection, volume depletion, bone loss	Yes

Note: Available medications with demonstrable histological benefit in patients with biopsy-confirmed NASH. None of the medications are approved for treatment of NASH but can be used in carefully selected individuals with NASH and comorbid conditions such as diabetes and obesity or for off-label use.
Abbreviations: CV, cardiovascular; NA, not applicable; po, by mouth; s.c., subcutaneous; SGLT-2i, sodium glucose cotransporter-2 inhibitor; T2DM, type 2 diabetes mellitus.
[a]Study with small sample size and underpowered to determine key histological outcomes (ie, fibrosis).
[b]Phase 3 trial to determine efficacy currently enrolling.

of 8.1%, suggesting a possible benefit in NASH.[434] Similar reductions in liver fat have been observed in other trials.[434,435]

SGLT-2i

The SGLT-2i target renal glucose resorption from the glomerular filtrate and are approved for the treatment of T2DM.[461] Furthermore, they induce 2%–3% weight loss and have cardiorenal protective benefits.[433,436,455,456] Available studies evaluating the role of SGLT-2i in the treatment of NAFLD/NASH are limited by relatively small sample sizes and lack of histological outcomes.[437,438,462–464] Within these limitations, available data suggest SGLT-2i improve hepatic steatosis; however, the therapeutic impact of SGLT-2i on liver histology needs to be better defined.[465]

Available agents without evidence of histological benefits in NASH

Metformin has been extensively evaluated in patients with NASH but it does not improve histology.[466–469] Ursodeoxycholic acid has pluripotent hepatic effects related to changes in the bile acid pool, cytoprotection, and immune modulation. Although initial studies suggested benefits in NASH,[470–472] Ursodeoxycholic acid failed to demonstrate any histological benefit in an RCT of patients with NASH.[473,474] In short-term phase 2 RCTs, dipeptidyl peptidase-4 inhibitors have not proven efficacious to treat NAFLD.[475–477] Other available drugs not found to have liver-specific benefits include n-3 polyunsaturated fatty acids[478,479] and ezetimibe,[480,481] although some of these approaches are being revisited with different formulations such as alternate ratios of N3:N6 fatty acids or structurally engineered fatty acids.

The effect of silymarin (milk thistle) in patients with NASH remains inconclusive. In phase 2 RCTs,[482,483] silymarin was safe and well tolerated but did not improve NASH histology. Some studies show improvement in NITs compared with baseline and placebo,[482–484] suggesting a possible beneficial effect on fibrosis[483]; however, this remains to be confirmed on histology in larger trials.

Guidance statements:

23. There are currently no FDA-approved medications for the treatment of NAFLD, but drugs approved to treat associated comorbidities with potential benefit in NAFLD may be considered in the appropriate clinical setting.

24. Semaglutide can be considered for its approved indications (T2DM/obesity) in patients with NASH, as it confers a cardiovascular benefit and improves NASH.

25. Pioglitazone improves NASH and can be considered for patients with NASH in the context of patients with T2DM .

26. Vitamin E can be considered in select individuals as it improves NASH in some patients without diabetes.

27. Available data on semaglutide, pioglitazone, and vitamin E do not demonstrate an antifibrotic benefit, and none has been carefully studied in patients with cirrhosis.

28. Metformin, ursodeoxycholic acid, dipeptidyl peptidase-4, statins, and silymarin are well studied in NASH and should not be used as a treatment for NASH as they do not offer a meaningful histological benefit.

