Non-alcoholic fatty liver disease

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Non-alcoholic fatty liver disease (NAFLD) has a global prevalence of 25% and is a leading cause of cirrhosis and hepatocellular carcinoma. NAFLD encompasses a disease continuum from steatosis with or without mild inflammation (non-alcoholic fatty liver), to non-alcoholic steatohepatitis (NASH), which is characterised by necroinflammation and faster fibrosis progression than non-alcoholic fatty liver. NAFLD has a bidirectional association with components of the metabolic syndrome, and type 2 diabetes increases the risk of cirrhosis and related complications. Although the leading causes of death in people with NAFLD are cardiovascular disease and extrahepatic malignancy, advanced liver fibrosis is a key prognostic marker for liver-related outcomes and overall mortality, and can be assessed with combinations of non-invasive tests. Patients with cirrhosis should be screened for hepatocellular carcinoma and oesophageal varices. There is currently no approved therapy for NAFLD, although several drugs are in advanced stages of development. Because of the complex pathophysiology and substantial heterogeneity of disease phenotypes, combination treatment is likely to be required for many patients with NAFLD. Healthy lifestyle and weight reduction remain crucial to the prevention and treatment of NAFLD.

Introduction

Over the past four decades, non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disorder (with a global prevalence of around 25% of the adult population)[1] and is recognised to have a close, bidirectional association with components of metabolic syndrome.[2] Although less than 10% of people with NAFLD develop liver-related complications, a key challenge is to identify those who are at the highest risk among the many people affected by NAFLD. Due to its high prevalence, NAFLD is now the most rapidly increasing cause of liver-related mortality worldwide[3] and is emerging as an important cause of end-stage liver disease,[4] primary liver cancer,[5] and liver transplantation with a substantial health economic burden. Despite the growing concern, NAFLD is underappreciated as an important chronic disease[6] and there are few national strategies or policies for NAFLD.[7]

This Seminar describes the epidemiology, natural history, and risk factors for progression of NAFLD. We highlight progress in non-invasive tests to assess liver disease severity and the importance of a collaborative approach to diagnosis, risk stratification, and management to improve health outcomes for people with NAFLD.

Search strategy and selection criteria

We searched PubMed and MEDLINE to identify studies and reviews published between Jan 1, 1980, and Dec 31, 2020, relevant to the scope of this Seminar with the terms "non-alcoholic fatty liver disease", "non-alcoholic steatohepatitis", "NAFLD", "NASH", "fatty liver", "epidemiology", "prevalence", "incidence", "disease burden", "non-invasive tests", "liver fibrosis", "blood tests", "liver stiffness measurement", "natural history", "pathogenesis", "treatment", "pharmacotherapy", and "risk stratification". Articles were considered regardless of language. We selected references that provided current, evidence-based insight into non-alcoholic fatty liver disease. Most of the articles selected were published within the past 5 years, although we also included highly referenced, older publications that contributed to new knowledge or understanding of non-alcoholic fatty liver disease.

Definition

NAFLD is the liver component of a cluster of conditions that are associated with metabolic dysfunction. Although fatty liver hepatitis resulting in cirrhosis was described nearly 20 years beforehand,[8] the term non-alcoholic steatohepatitis (NASH) was first coined by Ludwig and colleagues in 1980.[9] NAFLD is defined by the presence of steatosis in more than 5% of hepatocytes in association with metabolic risk factors (particularly, obesity and type 2 diabetes) and in the absence of excessive alcohol consumption (≥30 g per day for men and ≥20 g per day for women) or other chronic liver diseases.[10] Current nomenclature suggests that NAFLD is more of a diagnosis of exclusion than of inclusion, and there is an ongoing debate about the limitations of the present terminology and diagnostic criteria.[11,12] In 2020, an international panel of experts proposed the concept of metabolic dysfunction-associated fatty liver disease (MAFLD) to highlight the contribution of cardiometabolic risk factors to the development and progression of liver disease (even among patients with other liver diseases);[11] however, MAFLD is not the currently accepted nomenclature by the American Association for the Study of Liver Diseases or the European Association for the Study of Liver Diseases.

NAFLD is an umbrella term for a broad range of clinicopathological findings. Histologically, NAFLD encompasses a disease continuum (figure 1 A–C) that includes steatosis with or without mild inflammation (non-alcoholic fatty liver, NAFL) and a necroinflammatory subtype (NASH), which is additionally characterised by the presence of hepatocellular injury (hepatocyte ballooning). The predominant drivers of disease can vary substantially among patients with NAFLD. Furthermore, disease progression and response to treatment are heterogeneous. Information about disease activity and, in particular, the

