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Non-alcoholic fatty liver disease: controlling an emerging epidemic, challenges, and future directions

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Abstract

Non-alcoholic fatty liver disease (NAFLD) affects over 30% of the United States population and is projected to become a leading cause of chronic liver disease by 2020. As a result, the economic and societal burden of NAFLD is far-reaching. The cost of managing NAFLD complications has an estimated 10 year economic burden of $908 billion. This review provides an overview of current knowledge on NAFLD, with emphasis on identifying gaps in its diagnosis and management, and proposes future directions to address these limitations. Despite the increasing prevalence of NAFLD, there is limited knowledge and practice regarding its natural history, staging, diagnosis, and management. Though a challenging task, opportunities for bridging these gaps should focus on the development of noninvasive biomarkers, the elucidation of biological pathways, the creation of up-to-date screening guidelines, and the organization of clinical trials of longer duration to determine clinical endpoints and assess the safety of new treatment options.

Keywords Non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, liver transplantation, cirrhosis

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Introduction

Non-alcoholic liver disease is histologically similar to alcoholic liver disease but without a history of alcohol consumption. Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of disease from non-alcoholic fatty liver (NAFL), characterized by hepatic fat accumulation without inflammation, to non-alcoholic steatohepatitis (NASH), characterized by hepatic fat deposition with inflammation, accumulating fibrosis, and ultimately liver cirrhosis [1]. NASH-related cirrhosis is currently a leading cause of chronic liver disease and is associated with hepatocellular cancer. It has emerged as the second leading indication for liver transplant evaluation in the United States [2,3].

NAFLD is a leading cause of liver-related morbidity and mortality; the literature shows that it is also associated with increased overall mortality from cardiovascular causes, increased incidence of type 2 diabetes, and increased risk of chronic kidney diseases [4,5]. Agarwal *et al* reported a cross-sectional study that identified NAFLD as an independent predictor of coronary artery disease, hypertension, and elevated low-density lipoprotein cholesterol [6]. Risk factors related to NAFLD include increasing age, obesity, insulin resistance, and small nucleotide polymorphisms in two genes, *PNPLA3* (encoding patatin-like phospholipase domain-containing protein 3) and *TM6SF2* (encoding transmembrane 6 superfamily member 2) [7].

Despite the alarming rate of non-alcoholic liver disease, there are limitations in knowledge and unmet needs in the management of NAFLD among medical providers. In a survey conducted among primary care physicians, 58% expressed a lack of confidence in their knowledge and management of fatty liver disease [8]. The challenge in diagnosing NAFLD may stem from the fact that most patients are asymptomatic and are typically only identified by routine blood tests showing elevated liver enzymes. Nevertheless, a subset of patients can have normal liver enzymes and thus remain undiagnosed.

Numerous studies have looked at the management of fatty liver disease; however, there is no consensus on the optimal management of NAFLD. Currently, there are no drug therapies approved by the Food and Drug Association (FDA) for the treatment of NAFLD. This article aims to review current knowledge on NAFLD, with emphasis on identifying gaps in its diagnosis and management, and proposes future directions to address these limitations.

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Methodology

Using PubMed, MEDLINE, CINAHL, EMBASE, Scopus, and Cochrane Databases, we searched for articles using the keywords "Non-alcoholic fatty liver disease", "Non-alcoholic steatohepatitis," "Fatty liver," "Liver fibrosis," "Cirrhosis," and "Chronic liver disease" between 2005 and 2017. Articles published in languages other than English were excluded. Original articles, case-control trials, clinical reviews, meta-analyses, randomized trials and clinical guidelines were reviewed.

Epidemiology of NAFLD

NAFLD is currently the most common liver disorder, particularly in Western countries. Worldwide, the prevalence of NAFLD is about 25%, with the highest rates reported in South America (31%) and the Middle East (32%), followed by Asia (27%), the USA (24%) and Europe (23%); NAFLD is less common in Africa (14%) [9]. Reports from the National Health and Nutrition Examination Survey have shown that the prevalence of fatty liver disease in patients with chronic liver disease increased from 47% to 75% between 1999 and 2008 [10]. Overall, the prevalence of NAFLD is increasing, particularly in the United States, and it has been projected to become a leading cause of chronic liver disease by 2020 [2].