SURROGATE MARKERS OF HISTOLOGICAL TREATMENT RESPONSE

Although many studies have linked NITs with liver histology or clinical outcomes, data on biomarkers in a dynamic context to signal treatment response are still evolving.[485] ALT reduction correlates with histological improvement and ALT normalization can predict NASH resolution in response to lifestyle modification as well as various therapeutic interventions.[367,427,433,486,487] A decrease of $\geq$ 17 IU/L in ALT was associated with a higher odds of histological response in the FLINT trial of obeticholic acid.[486] Additional data are needed to identify the benchmark for serum ALT decline associated with fibrosis improvement and whether different thresholds are needed with different mechanisms. An analysis from the REGENERATE trial of obeticholic acid demonstrated that in addition to improvements in ALT, improvement in FIB-4, FAST, ELF, VCTE, and other markers correlated with histological fibrosis reduction, suggesting that histological response may be tracked using NITs.[488] Several studies and a meta-analysis have shown that $\geq$30% decline in MRI-PDFF is associated with 5-fold improved odds of NASH resolution, but thresholds for changes in liver stiffness measures that correlate with treatment-induced fibrosis improvement are not well established.[179,489–491] Additional studies are needed to better understand the long-term association among changes in liver fat, histological response, and clinical outcomes.

Improvements in FIB-4 or serum biomarkers such as ELF, liver stiffness, or combination parameters (Table 5) have been associated with histological response, but the exact thresholds of improvement remain to be validated in large multicenter studies within this context of use.[488]

Additional data are needed to determine if changes in NITs that correlate with treatment response are mechanism-specific or treatment agnostic. Validation of existing biomarkers as measures of treatment response will accelerate the development and approval of therapeutic agents and justify their adoption into clinical practice.

TABLE 7 Summary of key concepts to guide clinical practice

Screening for advanced fibrosis and risk stratification

- General population-based screening for NAFLD is not advised
- High-risk individuals, such as those with T2DM, medically complicated obesity, family history of cirrhosis, or more than mild alcohol consumption, should be screened for advanced fibrosis
- All patients with hepatic steatosis or clinically suspected NAFLD based on the presence of obesity and metabolic risk factors should undergo primary risk assessment with FIB-4
- In patients with pre-DM, T2DM, or 2 or more metabolic risk factors (or imaging evidence of hepatic steatosis) primary risk assessment with FIB-4 should be repeated every 1–2 y, due to limitations in the performance of FIB-4 in the context of T2DM. When available, a secondary assessment of liver fibrosis severity may be considered
- If FIB-4 $\geq$1.3, VCTE, MRE, or ELF may be used to exclude advanced fibrosis
- An elevated FIB-4 followed by elevated liver stiffness or an increased ELF can be used as a sequential strategy to identify advanced fibrosis
- In the nongastroenterology/hepatology setting, patients with suspected advanced NASH or discordant NITs should be referred to a specialist for evaluation, management, and/or further diagnostic evaluation
- Patients with NASH cirrhosis are at highest risk for liver-related outcomes and require routine surveillance for HCC, esophageal varices, and monitoring for decompensation
- ELF $>$11.3 has been linked to hepatic decompensation in the setting of advanced fibrosis and should prompt screening accordingly

Pearls for the assessment of NAFLD

- Aminotransferase levels are frequently normal in patients with advanced liver disease due to NASH and should not be used in isolation to exclude the presence of NASH with clinically significant fibrosis
- Normative values for ALT reported by most laboratories exceed what is considered a true normal. As a general rule, ALT $>$30 U/L should be considered abnormal
- Although standard ultrasound can detect hepatic steatosis, it is not recommended as a tool to identify hepatic steatosis due to low sensitivity across the NAFLD spectrum
- CAP as a point-of-care technique may be used to identify steatosis. MRI-PDFF can additionally quantify steatosis

Disease modifying interventions in patients with NAFLD

- Patients with NAFLD who are overweight or obese should be prescribed a diet that leads to a caloric deficit. When possible, diets with limited carbohydrates and saturated fat and enriched with high fiber and unsaturated fats (eg, Mediterranean diet) should be encouraged due to their additional cardiovascular benefits
- Patients with NAFLD should be strongly encouraged to increase their activity level to the extent possible. Individualized prescriptive exercise recommendations may increase sustainability and have benefits independent of weight loss
- Bariatric surgery should be considered as a therapeutic option in patients who meet criteria for metabolic weight loss surgery as it effectively resolves NAFLD or NASH in the majority of patients without cirrhosis and reduces mortality from CVD and malignancy

