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REVIEW

Clinical Trials and Investigations

Preparing for the NASH epidemic: A call to action

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Abstract

Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are common conditions with a rising burden. Yet there are significant management gaps between clinical guidelines and practice in patients with NAFLD and NASH. Further, there is no single global guiding strategy for the management of NAFLD and NASH. The American Gastroenterological Association, in collaboration with 7 professional associations, convened an international conference comprising 32 experts in gastroenterology, hepatology, endocrinology, and primary care providers from the United States, Europe, Asia, and Australia. Conference content was informed by the results of a national NASH Needs Assessment Survey. The participants reviewed and discussed published literature on global burden, screening, risk stratification, diagnosis, and management of individuals with NAFLD, including those with NASH. Participants identified promising approaches for clinical practice and prepared a comprehensive, unified strategy for primary care providers and relevant specialists encompassing the full spectrum of NAFLD/NASH care. They also identified specific high-yield targets

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for clinical research and called for a unified, international public health response to NAFLD and NASH.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD)—hepatic steatosis on imaging or histology in the absence of known causes—is rapidly becoming the most common cause of chronic liver disease worldwide (1). Nonalcoholic fatty liver is histologically defined as the presence of ≥5% hepatic steatosis without evidence of hepatocellular injury, and nonalcoholic steatohepatitis (NASH) is defined as the presence of ≥5% hepatic steatosis and inflammation with hepatocyte injury (eg, ballooning), with or without fibrosis (2). At least 20% to 30% of patients with NAFLD develop NASH, which can lead to cirrhosis and associated complications, including hepatocellular cancer (HCC) (2). NASH is also associated with an increased risk of cardiovascular disease (3) and increased cardiovascular and liver-related mortality (4–6).

Although most patients with NAFLD and NASH have traditionally been diagnosed and managed by hepatologists, the recent availability of noninvasive diagnostic procedures is expanding the role of other health care professionals likely to see patients with these conditions, particularly gastroenterologists, endocrinologists, obesity medicine specialists, and primary care providers (PCPs). Previous research has suggested that effectively treating NASH will require more education about both NAFLD and NASH among specialists and PCPs (7). Some published data also showed significant management gaps between published guidance and clinical practice in patients with NAFLD and NASH (8,9). Much of this disparity could come from a lack of recognition of the importance of NAFLD/NASH and an absence of a unified strategy that encompasses all disciplines involved in managing these patients across the full disease spectrum.

To address this need, the American Gastroenterological Association (AGA) conducted a needs assessment survey of health professionals likely to be engaged in managing adult patients with NAFLD/NASH, followed by a virtual conference of international experts representing 7 professional societies to review the current research and outline the future agenda for clinical practice, research, and policy. The overarching goal was to call for a unified, international public health response to NAFLD and NASH. This report summarizes the results from the survey and the virtual conference, "Preparing for a NASH Epidemic: A Call for Action." Although NAFLD is an important and growing problem in children, the current effort was limited to adults with NAFLD and NASH. Therefore, we do not cover pediatric NAFLD in this report.

NASH NEEDS ASSESSMENT SURVEY

The NASH Needs Assessment Survey was conducted in May 2020. The survey sought to assess participants' knowledge related to screening, diagnosis, and management of NAFLD and NASH; compare current diagnostic and treatment patterns with the most recent practice guidance on NAFLD/NASH; and identify the educational needs that could serve as targets to improve implementation of guideline-based treatment of NAFLD and NASH. The survey included 24 questions regarding screening, diagnosing, and managing NASH (see online Supporting Information for the full survey). In total, 751 gastroenterologists, hepatologists, endocrinologists, and PCPs from 46 states across the United States completed the survey. More than 50% of survey participants were PCPs. Respondents had spent an average of 19.5 years in practice (range, 2–35 years).

The survey revealed significant gaps in knowledge about who to screen and how to diagnose and treat patients at high risk for NASH, including disparities between published practice guidance and clinical practice (Table 1). Most respondents (67%) from all practice types were aware that up to one-quarter of the general population may have NAFLD. However, there were shortfalls in the knowledge about prevalence in several high-risk groups. For example, only 35% of all respondents—including 28% of endocrinologists, 32% of PCPS, and 46% of gastroenterologists/hepatologists—recognized that almost all patients with severe obesity are likely to have NAFLD. Only 49% of endocrinologists and 45% of PCPs recognized that NAFLD is very common in patients with type 2 diabetes (T2D) (Table 1).

Most participants reported that they screen patients with abnormal liver chemistries (96%), those with T2D (87%), and those who are older than 50 years with hypertension and hyperlipidemia (70%) for the presence of NAFLD. Most were also aware of the best practices in the initial evaluation of patients with suspected NAFLD, including the need to exclude competing etiologies (96%) and evaluation for commonly associated comorbidities, such as T2D, obesity, and dyslipidemia (96%). However, only 41% recognized that initial evaluation of patients with suspected NAFLD should not include cross-sectional abdominal imaging (eg, contrast-enhanced computed tomography) to screen for HCC. There were no significant differences in the responses among gastroenterologists/hepatologists, endocrinologists, and PCPs.