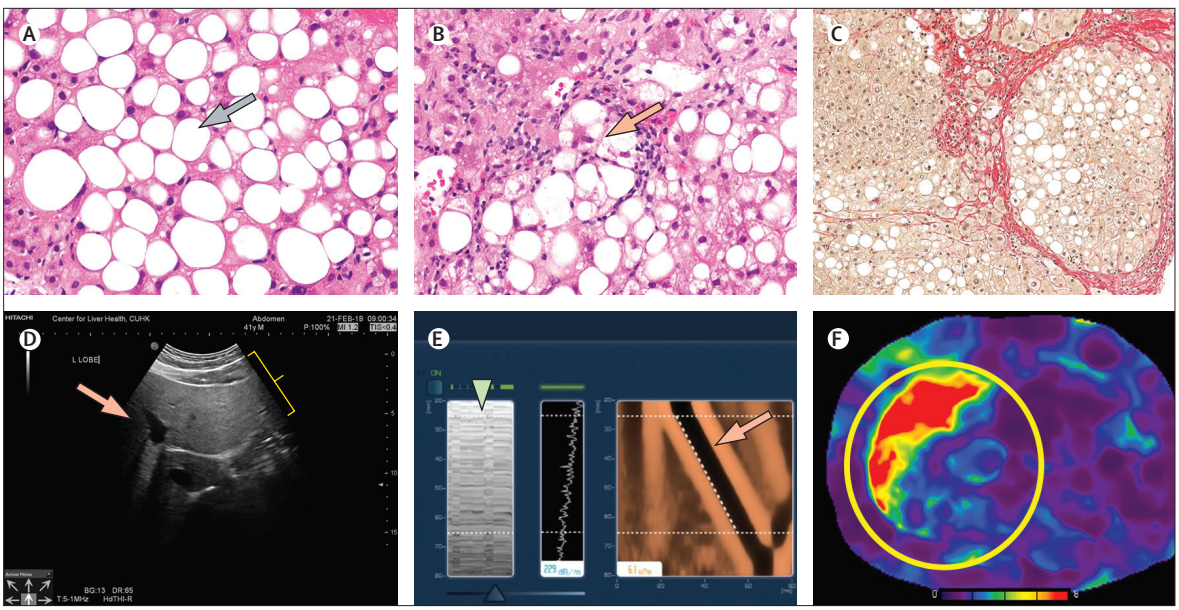

Figure 1: **Histological and radiological assessment of non-alcoholic fatty liver disease**
(A) Non-alcoholic fatty liver is characterised by macrovesicular steatosis (large round non-staining areas represent lipid droplets in hepatocytes [grey arrow]; haematoxylin and eosin stain; magnification ×40) with no or little necroinflammation. (B) Apart from fat accumulation, non-alcoholic steatohepatitis (NASH) is characterised by the presence of lobular inflammation and hepatocyte ballooning. At the centre of the image is a ballooned hepatocyte surrounded by inflammatory cells (red arrow; haematoxylin and eosin stain; magnification ×40). (C) As disease progresses, accumulating liver fibrosis will eventually result in cirrhosis. On the right of this image is a cirrhotic nodule surrounded by thick fibrous tissue. In some cases, steatosis and necroinflammation might reduce or disappear as the disease progresses to cirrhosis, a condition referred to as burned-out NASH (sirius red; magnification ×10). (D) Ultrasonography, the most common method to diagnose fatty liver, characterised by bright liver echotexture (yellow bracket) and blurring of deeper structures (red arrow). (E) Vibration-controlled transient elastography, a point-of-care measurement of liver stiffness for the estimation of fibrosis that can also estimate hepatic steatosis using the controlled attenuation parameter. The machine is equipped with an M-mode ultrasound for the localisation of liver parenchyma (green triangle). The elastogram (red arrow) represents the measurement of liver stiffness. A steeper slope indicates that the shear-wave velocity is higher, and the liver is stiffer. (F) Magnetic resonance elastography of a patient with NASH cirrhosis, currently one of the most accurate non-invasive tests of liver fibrosis, with the colour scheme reflecting stiffness in different parts of the liver. Red colour shows areas with greater stiffness (yellow circle).

extent of liver fibrosis is necessary to assess the severity of liver disease and provide prognostic information. Growing insights from metabolomics, genomics, and other areas will enable disease phenotyping and facilitate potential disease stratification in the future.

Epidemiology and disease burden

NAFLD is now the most common cause of chronic liver disease worldwide, with a prevalence that varies from 13·5% in Africa to 31·8% in the Middle East,[1] which is likely driven by differences in overall caloric intake, physical activity, body fat distribution, socioeconomic status, and genetic composition. Because of its close association with the metabolic syndrome, NAFLD is seen in 47·3–63·7% of people with type 2 diabetes and up to 80% of people with obesity.[13,14] However, some people with a healthy body-mass index (eg, <25 kg/m² in White people and <23 kg/m² in Asian people) can still develop NAFLD, often described as non-obese or lean NAFLD.[15] These patients usually have central obesity or other metabolic risk factors.[16]

Although less than 10%[17,18] of patients with NAFLD develop cirrhotic complications and hepatocellular carcinoma during the 10–20 years after diagnosis, the absolute numbers are substantial given the high disease prevalence. In people with other conditions (eg, alcohol-related liver disease, and viral or autoimmune hepatitis), fatty liver frequently coexists and might have a synergistic role in liver injury.[19] Importantly, the disease and economic burden of NAFLD will probably increase during the coming decades.[20,21] Health-care utilisation and expenditure are particularly high among patients with NAFLD and advanced fibrosis or type 2 diabetes and those requiring hospital admission.[22,23] Little information is available regarding the effect of NAFLD on patients' daily lives,[24] which will be important data to collect in future intervention or treatment studies.

The number of cases of childhood obesity, an important risk factor for NAFLD, is still increasing; in the USA, the prevalence of obesity among children aged 2–5 years increased from 8·4% in 2011–12 to 13·9% in 2015–16.[25] Although the increase appears to have slowed in many high-income countries, the rise in body-mass index among children and adolescents has accelerated in east and south Asia.[26] Among children, the pooled mean prevalence of NAFLD is 7·6% in the general population and 34·2% in clinics for paediatric obesity.[27] Individuals with disease onset in childhood have a higher risk of developing liver-related events and other comorbidities

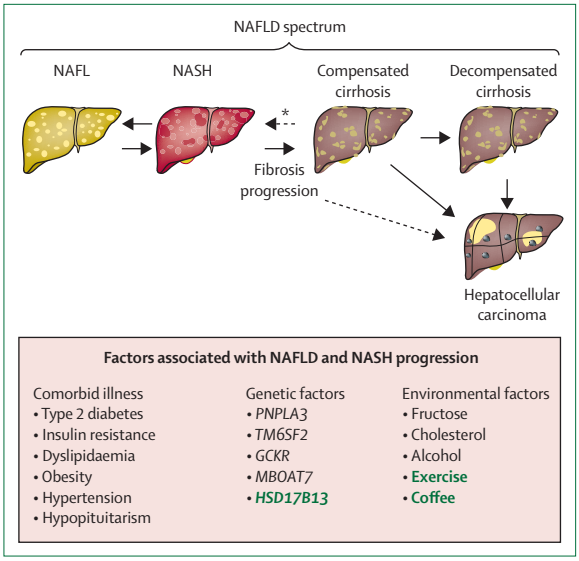

Figure 2: **Spectrum of NAFLD**
Factors in black have an established association with NAFLD and NASH progression (broadly classified into comorbid illness, genetic factors, and environmental factors).[34] Green indicates a protective factor. NAFL=non-alcoholic fatty liver. NAFLD=non-alcoholic fatty liver disease. NASH=non-alcoholic steatohepatitis. *Fibrosis regression.

associated with metabolic syndrome during their lifetime than those with disease onset in adulthood.[28]

Natural history

The relationship between NAFLD and all-cause mortality is unresolved, with some studies detecting a modest increase in risk of all-cause mortality compared with the general population,[29–31] and others reporting no association between NAFLD and mortality.[32,33] NAFLD is a heterogeneous condition with varying rates of disease progression and clinical outcomes, which might be driven by the varying predominant mechanisms for the development of the disease (figure 2).[35] In the majority of patients, liver disease is stable or slowly progressive and will not result in cirrhosis or liver-related death. However, a small proportion of affected individuals develop advanced fibrosis and are at risk of developing complications of end-stage liver disease and hepatocellular carcinoma. Recognising the diversity in disease progression and the factors that influence it is instrumental to developing guidance for patient care.