Off-label use of approved medications for comorbid conditions

- There are currently no FDA-approved medications for the treatment of NAFLD, but drugs approved to treat associated comorbidities with potential benefit in NAFLD may be considered in the appropriate clinical setting
- Semaglutide can be considered for its approved indications (T2DM/obesity) in patients with NASH as it confers a cardiovascular benefit and improves NASH
- Pioglitazone improves NASH and can be considered for patients with NASH in the context of patients with T2DM
- Vitamin E can be considered in select individuals as it improves NASH in some patients without diabetes
- Available data on semaglutide, pioglitazone, and vitamin E do not demonstrate an antifibrotic benefit, and these compounds have not been carefully studied in patients with cirrhosis
- Metformin, UDCA, DPP-4, statins, and silymarin are well studied in NASH and should not be used as a treatment for NASH as they do not offer a meaningful histological benefit
- Statins are safe and recommended for CVD risk reduction in patients with NAFLD across the disease spectrum, including compensated cirrhosis
- Limited data exist on the safety and efficacy of statins in patients with decompensated cirrhosis, although statin use could be considered in patients with high CVD risk with careful monitoring
- Hypertriglyceridemia can be managed through lifestyle changes and supplementation with omega-3 fatty acids, icosapent ethyl, or fibrates

Role of alcohol

- In patients with NAFLD, alcohol can be a cofactor for liver disease progression, and intake should be assessed on a regular basis
- Patients with clinically significant hepatic fibrosis ($\geq$F2) should abstain from alcohol use completely

Other considerations

- Improvement in ALT or reduction in liver fat content by imaging in response to an intervention may indicate histological improvement in disease activity
- First-degree relatives of patients with NASH cirrhosis should be counseled regarding their increased individual risk and offered screening for advanced hepatic fibrosis

Abbreviations: ALT, alanine aminotransferase; CAP, controlled attenuation parameter; CVD, cardiovascular disease; DM, diabetes mellitus; DPP-4, dipeptidyl peptidase-4; ELF, Enhanced Liver Fibrosis; FDA, US Food and Drug Administration; FIB-4, fibrosis-4 index; GI, gastrointestinal; MRE, magnetic resonance elastography; MRI-PDFF, MRI–proton density fat fraction; NIT, noninvasive test; T2DM, type 2 diabetes mellitus; UDCA, ursodeoxycholic acid; VCTE, vibration-controlled elastography.

Guidance statements:
29. Improvement in ALT or reduction in liver fat content by imaging in response to an intervention can be used as a surrogate for histological improvement in disease activity.

Key points:

- *ALT reduction of $\geq$17 U/L is associated with histological improvement; however, thresholds may differ for type of histological response (eg,*

NASH resolution or fibrosis improvement) and may be mechanism of action specific.

Future directions

The number of trials in NASH has increased exponentially over the last 10 years. Several therapeutic agents for NASH are in late-stage development, with safety and histological efficacy profiles that may be soon approvable by the FDA. Further validation of biomarkers that predict liver-related outcomes, identify patients who may benefit from treatment, and predict response to therapeutic intervention is underway, and the anticipated acceptance of biomarkers as surrogates of future liver-related events and treatment response will greatly accelerate drug development for single or combination approaches. Adoption of AI-based technologies will allow more accurate quantification of fibrosis and highlight early signs of treatment response. Furthermore, AI may help diminish variability in histological assessment currently plaguing clinical trials. Finally, rapidly evolving knowledge in genetic disease modifiers (eg, PNPLA3 and others) as well as the identification of distinct disease phenotypes using a variety of techniques will enable more individualized approaches to the future management of patients with NAFLD. These advances will likely lead to rapid changes in the current recommendations (Table 7) for diagnosing and management of patients with NAFLD.

AUTHOR CONTRIBUTIONS

All authors contributed to the conceptualization, intellectual content, drafting of the original manuscript, and critical revision for important intellectual content. All authors provided final approval of the manuscript.

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