More than 80% of participants were aware that noninvasive tests, including the NAFLD fibrosis score, Fibrosis-4 Index, and imaging-based tests, such as vibration-controlled transient elastography or magnetic resonance elastography, are clinically useful tools for identifying NAFLD/NASH patients with a high likelihood of advanced liver fibrosis. However, 78% also thought that abdominal ultrasound can identify NAFLD patients with NASH.

Most participants were aware that 7% to 10% weight loss is recommended for patients with NAFLD, but fewer than half of the participants were aware that pioglitazone or vitamin E can be recommended as treatment in select patients with NASH. Most respondents (>80%) wanted more education about screening, diagnosis, and treatment of NAFLD/NASH.

TABLE 1 Key results from the nonalcoholic steatohepatitis (NASH) needs assessment survey

Variable	All participants ($n = 751$)	Gastroenterologists/ hepatologists ($n = 175$)	Endocrinologists ($n = 175$)	Primary care ($n = 401$)
Proportions of the key patient groups likely to have NAFLD				
Patients with severe obesity	35	46	28	32
Patients with T2D	50	62	49	45
Patients with dyslipidemia	40	47	41	36
General population	67	79	65	62
Patient groups that should be screened for NAFLD				
Patients with abnormal liver chemistry	96	97	97	85
Patients with T2D	87	88	94	83
Patients older than 50 years who have hypertension and hyperlipidemia	70	81	73	67
Approaches to the initial evaluation of the patient with suspected NAFLD				
Exclude competing etiologies for steatosis and coexisting common chronic liver disease	96	95	95	97
Consider the presence of commonly associated comorbidities, such as obesity, dyslipidemia, insulin resistance, or diabetes	95	97	93	95
Cross-sectional abdominal imaging (such as contrast-enhanced CT scan) to screen for HCC	41	50	39	38
Knowledge about strategies for noninvasive diagnosis of steatohepatitis and advanced fibrosis in NAFLD				
NAFLD fibrosis score or Fibrosis-4 Index are useful tools for identifying NAFLD patients with high likelihood of advanced fibrosis	82	94	86	75
VCTE (FibroScan) or MRE (imaging) are useful tools for identifying advanced fibrosis in patients with NAFLD	81	93	85	74
Abdominal ultrasound is a useful tool for identifying NAFLD patients with steatohepatitis	16	29	18	9
Appropriateness of treatments for NASH				
GLP-1 agonists	16	21	15	15
Metformin	17	33	17	11
Obeticholic acid	15	33	13	9
Omega-3 fatty acids	23	37	23	16
Pioglitazone[a]	53	53	77	42
Ursodeoxycholic acid	22	49	17	12
Vitamin E for nondiabetic adults[a]	40	71	51	38

Data represent percentages of participants who answered the item correctly.

Abbreviations: CT, computed tomography; GLP-1, glucagon-like peptide 1; HCC, hepatocellular cancer; MRE, magnetic resonance elastography; T2D, type 2 diabetes; VCTE, vibration-controlled transient elastography.

[a]The estimates for pioglitazone and vitamin E indicate percentages of participants who would consider treatment overall (with or without liver biopsy).

A CALL-TO-ACTION CONFERENCE

To address these knowledge gaps, the AGA convened a virtual conference of international experts in gastroenterology, hepatology, endocrinology, obesity management, and primary care on July 10, 2020. Participants represented key opinion leaders from 8 professional societies, and practiced in the United States, Europe, Australia, and Asia. See the online Supporting Information for the names and affiliations of all participants.

In a series of preconference meetings conducted over 2 months (May and June 2020), these key opinion leaders met and discussed the most important and potentially controversial aspects of the current NAFLD/NASH landscape, including epidemiology, risk factors, screening, diagnosis, and management issues. Formal presentations by each participant followed during the 1-day conference, which included the best-available evidence about their topic. Subsequent to the meeting, workgroups (predefined by subject) reviewed, discussed, and collated a summary from all presentations in their respective sections, followed by an internal review of the summary

from all workgroup members. The final manuscript (including summaries from each workgroup) was then submitted to the full group for a second round of input and approval. The sections here detail the discussion, conclusions, and recommendations for clinical practice and future research that emerged from this process.

BURDEN OF NAFLD and NASH

The clinical burden of both NAFLD overall and NASH specifically has increased steadily since the 1980s. NAFLD currently affects 25% of the global population and >60% of patients with T2D(10). Studies evaluating the prevalence of NASH suggest that it may involve an estimated 1.5% to 6.5% of the general population and as many as 37% of people with T2D (10). Prevalence of NASH is expected to increase by 63% between 2015 and 2030 (11). Although these numbers seem substantially lower than those for NAFLD overall, they still translate to 4.9 million to 21 million Americans and more than 100 million individuals worldwide. Modeling data estimate that the number of patients with NASH-related advanced fibrosis will likely double by 2030, resulting in 800,000 liver-related deaths (11).