Studies assessing paired liver biopsy samples although prone to ascertainment and selection bias,[36] contribute important data on the rate of disease progression. Although fibrosis can develop in livers affected by NAFL or NASH, fibrosis progression occurs at a more rapid rate in people with NASH, which is likely driven by necroinflammation.[37,38] A meta-analysis of NAFLD studies assessing paired liver biopsy samples found that fibrosis worsened by one stage (from baseline stage 0 fibrosis) on average during 7·1 years for patients with NASH and by one stage over 14·3 years for patients with NAFL.[36] The histological scoring system for staging fibrosis ranges from stage 0 (no fibrosis) to stage 4 (cirrhosis). The natural course of NAFLD is inconstant and is characterised by bidirectional and concordant changes in both disease activity and fibrosis stage.[39] Nevertheless, the presence of fibrosis, in particular advanced fibrosis (stage 3 and 4), is a key prognostic marker for liver-related outcomes and overall mortality.[17,18,40] In a meta-analysis of 13 studies comprising 4428 patients with NAFLD, patients with stage 4 fibrosis (cirrhosis) had higher all-cause mortality (relative risk [RR] 3·42, 95% CI 2·63–4·46) and liver-related mortality (RR 11·13, 4·15–29·84) than those without fibrosis.[40]

Although there is substantial collinearity between the presence of NASH and clinically significant fibrosis, this collinearity diminishes at the cirrhotic stage as features such as steatosis or those specific to NASH might no longer be visible.[41] Hence, most people with cryptogenic cirrhosis (cirrhosis of unknown cause) with metabolic comorbidities and no other known cause of liver disease are likely to have burned-out NASH.[42] It is not uncommon for individuals with NAFLD to be undiagnosed for decades, even well after cirrhosis has developed. NAFLD is often not recognised until patients have evidence of portal hypertension (eg, splenomegaly, and thrombocytopenia) or develop liver related complications. Progression from compensated cirrhosis to decompensated disease (eg, ascites, hepatic encephalopathy, or bleeding gastro-oesophageal varices) with complications of portal hypertension or liver failure occurs at a rate of approximately 3–4% per year.[43] Cirrhosis is also the strongest risk factor for the development of hepatocellular carcinoma; the annual incidence of hepatocellular carcinoma is 10·6 per 1000 person-years in patients with NASH cirrhosis.[44] Although approximately 20% of NAFLD-related hepatocellular carcinoma occurs in patients with non-cirrhotic livers, the overall risk of hepatocellular carcinoma in the absence of cirrhosis is very low (annual incidence of 0·08 per 1000 person-years).[44] Driven by its high prevalence in the general population, NAFLD is now the second leading cause of end-stage liver disease[45] and the second most common cause of primary liver cancer among adults waiting for liver transplantation in the USA.[5] Similarly in Europe, NAFLD now accounts for 8·4% of annual transplantations, and among all people receiving a liver transplant, hepatocellular carcinoma was found in a greater proportion of individuals with NAFLD (39·1%) than without NAFLD (28·9%, p<0·001).[46] Although the increase in liver transplantation for NASH cirrhosis might partly reflect a higher awareness of NAFLD as a cause of end-stage liver disease, natural history and modelling studies suggest that not only the total, but also the relative proportion of those with advanced liver disease and liver-related outcomes (including hepatocellular carcinoma) due to NAFLD, are increasing.[20,47]

Despite the risk of progressive liver disease, the leading cause of death in patients with NAFLD is cardiovascular

disease, followed by extrahepatic malignancy (eg, colorectal cancer or breast cancer). These causes of death are likely to be due to cardiometabolic risk factors that are shared in NAFLD and cardiovascular disease, although it is unclear to what extent NAFLD has a direct causative role in the development of cardiovascular disease.[48] The bidirectional relationship between NAFLD and some metabolic syndrome features (particularly type 2 diabetes and hypertension), in addition to its characteristic proatherogenic lipid profile,[49] is one mechanism by which NAFLD might augment cardiovascular risk. Patients with NAFLD have a 1·9-times higher risk of incident cancers than the general population, particularly cancers involving the liver, gastrointestinal tract, and uterus.[50] The biological mechanisms might be driven by the association of NAFLD with visceral adiposity and chronic low-grade inflammation, but this mechanism has not yet been determined.[51]

Patients with NAFLD, particularly those with clinically significant fibrosis, have a higher risk of severe COVID-19 than patients without NAFLD.[52] The risk of severe illness from SARS-CoV-2 infection might be independent of metabolic comorbidities,[52] although diabetes and obesity are also established risk factors.

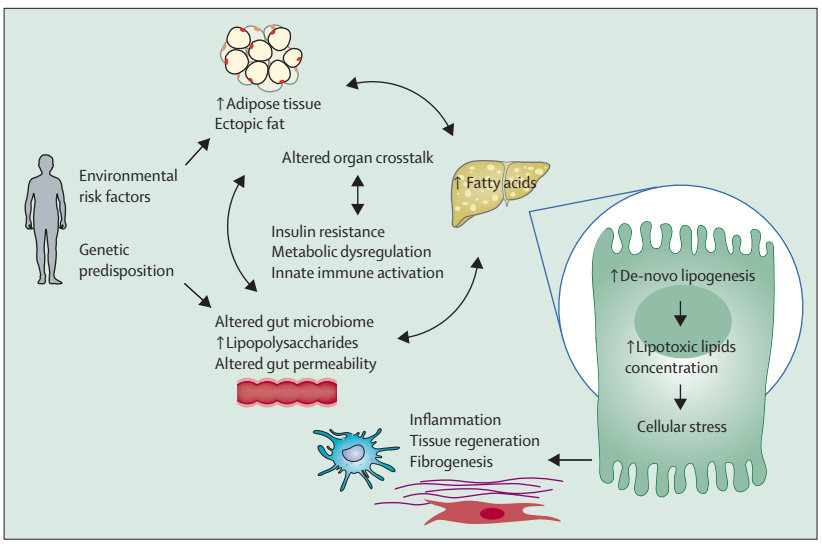

Figure 3: **Multiple pathways and interactions between different organs, affect the pathogenesis of non-alcoholic fatty liver disease**
In the setting of environmental risk factors and heritable factors, crosstalk between the liver, adipose tissue, and gastrointestinal tract leads to systemic inflammation and insulin resistance, resulting in increased hepatic delivery of fatty acids and de-novo lipogenesis. This metabolic milieu leads to the formation of lipotoxic lipids that contribute to cellular stress with subsequent stimulation of inflammation, tissue regeneration, and fibrogenesis.