The prevalence of NAFLD tends to parallel that of high risk groups with metabolic syndrome, though NAFLD can occur in patients with a normal basic metabolic index. A high prevalence of comorbid conditions in patients with NAFLD, and *vice versa*, have long established a directional causal relationship that warrants future investigation [11]. Among patients with type two diabetes the prevalence of NAFLD ranges from 33% to 66%, while the prevalence of diabetes among patients with NAFLD has been reported to be 43% [9,12-15]. Among patients with obesity, the prevalence of NAFLD can exceed 95% [16,17]. Additionally, other comorbid conditions have been reported among patients with NAFLD, including hyperlipidemia (69%), hypertriglyceridemia (41%), metabolic syndrome (43%), and hypertension (39%) [9].

The majority of patients diagnosed with NAFLD are in their 40s or 50s; however, there are conflicting data with regard to sex distribution [2]. A population-based study found the prevalence of NAFLD/NASH to be higher in Hispanics (58.3%) compared to whites (44%) and blacks (35.1%) [18] (Fig. 1). The difference in racial and ethnic prevalence may be dependent on an interplay of socioeconomic, behavioral and genetic factors. However, while the prevalence of NAFLD may vary with sex and ethnicity, increasing age has been associated with the occurrence and stage of liver disease [19].

Clinical and economic burden of fatty liver disease

Using prediction models, Younossi *et al* reported that the annual clinical burden of NAFLD is expected to increase, with over 12 million cases of NAFL and over 600,000 cases of NASH predicted [20]. Similar trends in annual economic burden are predicted to affect Europe and the US with over $103 billion per year in direct cost. A further increase in the cost of managing disease-related complications is estimated to bring the 10-year economic burden of NAFLD as high as $908 billion.

The annual cost is further compounded by societal cost due to the loss of quality-adjusted life years as a result of NAFLD and resulting complications [20]. Incorporating societal loss leads to an estimated value of $292.2 billion. The economic burden is predicted to rise as the clinical consequences of NAFLD increase. It is worth noting that the cost of treatment was not accounted for in these models.

Medicare data in patients with NAFLD have shown that the mean yearly inflation-adjusted value in outpatient care increased from $2624 ± $3308 in 2005 to $3608 ± $5132 in 2010, with a median total hospital charge of $36,289 in 2010 [20,21]. The current trajectory results in Medicare patients with NAFLD utilizing an enormous amount of inpatient and outpatient care resources [22].

Clinical course

Outcomes of patients with NAFLD have been studied before; however, previous studies were limited by the number of patients and short follow-up times. Overall, NAFL without steatosis progresses slowly, unlike NASH, which has a greater potential to progress to cirrhosis and its related complications. Approximately 30% of patients with NAFLD develop NASH [23]. About 20-40% of patients with NASH are likely to develop progressive liver fibrosis [3]. In less than 5% of NASH patients, fibrosis progresses to cirrhosis [24]. However, there are limited prospective data evaluating the progression of NAFLD to hepatocellular carcinoma (HCC). Ekstedt *et al*, in a follow up of patients with biopsy-proven NAFLD over a period of 26.4 years, observed a mortality rate of 5% due to HCC [25]. White *et al*, in a systematic review of patients with NAFLD and NASH, showed that the cumulative incidence of HCC ranged from 2.4% over 7 years to 12.8% over a period of 3 years [26]. A Veterans Affairs study by Mittal *et al* showed that HCC accounted for 8% of NAFLD cases [27].

The Prognostic Relevance of Liver Histology in NAFLD (PRELHIN) study has shed light on independent risk factors associated with death or liver transplantation among patients with NAFLD. Age, diabetes, and stage of fibrosis were independently associated with death or liver transplantation [28]. However, advanced fibrosis was the only known histological variable to be predictive of liver-related complications. A review of the literature indicates that fibrosis is the strongest predictor of mortality [23]. However, the natural history of NASH is heterogeneous and it remains difficult to predict which subset of patients are likely to progress. Large clinical trials with longer follow-up times accounting for comorbidities are needed to elucidate the details surrounding the natural history of the disease.

Barriers in controlling NAFLD

Who should be screened?