NASH is already the number 1 indication for liver transplantation in women, patients older than 54 years, and Medicare recipients (12). Beyond the significant impairment of quality of life experienced by individuals with NASH and advanced fibrosis (10,13), Younossi et al (14) estimated in 2017 that the overall lifetime direct costs of NASH in the United States would be $222.6 billion, and approximately $95.4 billion over the next 2 decades, suggesting a substantial economic burden.

RISK FACTORS FOR NAFLD, NASH, AND RELATED COMPLICATIONS

Patients with obesity or T2D are at a higher risk of developing NAFLD/NASH (15,16). Conversely, patients with NAFLD are at an increased risk of T2D (17). NAFLD and especially NASH are independently associated with several liver-related complications, including cirrhosis, HCC, and liver-related mortality. Patients with NAFLD also have a 2-fold increase in risk of cardiovascular disease (18,19). Indeed, individuals with NAFLD/NASH are twice as likely to die of cardiovascular disease as liver disease (17). The risk of cardiovascular disease in NAFLD is not completely explained by the shared risk factors, and might be related in part to abnormalities of cardiac structure and function (17).

In patients with NAFLD, the strongest histologic determinant of hepatic and overall outcomes is the presence and stage of fibrosis, although the presence of NASH is the driving force for fibrosis development. Patients with histologic evidence of fibrosis higher than stage 2 are at higher risk for adverse outcomes (hepatic decompensation, HCC, and liver-related mortality), and this risk increases as fibrosis advances to cirrhosis (5). Specifically, a recent meta-analysis found that, compared to NAFLD patients with no fibrosis (stage 0), patients with fibrosis were at an increased risk for all-cause mortality, and this risk increased with the stage of fibrosis: stage 1: risk ratio (RR) vs stage 0, 1.58 (95% confidence interval [CI], 1.19–2.11); stage 2: RR, 2.52 (95% CI, 1.85–3.42); stage 3: RR, 3.48 (95% CI, 2.51–4.83); and stage 4: RR, 6.40 (95% CI, 4.11–9.95). The results were more pronounced for risk of liver-related mortality, which increased exponentially with each increase in fibrosis stage, from an RR of 1.41 (95% CI, 0.17–11.95) for stage 1 to an RR of 9.57 (95% CI, 1.67–54.93) for stage 2, and an RR of 42.30 (95% CI, 3.51–510.34) for stage 4 fibrosis (5).

Notably, fibrogenesis does not proceed linearly from simple fatty liver to NASH to cirrhosis, but progresses and regresses in up to 30% of patients during a mean period of 5 years (20). Furthermore, many patients with isolated hepatic steatosis, previously thought to be benign, are likely to progress to NASH (20). On average, patients with NASH and NAFLD progress 1 stage of fibrosis every 7 and 14 years, respectively (21). Older age, visceral obesity, T2D, and hypertension are associated with fibrosis progression (21,22). T2D and number of metabolic comorbidities are also associated with an increased risk of liver-related mortality and HCC (23,24). The severity of steatosis, however, has a modest (if any) correlation with the severity of liver histology (25), and the relationship between severity of steatosis and cardiovascular disease remains unclear.

Screening and diagnosis

Effectively screening for and timely diagnosis of NAFLD may prevent progression to NASH and associated complications. Because PCPs are on the front lines of managing individuals with NAFLD, screening patients at risk, stratifying patients based on their risk for advanced fibrosis, and positioning themselves to provide effective management and referrals are important. A recent study showed that screening for NAFLD followed by intensive lifestyle interventions or pioglitazone was cost-effective in patients with T2D diagnosed with clinically significant fibrosis, providing support for these recommendations (26).

To recognize NAFLD, the PCP must be aware of the following facts:

1. NAFLD is the one of the most common causes of abnormal liver enzymes, but serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) can be normal in many cases of NAFLD/NASH at all stages, including in patients with advanced fibrosis (27).
2. Liver fibrosis has been linked to morbidity and reduced overall patient survival (28).
3. NAFLD and fibrosis are reversible with weight loss (29).
4. Alcohol causes fatty liver disease with many histologic features of NAFLD. Although good clinical history is extremely important, one way to differentiate alcoholic from nonalcoholic fatty liver is the AST/ALT ratio, which is generally ≥2 in patients with alcohol

as the underlying cause. In certain patients, selective testing for alcohol metabolites may also be appropriate.

Clinical practice guidelines do not recommend screening for NAFLD in the general population, but case finding for NASH and significant fibrosis is advised for key high-risk groups, such as those with moderate to severe obesity (BMI >35 kg/m^2), T2D of more than 10 years' duration or in people older than 50 years, or metabolic syndrome (30). The American Diabetes Association's 2020 Standards of Medical Care in Diabetes also recommend evaluating patients with prediabetes or T2D with steatosis or elevated ALT for NASH and fibrosis (31).