Pathogenesis

The primary driver of NAFLD is overnutrition, which causes expansion of adipose depots as well as accumulation of ectopic fat (figure 3). In this setting, macrophage infiltration of the visceral adipose tissue compartment creates a proinflammatory state that promotes insulin resistance. Inappropriate lipolysis in the setting of insulin resistance results in unabated delivery of fatty acids to the liver, which, along with increased de-novo lipogenesis, overwhelms its metabolic capacity. The imbalance in lipid metabolism leads to the formation of lipotoxic lipids that contribute to cellular stress (ie, oxidative stress and endoplasmic reticulum stress), inflammasome activation and apoptotic cell death, and subsequent stimulation of inflammation, tissue regeneration, and fibrogenesis.[53,54] Inflammatory and profibrogenic macrophages are implicated in the progression of liver fibrosis and might also have a role in chronic inflammatory processes in other tissues.[55]

These pathogenic pathways of NAFLD are influenced by multiple metabolic, genetic, and microbiome-related factors that are not completely understood. NAFLD has a heritable component, with genetic differences between individuals influencing disease risk estimates by 20–70%.[56] A single-nucleotide polymorphism in the *PNPLA3* gene is the best characterised genetic variant associated with susceptibility to NAFLD.[57] However, known genetic variants account for a small proportion (10–20%) of overall heritability,[56] although this proportion varies across populations. These genes or genetic variants might influence multiple traits—sometimes with divergent effects on NAFLD and comorbid conditions such as coronary artery disease—and several genetic risk variants show a synergistic interaction with obesity.[58,59]

Interdependence and crosstalk between the liver and other organs (particularly, adipose tissue and the gut) might also contribute to metabolic dysregulation and inflammation in NAFLD.[60–62] Alterations in gut microbiota composition are seen in patients with NAFLD and some data suggest that there is a faecal-microbiome signature associated with advanced fibrosis.[63,64] However, confirmation of these bacterial signatures in different patient cohorts and geographical regions controlling for environmental factors is required to determine the signature's clinical significance and use for future diagnostic purposes. Factors produced by bacteria (eg, lipopolysaccharide or short-chain fatty acids) or derived from bile acid metabolism could influence liver inflammation and disease progression in NAFLD, although as yet, clear causal effects have not been established.

Risk stratification and assessment of disease severity

NAFLD is most often diagnosed by imaging, although it can be inferred from clinical risk scores (eg, fatty liver index) or identified histologically. In routine practice, the most commonly used test is abdominal ultrasonography (figure 1D). On abdominal ultrasonography, hepatic steatosis is characterised by a bright liver echotexture and blurring of the hepatic vasculature.[65] Abdominal ultrasonography has two important limitations: advanced fibrosis can coarsen hepatic echotexture and blur vascular pattern; and its sensitivity is low when steatosis is mild (<30%). MRI-based measurements of hepatic

Panel*: Non-invasive fibrosis scores

Non-alcoholic fatty liver disease fibrosis score

$-1{\cdot}675 + 0{\cdot}037 \times$ age (years) $+ 0{\cdot}094 \times$ body mass index (kg/m^2) $+ 1{\cdot}13 \times$ impaired fasting glycaemia or diabetes (yes=1, no=0) $+ 0{\cdot}99 \times$ aspartate aminotransferase to alanine aminotransferase ratio $- 0{\cdot}013 \times$ platelet count ($\times 10^9$/L) $- 0{\cdot}66 \times$ albumin concentration (g/dL)

- Patients at low risk of advanced fibrosis have a score of less than –1·455 (age <65 years) or less than 0·12 (age ≥65 years); a score greater than 0·675 is suggestive of advanced fibrosis
- Interpret with caution in patients who are younger than 35 years; the score is less accurate in patients who are younger than 35 years
- There is a high rate of intermediate scores

Fibrosis-4 index for liver fibrosis

$$\frac{\text{Age (years)} \times \text{aspartate aminotransferase concentration (IU/L)}}{\text{platelet count } (\times 10^9/\text{L}) \times \sqrt{(\text{alanine aminotransferase concentration [IU/L]})}}$$

- Patients at low risk of advanced fibrosis have an index of less than 1·3 (age <65 years) or less than 2·0 (age ≥65 years); a score greater than 3·25 is suggestive of advanced fibrosis
- Interpret with caution in patients who are younger than 35 years; the score is less accurate in patients who are younger than 35 years

*Low platelet count suggestive of advanced fibrosis; concentration of alanine aminotransferase falls and aspartate aminotransferase is stable or rises with increasing fibrosis.

For more on **non-alcoholic fatty liver disease fibrosis score** see https://www.mdcalc.com/nafld-non-alcoholic-fatty-liver-disease-fibrosis-score

For more on the **fibrosis-4 index for liver fibrosis** see https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis

steatosis (eg, MRI proton density fat fraction) can detect as little as 5% fat and are sensitive to dynamic change, but are more often used in the research setting and in clinical trials to evaluate the efficacy of NASH treatments, rather than in routine practice.[66,67]

Risk factors for progressive disease

Type 2 diabetes is associated with a more than two-times increased risk of advanced fibrosis, cirrhosis-related complications, and liver disease mortality (figure 2).[68] Obesity (ie, body-mass index >30 kg/m²), lipid abnormalities (ie, low concentrations of HDL cholesterol and high concentrations of triglycerides), and hypertension are also associated with an increased risk of severe liver disease, although the effect sizes are smaller than for type 2 diabetes.[68] Patients with NAFLD who are older than 60 years have a higher prevalence of advanced fibrosis than younger patients,[69] reflecting a longer duration of metabolic dysfunction and liver disease. A variant of the *PNPLA3* gene is associated with NAFLD histological severity and development of hepatocellular carcinoma as well as liver-related and all-cause mortality.[56,70,71] However, the clinical role of genotyping of variants has not been established.[72]

Non-invasive tests of disease severity

Clinicians usually use liver enzyme concentrations (eg, serum alanine aminotransferase and aspartate aminotransferase) to assess and monitor patients with liver diseases. However, liver enzyme concentrations can be normal in more than half of patients with NAFLD, and correlate poorly with the histological severity.[73] Traditionally, liver biopsy was used to characterise and quantify histological features of steatosis, inflammation, hepatocyte ballooning, and fibrosis. However, this invasive procedure is not suitable for widespread use to assess disease stage or determine progression or response to therapy. In addition to its risk and cost, liver biopsy is prone to sampling bias.[74] Intraobserver and interobserver variability in histological assessment is also well documented in liver biopsy.[75,76] Therefore, researchers have developed and validated several non-invasive tests for NAFLD.