Notwithstanding the gravity of the problem, along with the projected healthcare burden, multiple limitations and unmet needs in the management of NAFLD remain to be addressed. There are no clear screening guidelines for NAFLD. A survey conducted in Australia showed that non-hepatologists underestimated the prevalence of NAFLD, both in the general population and in high-risk patients [29]. The study also reported that only a few patients were referred to hepatologists. A similar trend was demonstrated in a French study showing that only 20% of NAFLD patients seen by a gastroenterologist were referred by other specialists [30]. Both studies showed that, when considering screening patients for NAFLD, there was an over-reliance on elevated liver enzymes, particularly elevated transaminases, instead of metabolic risk factors. Guidelines from the American Association for the Study of Liver Diseases (AASLD) do not recommend screening for NAFLD in family members or high-risk groups attending primary care, diabetic, or obesity clinics because of the lack of long-term benefits and cost-effectiveness [19].

Some hepatology societies recommend screening for NAFLD with liver function tests and ultrasound of the abdomen. The challenges with these diagnostic tests include the lack of standardization of ultrasound instruments in defining steatosis and the presence of normal transaminases in some patients with NAFLD, which does not correlate with histological disease [31]. Despite these challenges, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) recently released guidelines recommending screening children aged 9-11 years with obesity and other children with risk factors using an alanine aminotransferase test [32]. The caveat, however, is that NAFLD can occur in non-obese patients without metabolic syndrome or type 2 diabetes mellitus.

Furthermore, according to the National Guideline Centre (UK), the use of routine liver function tests to diagnose NAFLD is ill-advised in children and young adults, and the Centre recommends using liver ultrasound in high-risk patients or patients suspected of having NAFLD [33]. Similar clinical guidelines have been issued by other European bodies [34]. Given these recent guidelines in the pediatric population, updated guidelines for adults are long overdue. Having a more standardized validated model that incorporates risk factors such as age, family history of NAFLD, metabolic syndrome, ethnicity, and sleep apnea will streamline the process of screening, especially among primary care providers. This approach will aid the earlier detection of NAFLD. Further research is need to define this model and determine screening intervals in high-risk patients.

Diagnostic challenges

Most patients with NAFLD are asymptomatic and are diagnosed following incidental laboratory findings. The diagnosis of NAFLD requires a combination of clinical history, serologic testing, and radiologic findings (ultrasonography, computer tomography scan, or magnetic resonance imaging) [35-37] (Table 1). Ultrasonography, though widely available, has limited diagnostic capacity. Computed tomography scanning, though more sensitive, entails a risk of exposure to radiation. In contrast, more

Table 1 Sensitivities and specificities of imaging modalities used to detect hepatic steatosis

Modality	Severity	Sensitivity (%)	Specificity (%)
US	Mild	55-67	77-93
US	Moderate-to-severe	81-100	98
CT	Mild	73	91
CT	Moderate-to-severe	82	100
MRS	Overall	80-91	80-87
MRI	Overall	77-90	87-91

US, ultrasound; CT, computer tomography; MRS, magnetic resonance spectroscopy; MRI, magnetic resonance imaging

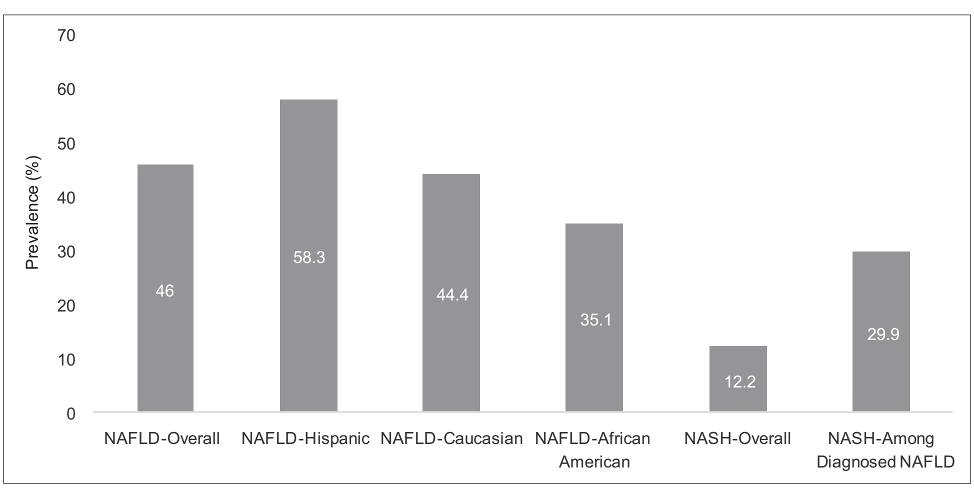

Figure 1. Prevalence of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatiits (NASH). Data updated from: Williams CD *et al* [19]. Used with the permission of Elsevier Inc.

sensitive imaging modalities, such as magnetic resonance spectroscopy and magnetic resonance imaging, are expensive. Diagnosis is usually by exclusion, after secondary causes of fat accumulation have been ruled out [33,34]. Further research is required to develop cost-effective and less invasive modalities for diagnosing NAFLD.