Diagnosing NAFLD/NASH begins with evaluating patients for alternative or coexisting causes of liver disease, such as viral hepatitis or significant alcohol intake, through history and laboratory testing (Table 2). The accuracy of ultrasound for the detection of moderate and severe steatosis is quite high, >80% in a meta-analysis compared to that of liver biopsy. However, ultrasound has suboptimal sensitivity for mild steatosis (32,33). Among patients with a high pretest probability of NAFLD, moving directly to risk stratification without an ultrasound to confirm steatosis may be appropriate.

Although an optimal strategy for risk stratification of individuals with NAFLD/NASH in primary care and specialist clinics remains undefined, the guiding principle is to rule out advanced fibrosis by simple, noninvasive fibrosis scores (such as NAFLD fibrosis score or Fibrosis-4 Index). Patients at intermediate or high risk may require further assessment with a second-line test—elastography, or a serum marker test with direct measures of fibrogenesis (such as enhanced liver fibrosis (34) or fragments of propeptide of type III procollagen (35), and may require referral to a hepatology clinic (Figure 1). Of note, the enhanced liver fibrosis and propeptide of type III procollagen tests are not approved in the United States, limiting their use in clinical practice. In contrast, elastography-based tests are available and can be used for risk stratification. Several recent studies show that this sequential use of noninvasive tests reduces unnecessary referrals to specialists, increases the detection of advanced fibrosis and cirrhosis, and hence may be cost-effective (36,37).

TABLE 2 Initial evaluation in patients with suspected nonalcoholic fatty liver disease (NAFLD)

History and medical review	Investigations
Obesity	Liver biochemistries (ALT, AST)
T2D	Exclude/identify other liver diseases[a]
Metabolic syndrome	HBV and HCV serology (and viral load)
Alcohol intake	Auto antibodies (ANA, AMA, ASMA)
<14 drinks/wk for women	Serum ferritin, A1AT
<21 drinks/wk for men	Liver ultrasound: increased echogenicity
No known pre-existing liver disease	—

Abbreviations: A1AT, α1 antitrypsin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASMA, anti–smooth muscle antibody; HBV, hepatitis B virus; HCV, hepatitis C virus; T2D, type 2 diabetes.

[a]NAFLD can coexist with other chronic liver diseases. Of note, 21% of patients with NAFLD may have elevations in autoantibodies in the absence of autoimmune hepatitis (85), and 20% may have high serum ferritin (>300 ng/mL in women and >450 ng/mL in men). Elevated serum ferritin is associated with advanced hepatic fibrosis (86) in patients with NAFLD.

Once diagnosis and initial risk stratification have been completed, a more detailed assessment of liver fibrosis is essential. Accurate fibrosis staging provides information regarding prognosis, need for pharmacotherapy, intensive lifestyle modification and/or bariatric surgery, and screening/surveillance for varices and HCC. The most commonly used imaging techniques to evaluate fibrosis are vibration-controlled transient elastography and magnetic resonance elastography. Vibration-controlled transient elastography uses ultrasound waves to investigate the presence or absence of advanced fibrosis with a specificity of 92% (38). Magnetic resonance elastography can identify the intermediate stages of fibrosis more readily, but is not as widely available and is much more costly (30).

Liver biopsy, historically required to diagnosis liver fibrosis and NASH, provides helpful information and should be considered for cases in which there is a diagnostic doubt, such as patients with indeterminate, unreliable, or conflicting noninvasive assessments, or as part of phase 2 or 3 clinical trials. In addition to excluding coexistent liver diseases, liver biopsy allows for assessment of disease activity in the form of lobular and portal inflammation and ballooning degeneration (a marker of liver-cell injury). These 2 processes are thought to be responsible for triggering the development of liver fibrosis.

Assessment of cardiometabolic risk in NAFLD/NASH is also important, especially in patients who are at intermediate to high risk of advanced fibrosis (39). The Atherosclerotic Cardiovascular Disease risk calculator has been validated in NAFLD patients and provides guidance for statin use (40).

Management

Most patients with NAFLD and many with NASH have a low risk of clinically significant fibrosis and can be managed by PCPs. Because NAFLD is not an isolated disease but a component of cardiometabolic abnormalities typically associated with obesity, the cornerstone of therapy is the same as that for people with obesity and cardiometabolic complications, namely lifestyle-based therapies (altered diet, such as reduced-calorie or Mediterranean diet and regular, moderate physical activity), and replacing obesogenic medications to decrease body weight and improve cardiometabolic health. The magnitude of weight loss correlates with decreases in intrahepatic triglyceride (IHTG) content, hepatocyte ballooning, and hepatic inflammation (29).