Among the histological features of NAFLD, the severity of liver fibrosis has the strongest correlation with liver-related morbidity and mortality.[40,47] Simple fibrosis scores, such as the NAFLD fibrosis score, Fibrosis-4 (FIB-4) index, and aspartate aminotransferase-to-platelet ratio index comprise demographic, clinical, and routine laboratory parameters and are inexpensive to use (panel).[66] Aspartate aminotransferase is an important component in these scores and tends to increase in concentration (relative to alanine aminotransferase) in advanced fibrosis. Although the overall accuracy of these scores is moderate, they have high negative predictive values to exclude advanced liver fibrosis, especially in community and primary care settings.[77] Patients with low fibrosis scores are also at a low risk of developing liver-related complications.[78]

Among blood biomarkers, the Enhanced Liver Fibrosis (ELF) score (combining hyaluronic acid, tissue inhibitor of metalloproteinase 1, and amino-terminal propeptide of type III procollagen [PIIINP]) has been tested in various cross-sectional studies and clinical trials.[79,80] The UK National Institute for Health and Care Excellence suggests that the ELF score be used for patients with NAFLD and suggests referring patients with a score of 10·51 or higher to hepatologists for evaluation.[81] Although available in many parts of the world, ELF is not yet approved by the US Food and Drug Administration (FDA). Furthermore, performance characteristics of ELF in NAFLD are incompletely delineated as they were mostly determined from cohorts with a high prevalence of advanced fibrosis.[82] Pro-C3 is another biomarker that is used to measure the propeptide cleaved from the intact collagen molecule and indicates fibrogenesis. Pro-C3 has been used in early phase clinical trials to infer the potential effect of new drugs on the prevention of fibrosis progression.[83]

Another method to estimate liver fibrosis in patients with NAFLD is to measure liver stiffness by ultrasound-based elastography (eg, vibration-controlled transient elastography, point-shear wave elastography, and two-dimensional shear wave elastography) and magnetic resonance elastography (figures 1E, F).[66,84,85] Among these methods, transient elastography has been most

extensively evaluated, is widely available, and can be used as a point-of-care test.[86] It is also possible to estimate hepatic steatosis by controlled attenuation parameter measurement at the same time. A liver stiffness cutoff of 6·5–7·9 kPa has approximately 90% sensitivity in excluding stage 3 and 4 fibrosis, whereas patients with cirrhosis typically have liver stiffness more than 12–15 kPa.[66,84,85,87] The liver stiffness measurement also correlates with future risk of hepatocellular carcinoma and cirrhotic complications.[88,89] The Baveno VI criteria combine liver stiffness measurement (≥20 kPa) by transient elastography with platelet count (<150 × 10^9 platelets per L) to identify patients at risk of having varices that need treatment, and have been validated in patients with NAFLD.[90,91]

Because many clinical trials are of patients with NASH (NAFLD activity score of ≥4 with at least one point each in steatosis, lobular inflammation, and hepatocyte ballooning) and fibrosis stage 2 or higher, several groups have proposed composite scores to identify these patients. One example of these composite scores is the FibroScan-aspartate aminotransferase (FAST) score, which comprises aspartate aminotransferase concentration, liver stiffness, and controlled attenuation parameter measurements by FibroScan.[92] In different settings, the FAST score has a C-statistic of 0·74–0·95 in identifying fibrotic NASH. Similarly, the NIS4 algorithm comprises four biomarkers (miR-34a-5p, alpha-2 macroglobulin, CHI3L1, and glycated haemoglobin) and has a C-statistic of 0·76–0·83.[93] Depending on regulatory approval, these scores might be used to select patients for pharmacological treatment.

Prevention, evaluation, and management of NAFLD in primary care and diabetes clinics

Since primary care is the initial point of contact for most people with health concerns (including metabolic risk factors), primary care clinicians have a key role in the prevention, diagnosis, risk stratification, and management of NAFLD. Few studies have examined primary prevention of NAFLD; nevertheless data suggest that improved diet quality[94] and sustained or increased physical activity[95–97] reduces the risk of developing NAFLD, even among individuals with high genetic risk.[94] Primary-care clinicians have a pivotal role in promoting and coordinating lifestyle interventions with dietary modification and exercise, and in management of metabolic comorbidities.

As we now have various non-invasive tests to diagnose fatty liver and liver fibrosis, one relevant concern is whether screening for NAFLD is worthwhile, particularly when patients participate in secondary prevention programmes for diabetes or metabolic syndrome. Recommendations from hepatology associations regarding screening patients for NAFLD are inconsistent; some guidelines[10,98] advocate screening in high-risk populations (eg, people with obesity, type 2 diabetes, or metabolic syndrome) whereas others do not, partly reflecting the paucity of available effective therapeutic interventions.[99] There are also concerns about the possible consequences of overdiagnosis of NAFLD, particularly regarding the potential physical harms of investigation and treatment, and psychosocial harms of labelling people with the disease.[100] Additional studies are needed to evaluate whether screening would improve clinical outcomes and whether it is cost-effective. Nevertheless, once NAFLD is diagnosed, we recommend risk stratification by assessing for the presence of advanced fibrosis or cirrhosis, and the evaluation of cardiovascular risk and comorbid illnesses.