Disease staging

After a diagnosis of NAFLD is made, it is imperative to determine the fibrotic stage of the disease. The extent of fibrosis has been shown to correlate with clinical outcomes. A prospective study involving patients with liver biopsies demonstrated that the presence and extent of fibrosis were the primary histological features of NAFLD that predicted decompensation and advanced disease [38]. There is growing interest in determining how to stage the extent of liver fibrosis noninvasively. The NAFLD fibrosis score (NFS), based on clinical data including age, body mass index, platelet count, and aspartate transaminase and alanine transaminase levels, has been validated as an effective biomarker in determining the extent of fibrosis [39]. Other noninvasive tools used to detect the presence of advanced fibrosis in NAFLD patients include the fibrosis-4 (FIB-4) score, aspartate-aminotransferase-to-platelet ratio, enhanced liver fibrosis panel, Fibrometer, FibroTest, and Hepascore [40]. A summary of clinical aids or biomarkers used to assess fibrosis can be seen in Table 2. Overall, the AASLD recommends the use of the NFS or the FIB-4 index for identifying NAFLD patients with a higher likelihood of having bridging fibrosis or cirrhosis [19].

Imaging techniques that measure liver stiffness, such as transient elastography (TE) and magnetic resonance elastography (MRE), have emerged as being more accurate in predicting liver fibrosis. TE can have conflicting results in obese patients, primarily because subcutaneous fatty tissue attenuates elastic share wave, reducing diagnostic reliability [41]. Additionally, though TE represents a convenient and noninvasive test, approximately 25% of results are unreliable or uninterpretable [42]. MRE is superior to TE and is excellent for identifying varying degrees of fibrosis in patients with NAFLD [43]. MRE has a specificity of 0.91 (95% confidence interval [CI] 0.83-0.96) and a sensitivity of 0.86 (95%CI 0.65-0.97) in identifying patients with advanced fibrosis [44]. The AASLD recommends the use of TE and MRE for identifying advanced fibrosis in patients with NAFLD [19].

Liver biopsy remains the gold standard for confirming the diagnosis of NASH and evaluating inflammation or fibrosis. However, liver biopsy is limited by its invasiveness, cost and sampling error. The lack of an accurate, noninvasive method for distinguishing NAFL from NASH with fibrosis remains one of the unmet needs in the management of patients with NAFLD. Other diagnostic methods show promising results in the use of hepatic collagen fractional synthesis rate (FSR), and plasma FSR, which correlates with hepatic fibrosis in humans [44]. However, larger studies are required to validate these findings.

Management

Challenges in non-pharmacological management

The increasing incidence of NAFLD requires an amplified effort to detect the disease early in its course and reduce its progression. Diet and exercise are the mainstay of management in patients with NAFLD. In a prospective study of patients with biopsy-confirmed NASH, a 10% loss in body weight led to a histological benefit in improved fibrosis of the liver [45]. The benefit of weight loss has also been demonstrated in a trial that randomized dietician-reinforced lifestyle intervention versus general recommendations for weight loss. The study observed a 64% resolution in liver fibrosis in the intervention group compared with 20% in the control group [46]. A recent meta-analysis showed that exercise, alone or combined with dietary

Table 2 Biomarkers used to detect the presence of progressive liver fibrosis

Test	Panel components	Sensitivity (%)	Specificity (%)	Fibrosis stage
AST/ALT ratio	AST, ALT	21	90	F3-F4
AST/platelet ratio	AST, Platelet	30	93	F2-F4
BAAT score	BMI, Age, ALT, Serum Triglycerides	71	80	F3-F4
BARD score	BMI, AST/ALT, Diabetes	87	33	F3-F4
ELF test	Age, HA, TIMP-1, PIIINP	80	90	F2-F4
Fibrometer	Platelet, G2 Macroglobulin, AST, Age, PT, HA, BUN	81	84	F2-F4
Fibrotest	α-2 Macroglobulin, Haptoglobin, GGT, Total Bilirubin, Apolipoprotein	15-77	77-90	F2-F4
FIB-4 Score	Age, AST, Platelet Count, ALT	26-74	71-98	F3-F4
Hepascore	Age, Sex, Bilirubin, GGT, HA, α2-Macroglobulin	76-87	84-89	F3-F4
NAFLD fibrosis score	Age, Hyperglycemia, BMI, Platelet, Albumin, AST/ALT	51	96	F3-F4