IHTG is extraordinarily sensitive to changes in energy balance; even 48 hours of a low-calorie diet can decrease IHTG by about 20%, and 7% weight reduction decreases IHTG by approximately 40% (41). The durability of these acute weight-loss–related changes

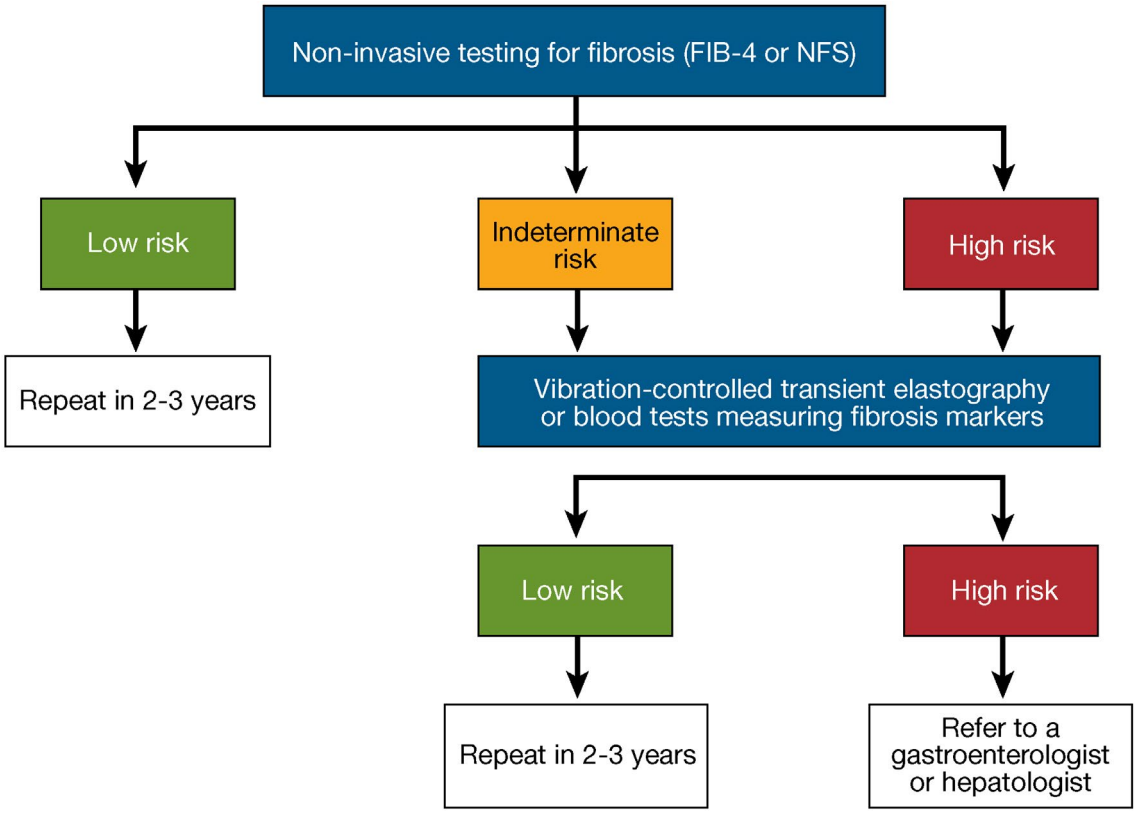

FIGURE 1 Algorithm for risk stratification in patients with NAFLD/NASH. FIB-4, Fibrosis-4 Index; NFS, NAFLD fibrosis score [Color figure can be viewed at wileyonlinelibrary.com]

remains to be determined. Furthermore, hepatic fibrosis is more resistant to weight loss and requires larger amounts (≥10%) and possibly longer duration of weight loss to achieve clinically meaningful outcomes. Regular endurance (42,43) or resistance exercise (44) in the absence of weight loss decreases IHTG content only slightly but improves metabolic health. US Food and Drug Administration–approved weight-loss medications can enhance weight loss induced by lifestyle therapy and may contribute to the successful management of patients with NAFLD. Patients at risk of significant fibrosis (based on their clinical profile, blood test panels, and/or imaging) should be referred to a hepatologist to discuss the need for further testing, including biopsy, appropriate follow-up (particularly for those patients with advanced fibrosis/cirrhosis), and possible inclusion in NASH clinical trials (Figure 1).

Patients with NASH and fibrosis stage 2 or higher are candidates for liver-directed pharmacotherapy (Table 3). Although there are currently no US Food and Drug Administration–approved drugs for treating NASH, vitamin E (800 IU/d) improves steatosis in NASH patients without T2D (45). Although randomized controlled trials have not shown similar efficacy in patients with T2D (46), one retrospective study of patients with NASH and either bridging fibrosis or cirrhosis, with or without T2D, associated vitamin E with greater transplant-free survival and lower rates of hepatic decompensation (47).

If diabetes is present, the PCP may opt to prescribe a medication for diabetes that can also treat NASH. Although metformin is first-line therapy for the pharmacologic management of T2D, it is not effective in treating NASH (2,25). Guidelines suggest that clinicians should instead consider using pioglitazone (a thiazolidinedione acting through activation of proliferator-activated receptor–γ and –α agonism), based on evidence from 5 randomized controlled trials showing that it reverses steatohepatitis in patients with (48–50) and without (45,49) diabetes. In the phase 3 Pioglitazone vs Vitamin E vs Placebo for Treatment of Non-Diabetic Patients with Nonalcoholic Steatohepatitis (PIVENS) trial, pioglitazone led to resolution of steatohepatitis in 47% of patients compared with 21% of patients in the placebo group ($p = 0.001$; vitamin E in 36%; $p = 0.05$), although pioglitazone did not meet the prespecified primary end point (45). Studies of patients with prediabetes or T2D with follow-up for up to 3 years have also consistently reported benefit with pioglitazone treatment (48–50).