Some local health districts and specialty networks are investigating integrated management plans and referral pathways for patients with NAFLD.[101–105] All pathways recommend testing for advanced fibrosis (bridging fibrosis [stage 3] and cirrhosis [stage 4]) in patients with a diagnosis of NAFLD, although the specific testing algorithms vary. Overall, expert opinion favours a pragmatic, staged approach with inexpensive simple fibrosis scores (eg, NAFLD fibrosis score or FIB-4) as a first step to identify individuals at low risk of advanced fibrosis, who can be managed in primary care. Individuals with indeterminate or high-risk simple scores require additional assessment with locally available second-line fibrosis tests (eg, ultrasound-based elastography or serum ELF test), and might require referral to secondary care for investigation of liver disease or management of advanced fibrosis. Patients without advanced fibrosis at initial assessment require ongoing monitoring in primary care to identify progressive liver disease, and retesting 3–5 years after initial assessment has been proposed (figure 4).[106]

People with type 2 diabetes have a high prevalence of NAFLD (40–70%), and are more likely to develop advanced fibrosis, cirrhosis, and hepatocellular carcinoma than people without diabetes.[107] In addition, multimorbidity and polypharmacy are common in patients with type 2 diabetes and NAFLD, highlighting a need for multidisciplinary management to address their complex health-care needs.[108] In secondary care diabetes clinics, the prevalence of advanced fibrosis among patients with NAFLD is 10–20%, [109–112] which is two to four times higher than in primary care. There is increasing recognition that an assessment of NAFLD and liver fibrosis needs to be incorporated into the routine care of patients with type 2 diabetes.[109] As a result, the American Diabetes Association now recommends that "Patients with type 2 diabetes and elevated liver enzymes (alanine aminotransferase) or fatty liver on ultrasound should be evaluated for the presence of non-alcoholic steatohepatitis and liver fibrosis."[113] However, alanine aminotransferase measurements are notoriously inaccurate and are within the normal range in most people with type 2 diabetes and NAFLD; thus with this strategy, many patients with clinically significant liver disease will not be diagnosed.

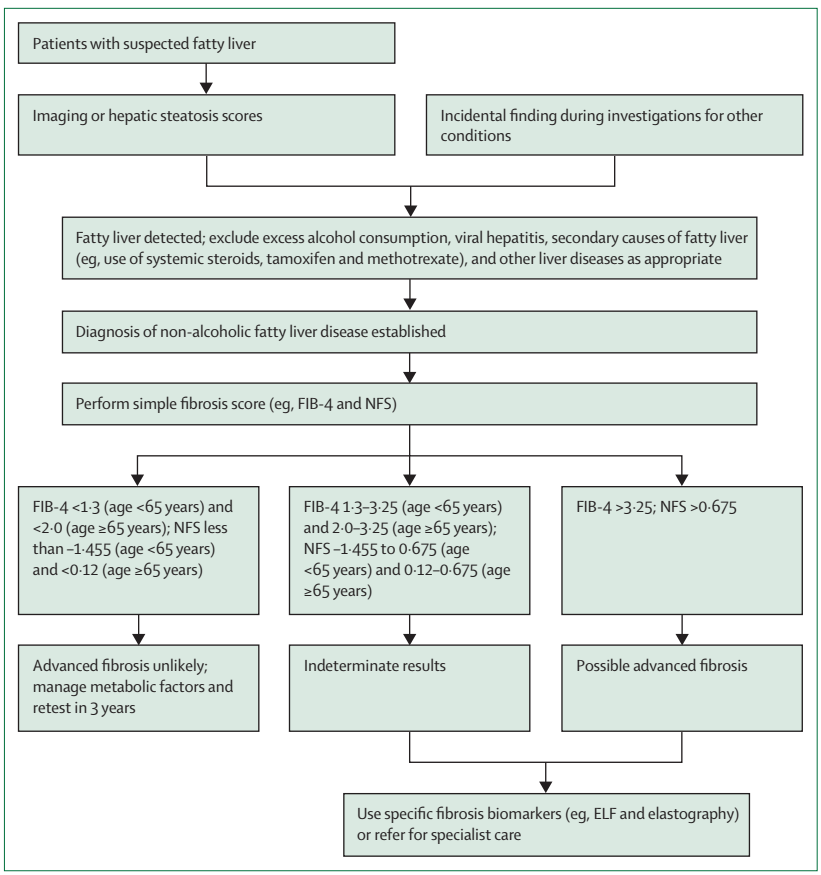

Figure 4: **Proposed diagnostic and referral pathway for non-alcoholic fatty liver disease in primary care**
To establish the diagnosis of non-alcoholic fatty liver disease, it is necessary to exclude concomitant liver diseases and secondary causes of hepatic steatosis. This process usually includes careful documentation of alcohol consumption and medication intake (eg, systemic steroids, tamoxifen, and methotrexate), and excluding viral hepatitis by checking HBsAg and anti-hepatitis C virus antibody. Additional assessment for less common causes of liver disease would depend on the clinical picture and local epidemiology. ELF=Enhanced Liver Fibrosis score. FIB-4=Fibrosis-4 index. NFS=non-alcoholic fatty liver disease fibrosis score.

Management of NASH

Although the liver related burden of NASH is substantial and increasing, cardiovascular disease and malignancy are the leading causes of death in people with NAFLD.[4,17,18,20] Therefore, management of NASH deserves a holistic approach that strives to minimise cardiovascular risk and to reduce drivers of steatosis and systemic inflammation.

The balance between nutrients and energy is pivotal in the development of NAFLD and NASH. Central obesity is an important driver of disease through the promotion of insulin resistance and proinflammatory signalling. Although the macronutrient content of the diet is important, weight loss of more than 5–7% reduces hepatic fat content and steatohepatitis, and, for weight loss in excess of 10%, even fibrosis is reduced in a large proportion of people, irrespective of method of weight loss.[114] Sustained weight loss is challenging because it requires a transformation of ingrained behaviour patterns. Even in the short term, success requires substantial personal commitment in addition to clear recommendations and support from the treatment team. Barriers to weight loss (eg, financial constraints, medical comorbidities, education, and little access to healthy food) should be considered when developing a treatment plan. Although not considered first-line therapy due to the surgical risk, bariatric surgery in patients with severe obesity can lead to substantial (15–25%) durable weight reduction and improvement in liver histological features of NASH and fibrosis.[115] Weight loss improves NAFLD and all of its associated cardiometabolic comorbidities, which then favourably affects cardiovascular and malignancy related risk. There is an independent contribution of NASH to cardiovascular and cancer risk but we do not yet know if liver targeted treatment interventions will reduce them.