AST, aspartate aminotransferase; ALT, alanine aminotransferase; BMI, body mass index; HA, hyaluronic acid; GGT, γ-glutamyltransferase; PIIINP, procollagen III amino-terminal peptide; TIMP1, tissue inhibitor of matrix metalloproteinase 1; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4; PT, prothrombin intervention, improves serum levels of liver enzymes and liver fat or histology in NAFLD patients [47]. Furthermore, resolution of liver fibrosis has therapeutic implications, since fibrosis has been shown to be a main predictor of disease progression and liver cirrhosis.

The ideal diet for patients is yet to be determined; however, certain lifestyle dietary habits have potential associations with NAFLD. A Mediterranean diet rich in polyunsaturated fatty acids and fiber during a 6-week crossover study resulted in a significant reduction in hepatic steatosis. It remains to be seen whether the short-term improvement in steatosis has long-term benefits in reducing disease progression [48]. A recent study reported that optimal sleep (defined as sleep hours ≥7 and ≤9/day) in addition to a diet comprising high consumption of low-fat dairy products, vegetables, and fish, was beneficially associated with insulin resistance and liver stiffness in NAFLD patients, independently of body weight status and energy intake [49]. Other studies have underscored the value of optimal sleep and its associSation with NAFLD [50].

A study comparing the effects of mild-, moderate- and high-intensity exercise regimens in patients with hepatic fat found that the highest exercise intensity program (>250 min per week) led to a significant reduction in hepatic fat [51]. While exercise alone improves hepatic steatosis in patients with NAFLD, it does not improve liver fibrosis. Current guidelines recommend a combination of dietary changes with exercise in the management of NAFLD [19].

Diet and weight loss are challenging, especially as regards keeping patients motivated. Usually, patients are told by healthcare providers to make lifestyle changes without being given much support. Most of these challenges arise from lack of behavioral knowledge and motivational techniques among healthcare providers. It is imperative that issues dealing with weight loss and dietary lifestyle changes are patient-centered and maintained to achieve the desired effects.

Table 3 Pharmacologic treatment options in nonalcoholic steatohepatitis

Drug	Mechanism of action
Orlistat	Oral inhibitor of gastric and pancreatic lipases
Metformin	Oral antihyperglycemic
Thiazolidinediones	Nuclear peroxisome proliferator-activated receptor-γ agonist
Liraglutide	Glucagon-like peptide-1 analog
Sitagliptin	Dipeptidyl peptidase 4 inhibitor
Statin	β-Hydroxy β-methylglutaryl-CoA reductase inhibitor
Ezetimibe	Cholesterol-absorption inhibitor
Ursodeoxycholic acid	Bile acid
Vitamin E	Antioxidant
Obeticholic acid*	Farnesoid X receptor agonist
Elafibranor*	Peroxisome proliferator-activated receptor α/δ agonist

**Ongoing clinical trials*

Limitations of pharmacologic treatment

Currently, there are no FDA-approved drugs for treating NASH. However, for some patients, a number of therapeutic options with varying efficacy are available, as listed in Table 3. Pioglitazone compared to placebo in nondiabetic patients showed a favorable improvement in NASH (34% vs. 19%, P=0.04; number needed to treat = 6.9) [52]. The same study, the PIVENS (pioglitazone or vitamin E vs. placebo in nondiabetic patients with NASH) trial, showed that the daily use of 800 IU of vitamin E significantly reduced steatosis and inflammation (43% vs. 19%, P=0.001; number needed to treat = 4.2) [52]. However, some safety concerns have been raised with regard to the use of vitamin E and pioglitazone; these include postmenopausal bone loss, risk of bladder cancer, hemorrhagic stroke and prostate cancer [53,54]. Other medications such as pentoxifylline have shown favorable results, though larger clinical studies are required to evaluate its therapeutic role [55].