Based on these data, the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, European Association for the Study of Diabetes, and European Association for the Study of Obesity guidelines suggest that pioglitazone can be used for NASH patients with diabetes. The guidelines also state that vitamin E (administered at a daily dose of 800 IU) may be considered in nondiabetic adults with biopsy-proven NASH (2,30). Pioglitazone can also reduce cardiovascular disease in patients with or without T2D, as reviewed elsewhere, although the US Food and Drug Administration has not approved it for this indication (51,52).

TABLE 3 Management of patients with nonalcoholic fatty liver disease and nonalcoholic steatohepatitis (NASH)

Variable	Lifestyle intervention[a]	Liver-directed pharmacotherapy	Diabetes care (in individuals with diabetes)	Cardiovascular risk reduction
Nonalcoholic fatty liver	Yes	No	Standard of care	Yes
NASH with fibrosis stage 0 or 1 (F0, F1)	Yes	No	Standard of care	Yes
NASH with fibrosis stage 2 or 3 (F2, F3)	Yes	Yes	Pioglitazone, GLP-1 receptor agonists[b]	Yes
NASH cirrhosis (F4)	Yes	Yes	Individualize[c]	Yes

[a]All patients require regular physical activity and healthy diet and to avoid excess alcohol intake; weight loss recommended.
[b]Among glucagon-like peptide 1 (GLP-1) receptor agonists, semaglutide has the best evidence of benefit in patients with NASH and fibrosis.
[c]Evidence for efficacy of pharmacotherapy in patients with NASH cirrhosis is very limited and should be individualized and used with caution.

Several glucagon-like peptide 1 (GLP-1) receptor agonists and SGLT2 inhibitors, which are increasingly used in T2D, as they reduce cardiovascular risk and promote weight loss, also potentially decrease hepatic steatosis in patients with NAFLD. GLP-1 receptor agonists (dulaglutide, exenatide, liraglutide, and semaglutide) have been tested in patients with T2D and NAFLD, with the most robust evidence to date involving semaglutide (53–57). A small phase 2 trial (involving 52 patients) that evaluated liraglutide, a synthetic long-acting GLP-1 receptor agonist available for treating T2D and obesity, resulted in weight loss, resolution of steatohepatitis, and slower progression of fibrosis than placebo, although gastrointestinal adverse effects were common (56). More recently, a report in 320 patients with biopsy-proven NASH offers the strongest evidence for the use of GLP-1 receptor agonists in patients with NASH using subcutaneously administered semaglutide at doses of 0.1, 0.2, or 0.4 mg/d (54). This 72-week study included a population in which 62% of patients had T2D and >70% had moderate to advanced stage F2–3 liver fibrosis. The primary outcome, NASH resolution without worsening of fibrosis, was achieved in 40%, 36%, and 59% of patients treated with semaglutide at doses of 0.1, 0.2, and 0.4 mg/d, respectively, vs 17% on placebo. Of note, the proportion of patients with liver fibrosis improvement (approximately 30%–44%) did not reach statistical significance in any arm. The reasons remain unclear, although worsening of fibrosis occurred in 10%, 8%, and 5% of the patients in the semaglutide 0.1, 0.2, and 0.4 mg groups, respectively, and in 19% of the patients in the placebo group (54). Of note, the dose used in the study is not currently available for prescription in patients with diabetes, but the weight loss and metabolic effects achieved were similar overall to the effects seen with currently available dose for management of diabetes. Physicians unfamiliar with or unable to prescribe these medications should consider referring patients to an endocrinologist, diabetologist, or obesity medicine specialist (53).

Another small recent study found that dulaglutide also reduced liver fat content and transaminases in people with T2D and NAFLD (55). These findings allow the possibility of treating diabetes, cardiovascular disease, and NASH simultaneously with diabetes medications, such as pioglitazone or a GLP-1 receptor agonist. SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin) have also been tested in NAFLD, but these studies have been small and do not examine the effect of these agents on liver histology (58).

Despite the promise of antidiabetes medications, the role of improving glycemic control on the natural history of NASH and development of cirrhosis remains poorly understood, and the role of glycemic control of disease progression in NASH remains to be established. Improving glycemic control with insulin therapy reduces liver steatosis (48), but its impact on liver histology (both NASH or fibrosis) and the natural history of the disease remain unknown. Cross-sectional (59) and longitudinal observational studies (60) do not show a clear correlation between hemoglobin A1c levels over time and liver histology or other clinical outcomes. Lowering hemoglobin A1c levels with pioglitazone treatment for 18 months has been associated with improvement in NASH and slower progression of fibrosis compared to patients with diabetes on placebo but, overall, the histologic response to pioglitazone does not appear to be linked to improved glycemic control, as it is similar in patients with vs those without diabetes (49).