Optimising management with existing therapeutics

There is currently no FDA or European Medicines Agency (EMA) approved therapy for NASH. However, several drugs that are currently available for other indications have been studied in phase 2b trials for NAFLD (table). Ursodeoxycholic acid, omega-3 fatty acids, and metformin have not shown histological benefit, whereas other therapies, such as vitamin E and pioglitazone, have[53] and are endorsed by current guidelines as possible treatment in selected patients with NASH.[99] The benefits of vitamin E (RRR-α-tocopherol [also known as d-α-tocopherol]) for NASH have been shown in several randomised controlled trials, including a phase 2b trial in which 84 participants were given vitamin E to reduce steatosis and improve histological NASH in patients without diabetes or cirrhosis.[116] In a randomised controlled trial of patients with type 2 diabetes and NASH assigned to 18 months of vitamin E alone (n=36), combination therapy of vitamin E with pioglitazone (n=37), or a placebo (n=32), only those assigned to combination therapy achieved the histological endpoint (ie, an improvement of NASH by >2 points without worsening of fibrosis).[120] Vitamin E use should be considered in the context of its potential adverse effects, which include an increased risk of bleeding, and its association between higher doses and adverse cardiovascular outcomes.[99] Although statins have no discernible histological benefit on NASH itself, they are safe and should be used as appropriate for cardiovascular risk reduction.

Most individuals with NASH are insulin resistant;[121] however, ameliorating insulin resistance (although important) is an insufficient therapeutic strategy if used alone. For example, metformin (a weak insulin sensitiser compared with thiazolidinediones) reduces the progression to type 2 diabetes and is an important diabetic treatment, but it has no effect on NASH disease activity. Conversely, some drugs that improve NASH histology have no effect on insulin resistance (eg, vitamin E, obeticholic acid, and many other drugs in development).[116,122,123]

	Effects on the liver	Quality of evidence	Other benefits	Key adverse events	Contraindications and cautions
Pioglitazone	Improves hepatic steatosis and necroinflammation, and can improve fibrosis	Several small* to moderate† phase 2 randomised controlled trials[116]	Improves insulin sensitivity and diabetic control	Weight gain, fluid retention, bone loss, and might increase bladder cancer	Contraindicated in patients with NYHA class III or IV heart failure; maximum dose 15 mg if used in combination with gemfibrozil or other strong CYP2C8 inhibitors
Vitamin E	Improves hepatic steatosis and necroinflammation; might prevent liver decompensation and mortality in patients with advanced liver fibrosis	Several small* to moderate† randomised controlled trials; data on clinical outcomes based on a retrospective cohort study with propensity score matching[116,117]	Neutral metabolic effects	A meta-analysis suggests a small increase in overall mortality at high doses; might increase risk of bleeding, prostate cancer, heart failure, and haemorrhagic stroke	Caution in patients with high cardiovascular risk and those at high risk of bleeding
GLP-1 agonists‡	Improves hepatic steatosis and necroinflammation	Several small* to moderate† randomised controlled trials[118]	Improves diabetic control, reduces major adverse cardiovascular events and weight	Nausea, vomiting, dyspepsia, diarrhoea, and constipation	Discontinue GLP-1 agonists immediately in case of acute pancreatitis; might cause acute kidney injury rarely; semaglutide might increase diabetic retinopathy complications
SGLT2 inhibitors§	Improves hepatic steatosis, necroinflammation, and liver enzymes	Several small* randomised controlled trials with non-invasive tests; two small* uncontrolled paired liver biopsy studies[119]	Improves diabetic control; modest weight reduction; might have renoprotective benefits; canagliflozin and empagliflozin reduce major adverse cardiovascular events	Genitourinary infection, acute kidney injury, and euglycaemic diabetic ketoacidosis; might increase the risk of fractures and limb amputations	Contraindicated if estimated glomerular filtration rate is less than 45 mL/min per 1·73 m²

NYHA=New York Heart Association. *Small was defined as less than 50 participants in the active group. †Moderate was defined as 50–100 participants in the active group. ‡For example, liraglutide and semaglutide. §For example, canagliflozin, dapagliflozin, and empagliflozin.

Table: **Potential use of off-label therapy for non-alcoholic steatohepatitis**

Thiazolidinediones, such as pioglitazone, might prevent the development of type 2 diabetes.[124] Multiple trials in patients with and without diabetes have shown that pioglitazone improves NASH activity[125] with a numerical, but not statically significant, improvement in fibrosis in phase 2b trials, including a US National Institutes of Health sponsored trial by the NASH Clinical Research Network that had 80 participants in the active group.[116,126] Although pioglitazone-associated average weight gain (2·4–4·8 kg) is a side-effect, it is less than the average weight gain associated with insulin (3–10 kg). Another factor limiting widespread use of pioglitazone in NASH is the risk of bone loss related to the negative effects of PPAR-γ activation on bone remodelling. It appears unlikely at this time that either vitamin E or pioglitazone will be studied in phase 3 studies; however, other drugs that modulate PPAR-γ and complementary mechanisms are being developed.

For individuals with concomitant type 2 diabetes, there is a growing list of antidiabetic medications that are cardioprotective and renoprotective.[127–129] Several of these medications, including several GLP-1 receptor agonists and SGLT2 inhibitors, are currently being studied in phase 2 and phase 3 trials to assess their efficacy on one of the two FDA-approved histological endpoints (NASH resolution without worsening of fibrosis; or an improvement in fibrosis of one stage or more without worsening of NASH). These agents have the additional benefit of inducing weight loss. Semaglutide 0·4 mg/day given subcutaneously was more effective than liraglutide and resulted in an 18% weight loss during a 52-week period with similar tolerability.[130] Semaglutide 2·4 mg a week given subcutaneously is currently being explored in several contexts to manage obesity.[131] All of these classes of drugs are being evaluated for the treatment of NASH. In a phase 2 randomised controlled trial, subcutaneous semaglutide 0·4 mg daily reached the primary endpoint of NASH resolution with no worsening of fibrosis in 59% of patients, compared with 17% in the placebo group ($p<0·001$).[132] It is difficult to discern if these effects are independent of weight loss; however, the results represent the highest rate of NASH resolution ever reported in NASH therapeutic trials.