Research in the past decade has led to the development of novel therapies. Obeticholic acid, a farnesoid X receptor agonist, was investigated for treating non-cirrhotic NASH patients in the farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, NASH (FLINT) trial. Comparing 25 mg of obeticholic acid per day with placebo, interim analysis showed that the efficacy criterion had been met, leading to discontinuation of the trial. Histological data showed significant improvement in steatohepatitis in 45% of patients versus 21% of patients who received placebo [56]. Obeticholic acid was also associated with weight loss. Its potential clinical efficacy and long-term safety are pending the results of a phase III clinical trial (NCT02548351).

Elafibranor, an agonist of the peroxisome proliferator-activated receptor-α/δ, was recently studied in patients with NASH. The primary outcome of reversal of NASH without worsening of fibrosis was not achieved (19% vs. 12%; P=0.045) [57]. However, using a *post-hoc* modified definition of NASH resolution, elafibranor (120 mg/d for 1 year) versus placebo showed resolution of NASH without worsening fibrosis (20% versus 11%, P=0.018). The use of elafibranor also resulted in improvement in serum lipid levels and liver enzymes. As with obeticholic acid, its potential clinical efficacy and long-term safety are pending the results of a phase III clinical trial (NCT01694849).

Given the increasing prevalence of NAFLD and its consequent public health implications, it is surprising that there are no FDA-recommended therapies. Currently, pioglitazone and vitamin E are the only recommended therapies according to guidelines in selected patients [58]. However, a joint workshop in 2013 sponsored by the FDA and the AASLD sought to shed light on the gaps hindering progress in this area [59]. The workshop identified a lack of endpoints based on clinical outcomes. Traditionally, all-cause mortality has been the endpoint in therapeutic clinical trials. To demonstrate a survival benefit, i.e., improvement in mortality rates, would require a large cohort of patients with early-stage NASH. Additionally, it would require a follow-up period of 10-15 years [59]. NAFLD-related cirrhosis is a slow, progressive disease that takes years to develop. Therefore, such a clinical trial would be costly and logistically challenging.

Surgical therapy and its limitations

Bariatric surgery in carefully selected patients can be effective in improving NAFLD, as well as other obesity-related comorbidities. A large prospective study with a 5-year follow up showed improvement or reversal of NASH, fibrosis, and NAFLD [60]. Despite these results, bariatric surgery is currently only indicated for the management of obesity and has not been approved as a primary treatment for NAFLD. The cost of the procedure, in addition to its invasiveness, limits its evaluation as a primary treatment modality for NASH. Newly emerging anti-obesity endoscopic procedures, such as intragastric balloon therapy, could play a role in the management of NASH [61]. However, none of these procedures have been clinically evaluated in patients with NAFLD.

Concluding remarks and future directions

There are many challenges facing patients affected by NAFLD. There are also many challenges faced by clinicians and researchers involved in the management of NAFLD. However, there are opportunities to overcome these challenges. There is increasing evidence that the pathogenesis of NAFLD is guided by an interaction of nutritional habits, genetics, and environmental factors. One area of future research is to explore specific pathways through which these factors interact, especially in the era of epigenetics. A deeper understanding of this complex interaction can lead to the development of guidelines for screening, early diagnosis, and the development of therapeutic strategies. Epigenetic studies will enable us to predict which subset of patients affected by NAFLD are likely to progress into more advanced stages of disease.

Furthermore, the use of noninvasive biomarkers to obviate the need for liver biopsy requires further investigation. Noninvasive staging methods will encourage more patients to enroll in clinical trials, which will further broaden our understanding of the disease. To this end, there is also a need for clinical trials of longer duration to determine clinical endpoints, as well as the long-term safety and durability of new treatment options.

Our review has also shown that there is a need to increase training among healthcare providers with respect to lifestyle behavioral changes and motivational interventions. A patient-centered approach is expected to yield better outcomes in terms of weight loss and its effect on liver fat accumulation. This should also be reflected in authoritative guidelines. The 2012 guidelines of the AASLD need to be updated to reflect current knowledge and trends in order to guide healthcare providers and patients.

NAFLD is emerging as the leading cause of chronic liver disease in the United States and presents an impending social and economic burden. If it is not addressed, a significant portion of healthcare expenditure and resources will be required to cater for NAFLD-related diseases, further increasing healthcare expenditure. There is a gap in our knowledge and therapeutic armamentarium that needs to be bridged before we can stem the tide.

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