Bariatric surgery is currently the most effective therapy available for obesity. The 2 most common procedures are sleeve gastrectomy and Roux-en-Y gastric bypass. Marked weight loss (approximately 25%–35%) induced by bariatric surgery has profound effects on steatosis, NAFLD activity score, hepatocyte ballooning, and lobular inflammation, and results in NASH resolution in most patients (61,62). Surgery-induced weight loss also has a considerable therapeutic effect in reducing stages 1 and 2 fibrosis, but is less effective in improving stages 3 and 4. Bariatric endoscopy is emerging as a new treatment for obesity, but the long-term durability of its effects remains to be determined. About 15% weight loss has been reported after therapy with a postprandial gastric aspiration device, which is associated with reduced plasma AST and ALT (63), whereas duodenal mucosal resurfacing has reduced Fibrosis-4 Index scores by mechanisms possibly unrelated to weight reduction (64). Intragastric balloon placement has also been associated with histologic improvement in individuals with NASH (65), although findings remain preliminary. Patients with advanced liver disease, especially with hepatic decompensation, have higher mortality after bariatric surgery. Overall, more efficacy and safety data are needed before these approaches can be recommended as treatment options for patients with NAFLD and NASH.

Special attention to the management of sedentary behavior, as well as to dyslipidemia, diabetes, and hypertension, is recommended for all individuals with NAFLD (66). Alcohol consumption should be

limited to 2 to 3 drinks per week in women and 4 to 5 drinks per week in men and avoided in patients with advanced fibrosis (67,68), although high-quality data on the exact risk of progressive liver disease in patients with advanced fibrosis are still needed. Many PCPs and nonhepatologists discontinue statins when liver enzymes are elevated (9,69,70). However, numerous studies have also demonstrated that statins are safe and efficacious in patients with NAFLD and NASH, and they can be used to treat dyslipidemia in these patients, including those with compensated cirrhosis. Statins have pleiotropic properties that may be directly beneficial in liver disease. In a meta-analysis of 13 studies, including 3 randomized controlled trials, statin use in cirrhosis was associated with a reduction in hepatic decompensation (hazard ratio, RR, 0.54; 95% CI, 0.46–0.62) and lower mortality (hazard ratio, 0.54; 95% CI. 0.47–0.61) (71).

However, because data remain limited regarding safety and risks of statins in patients with decompensated cirrhosis (72,73), statins should be avoided until we have stronger evidence to support their safety in these patients. The AGA clinical practice update provides some guidance and advises against statin use among patients with Child-Pugh class B or C cirrhosis (74). The underlying rationale is that the generally grave liver-related prognosis of patients with Child-Pugh class B or C cirrhosis makes it unlikely that they will benefit from the cardiovascular benefits associated with lipid-lowering therapy. In a large retrospective cohort study of statins in patients with cirrhosis, the survival benefit did not extend to patients with Child class C cirrhosis (75).

Emerging tools

Given the high prevalence of NAFLD and the limited patient awareness about this disease, applying artificial intelligence/machine learning tools to the big data repositories of electronic health records holds considerable potential for efficient disease identification and risk stratification (76). "Machine learning" is a subset of artificial intelligence in which computer algorithms are improved through experience (77). These tools can produce noninvasive calculated scores by using information about patient demographic and clinical characteristics from both narrative (ie, free text) and codified (eg, administrative disease codes and laboratory tests) sources. Artificial intelligence is also being tested to improve the accuracy and reliability of liver histologic interpretation using quantitative scoring systems for NAFLD/NASH radiologic and histopathologic features (78,79). However, although the availability of noninvasive tests to accurately assess response to treatment beyond histopathology would greatly facilitate the efficient enrollment in NASH treatment clinical trials, existing options still require further validation and eventual acceptance by regulatory agencies.

Several liver-targeted and other potential therapies are also currently under investigation, targeting a broad range of pathologic changes associated with NASH, including insulin resistance, alterations in the microbiome and gut permeability, oxidative stress, apoptosis, lipotoxicity, inflammation, and bile acid metabolism. Given the multiple pathways involved in NASH pathogenesis, combination regimens may ultimately be needed to treat NASH most effectively (80,81).

RECOMMENDATIONS

Develop more sensitive and specific diagnostic methods

The invasive nature and relatively high expense of liver biopsy limit its use and call for more sensitive and specific noninvasive diagnostic methods for NASH. Several novel noninvasive tools with the potential to provide more sensitive and specific diagnosis are currently under development. These include top–down approaches, such as multiomics and narrowing down to the minimum number of molecules that could provide the maximum positive and negative predictive value (82,83).

Adopt a multidisciplinary approach to NASH

Optimal care of patients with NASH may require clinicians from a variety of specialties, including primary care, hepatology, obesity management, and endocrinology, to tackle both the hepatic manifestations of the disease and the comorbid metabolic syndrome and cardiovascular risk, as well as screening and treating other comorbid conditions (eg, obstructive sleep apnea). When NAFLD progresses to NASH, multidisciplinary, team-based care involving these specialties is crucial. Improving the traditional model of primary, secondary, and tertiary care will require not only developing and validating algorithmic approaches (eg, who can be managed where and how), but also connectivity and multidirectional referrals among these practice settings. Examining other models of care, such as medical homes either dedicated to NAFLD/NASH or incorporated within similar homes that manage metabolic disease more broadly, could also be valuable in developing care models. These integrated models can create and align expertise and incentives among different specialties.