Emerging therapeutics of NASH

Numerous drugs with different mechanisms of action, targeting lipid metabolism, inflammatory, or fibrotic pathways, are in development as treatment for NASH.[53,133] To achieve full FDA approval, a therapeutic intervention is required to show a clinically meaningful benefit, defined

as an improvement in how a patient feels, functions, or survives. Since most patients with NASH have few liver-specific symptoms, full approval of these drugs will require the drug to reduce the development of liver-related events or mortality. Given the course of the disease in NASH—it often takes decades to produce liver-related events or death, even in the context of advanced fibrosis—ongoing trials are mainly focused on surrogate endpoints, such as histology, that are reasonably likely to translate into clinically meaningful benefit. The FDA is considering two histological endpoints for conditional approval of NASH therapeutic agents. These endpoints are: NASH resolution without worsening of fibrosis; or an improvement in fibrosis of one stage or more without worsening of NASH. In comparison, EMA requires statistically significant improvement in both histological endpoints. Alternatively, if a therapeutic agent is primarily evaluated for its antifibrotic effects, it should show an efficacy in improving fibrosis by two or more stages. Previously, efficacy of NASH therapeutic agents has been moderate with statistical significance hedging on a somewhat unpredictable placebo response rate and variability in histological interpretation, which is beyond the scope of this Seminar.[134]

REGENERATE, a trial that compared two doses of obeticholic acid (a potent farnesoid X receptor agonist) with placebo, was the first phase 3 trial to meet the primary endpoint of an improvement in fibrosis of one stage or more without worsening of NASH, recapitulating the findings of the FLINT phase 2b trial.[122,123] Although statistically significant, the magnitude of response was modest, which supports the notion that combination therapy will be required to adequately treat the majority of patients. Although obeticholic acid failed to achieve the NASH resolution endpoint, it did improve each of the individual histological features of NASH (eg, steatosis, inflammation, and hepatocyte ballooning). The REGENERATE trial was the first NASH treatment to meet its endpoint; however, two side-effects of the drug reduced enthusiasm for conditional approval. In the trial, pruritus occurred in 51% of patients given 25 mg of obeticholic acid, in 28% of those given 10 mg of obeticholic acid, and 19% of patients given placebo. The extent to which pruritus can be mitigated with other medications or dose reduction while retaining some degree of efficacy is unknown. Increase in LDL concentration is directly related to the drug's inhibition of the enzyme CYP7A1 and can be mitigated with the use of statins.[135] The cardiovascular effect of an increase in LDL concentration, or its reduction with a statin, when treated with obeticholic acid, or more broadly during CYP7A1 inhibition, is not yet known. The 2020 decision by the FDA to delay conditional approval of obeticholic acid until more efficacy and safety data are available might reflect some of these concerns. The FDA has requested the REGENERATE trial continues so that clinical outcome data can be reviewed in the future.[136]

Several drugs are in advanced stages of development for NASH; however, there have already been multiple failures related to disease heterogeneity, variable placebo response, low efficacy, and, in some cases, overinterpretation of phase 2 results.[137] Several phase 2b trials that showed favourable efficacy with respect to fat reduction and histological endpoints have already been continued in phase 3 trials, which will provide more definitive data.[138,139] Several advanced phase trials that focused on NASH cirrhosis have not met their endpoints; however, other trials using promising therapies from non-cirrhotic NASH trials are ongoing.[137] Future treatment will require combination therapy in most patients, consisting of a so-called backbone therapy and an additional agent, tailored to the individual. Currently, the independent benefit of drugs in development need to be shown before combination therapy is approved. Several combination trials are now underway. For example, the ATLAS trial showed a trend towards greater fibrosis improvement with cilofexor (a farnesoid X receptor agonist) and firsocostat (an acetyl-CoA carboxylase [ACC1] inhibitor) than either alone (21% *vs* 12% improvement) in patients with NASH and F3–4 fibrosis.[140] Patients receiving this combination treatment were also more likely to have a 2-point or better improvement in the NAFLD activity score than those receiving monotherapy. However, given the modest difference, more effective combinations will be needed.

Challenges and prospects

Although valuable progress has been made during the past 40 years in learning about the natural history and underlying biology of NAFLD, there are still many challenges. NAFLD is largely under-recognised by health-care professionals and the wider community. Implementation of strategies to identify, and appropriately manage, at-risk patients with advanced fibrosis will require action by clinicians in primary care, diabetes clinics, and other specialists who treat patients with metabolic risk factors, although substantial hurdles, such as cost and access to second-line tests, will need to be addressed. There is an increasing awareness of the need for a multipronged public health response to address NAFLD risk factors and the underlying obesogenic environment.[7,141]

There are several barriers to the development of highly effective therapeutic interventions. One of the most important challenges in the field is a continued reliance on liver biopsy for diagnosis. A reliable biomarker that can accurately diagnose and stage NAFLD across the entire disease spectrum does not yet exist.[66,142,143] A diagnostic biomarker, in conjunction with a prognostic biomarker (of which some currently hold promise), would allow the identification of high-risk individuals on whom resources should be concentrated. A second challenge is the substantial heterogeneity of NAFLD and the current limited understanding of disease phenotypes.

The ability to phenotype patients would permit more accurate prognostication, selection of appropriate therapy, and prediction of treatment response than is currently possible. Lastly, the refinement of therapeutic strategies into thoughtful combination approaches, tailored to the patient's individual disease drivers, are needed for increased response rates and a change in our attitude to screening.

Finally, regardless of the progress that has been, or will be, made in diagnostic tests and drug treatments, healthy lifestyle and weight reduction remains crucial for the prevention and treatment of NAFLD, as obesity is the main driver of this common liver disease and its associated metabolic comorbidities.

Contributors

All authors contributed equally to the Seminar, participating in the literature search, writing, revision, and approval of the final version.

Declaration of interests

VW-SW served as a consultant or advisory board member for 3V-BIO, AbbVie, Allergan, Boehringer Ingelheim, US Center for Outcomes Research in Liver Diseases, Echosens, Gilead Sciences, Hanmi Pharmaceutical, Intercept, Merck, Novartis, Novo Nordisk, Perspectum Diagnostics, Pfizer, ProSciento, Sagimet Biosciences, TARGET-NASH, and Terns; and served as a speaker for AbbVie, Bristol-Myers Squibb, Echosens, and Gilead Sciences. VW-SW has also received an unrestricted grant from Gilead Sciences for fatty liver research. MR is a scientific consultant or advisory board member for Centara, Madrigal, Gilead Sciences, Genfit, Galecto, Amgen, Alnylam, Thetis, Lipocine, Coherus, NGM Biopharmaceuticals, Enanta, Immuron, Fractyl, ProSciento, Gelesis, Merck, Metacrine, Viking Therapeutics, Allergan, Cymabay, Boehringer Ingelheim, Genentech, Sagimet Bio, Terns, Siemens, Novartis, Bristol-Myers Squibb, and Intercept Pharmaceuticals. MR has received independent research funding from Novartis, and owns no stocks and does not participate on speakers bureaus. EEP served as a consultant or advisory board member for CSL Behring and has received an unrestricted grant from Siemens Healthineers. EEP owns no stocks and does not participate on speakers bureaus.

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