Develop clinical care pathways

Developing clinical care pathways that use validated and efficient noninvasive tests and calculators is crucial to a multidisciplinary approach to managing NAFLD/NASH. Clinical care pathways, with careful explication of each step-in screening, diagnosis, and treatment, have been shown to improve the quality of health care delivery in other areas of medicine. Members of the NASH: A Call-to-Action Steering Committee and several other conference participants are currently developing such a pathway for NAFLD/NASH. Rapid and timely dissemination of these pathways to all stakeholders, especially the frontline PCPs, will be important in developing a systematic approach to managing NAFLD/NASH.

Pursue a unified, international public health response

The public health response to NAFLD remains rudimentary. There is no single guiding strategy in the United States or Europe. A survey of 29 European countries highlighted the absence of a concrete NAFLD/NASH management strategy or action plans in every one of these countries (84). This deficit has even more proximal roots. For example, not all hepatology/gastroenterology societies have clear screening, testing, or referral guidelines for NAFLD/NASH, and existing guidelines often conflict with one another (Table 4). Intersociety collaboration for harmonizing guidelines to optimize screening, diagnosis, and therapy is urgently required. Furthermore, because virtually all current guidance regarding HCC surveillance in NAFLD is derived from the viral hepatitis and alcoholic cirrhosis literature, new data and updated guidelines are needed that are specific to NAFLD/NASH-related cirrhosis. In addition, large cohorts with longitudinal data on clinical course and outcomes, particularly cohorts that allow the transition from childhood through adolescence to adulthood to be evaluated, are needed to inform the science and clinical practice of managing NAFLD/NASH.

There is also a large unmet need for programs that can increase disease awareness in the medical community and the general population. Finally, the closely interlinked nature with related metabolic diseases suggests that reducing the clinical and economic burden of NASH and NAFLD will require fundamental societal changes driven by policies to address failing public health systems and the social determinants of health.

SUMMARY AND CONCLUSIONS

The upward trend in NAFLD/NASH incidence and prevalence underscores the importance and urgency of developing and implementing effective screening, diagnosis, and treatment strategies in the United States and globally, particularly among emerging at-risk cohorts, such as patients with diabetes and obesity. This goal cannot be achieved if the different specialties engaged in managing this burgeoning population continue to work in separate silos. The Call-to-Action Meeting described in this report represents one of the first steps needed to align key stakeholders, including PCPs, endocrinologists, diabetologists, obesity medicine specialists, gastroenterologists, and hepatologists, on a collective action plan. Improving the spectrum of care for patients with NAFLD from screening, diagnosis, disease severity stratification, and treatment will require significant changes and innovations in technology, health care delivery, and policy. In addition, optimal care of patients with NAFLD/NASH will require a multidisciplinary team integrating primary care, hepatology, obesity medicine, and endocrinology/diabetology via well-defined care pathways, along with exploration of the high-yield targets for clinical research and practice identified by conference participants. These efforts should help the field move toward a collective strategy with shared goals and objectives that will improve care for the growing population of patients with NAFLD/NASH.O

TABLE 4 Summary of published nonalcoholic fatty liver disease (NAFLD) guidelines

Organization	Year	First-line diagnosis test	When to refer to hepatologist	Noninvasive tests
American Association for the Study of Liver Diseases (AASLD)	2018	Not clear in the guideline Routine screening for NAFLD in high-risk groups is not recommended	Not clear in the guideline	Diagnosis for NASH: liver biopsy Assessment for fibrosis: NFS or FIB-4
American Gastroenterological Association (AGA)	2012	Routine screening for NAFLD is not recommended	Not clear in the guideline	Metabolic syndrome can be used to target patients for liver biopsy
European Association for the Study of the Liver (EASL)	2016	Ultrasound + liver enzymes for patients with risk factors	Refer patients with abnormal liver enzymes or medium-/high-risk fibrosis markers to specialist	Diagnosis for NASH: liver biopsy Assessment for fibrosis: NFS or FIB-4
World Gastroenterology Organization (WGO)	2012	Ultrasound + liver enzymes for patients with risk factors	Not clear in the guideline	Diagnosis for NASH: liver biopsy
National Institute for Health Care and Excellence (NICE)	2016	Ultrasound + liver enzymes for patients with risk factors But routine liver function blood tests are not sensitive, and ultrasound is not cost-effective	Refer adults with advanced liver fibrosis to a hepatologist Refer children with suspected NAFLD to a pediatric specialist in hepatology	Assessment for advanced fibrosis: enhanced liver fibrosis (every 2–3 years)

Abbreviations: FIB-4, Fibrosis-4 Index; NFS, NAFLD fibrosis score.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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