Two years on, a perspective on MAFLD

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ABSTRACT

To provide clarity for research studies and clinical care, a set of positive criteria for adults and children with metabolic (dysfunction) associated fatty liver disease (MAFLD) was recently published and has subsequently been widely endorsed. The development and subsequent validation of the criteria for MAFLD has created a positive momentum for change. During the course of the ongoing discussion on the redefinition, some concerns have surfaced that we thought needs clarification. In this review, we provide a perspective on MAFLD and bringing clarity to some of the key aspects that have been recently raised.

INTRODUCTION

Thanks to the pioneering insights into scientists like Thomas Addison who in 1845 used the term 'fatty liver', Klatskin in 1979, and Jurgen Ludwig in 1980 who coined non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), our knowledge about this disease has exponentially increased. This legacy of scientific discovery for improving human health has transformed the lives of thousands of patients. On this journey, we often think of disease definitions as immutable. However, in reality, diagnostic criteria organically change over time, a key outcome of an expanding knowledge base.[1]

Metabolic (dysfunction) associated fatty liver disease (MAFLD) is a multisystem disorder with a heterogeneous disease course and outcomes that, for a majority, are clinically speaking, relatively silent. With its multifaceted origin, it is not surprising that no single clinical, laboratory, histological or radiographic feature can serve as a 'gold standard' for diagnosis or for classification. A natural outcome, particularly when initially described using the 'non' term, signifies that it is not another disease, in this case, alcohol-related. Because of this, the diagnosis of 'NAFLD' is still frequently delayed, sometimes for decades, with most patients diagnosed at the time of cirrhosis.[2] This highlights the core issues of both disease awareness and diagnostic criteria. The problem is compounded in practice by serious concerns about the consequences of missing MAFLD in the context of other known liver diseases.

It is important to identify MAFLD early, before numerous extrinsic factors and biologic pathways converge to accelerate the disease, sometimes irreversibly. Early diagnosis will allow us to target individuals using secondary prevention and treatment strategies more effectively, with the possibility of reversing or at least attenuating disease progression. There is a strong argument for the notion that many treatments, both pharmacological and non-pharmacological, can be more effective in early disease by targeting single organs or pathways before the disease becomes a complex and intertwined puzzle. We are in essence looking for the opportunity to diagnose and treat the equivalent of angina in coronary artery disease to prevent myocardial infarction. It has been suggested that finding a drug for MAFLD is highly challenging. This is potentially true for any disease in its advanced stage where targeting one pathway impacting the disease fails to take into account the now complex pathophysiology and tissue crosstalk. For example, for MAFLD, preneoplastic clonal expansion of hepatocytes or vascular remodelling is unlikely to be reversed by a single 'wonder drug'. Hence, the stratification of patients is the first step to developing plausible and useful treatments.

To provide clarity for research studies and clinical care, a set of positive criteria for adults and children with MAFLD was recently published and has subsequently been extensively validated (box 1).[3–5] Several foundational principles were considered when the diagnostic criteria were conceived. First, because MAFLD is believed to be a continuum of disease in children and adults, any distinction of disease between them would be arbitrary. Hence, the criteria were crafted to be applicable to all ages, cognisant of age-related adjustment in some of the variables. Second, there was a focus on removing alcohol as part of the diagnostic criteria. Instead, we chose to consider the disease as a single entity (much like diabetes) related to metabolic dysregulation, with other factors such as alcohol, genetic influences or the microbiota considered as disease modifiers. Third, we emphasised the

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Box 1 Diagnostic criteria of metabolic (dysfunction) associated fatty liver disease (MAFLD) in adults and children

Diagnostic criteria of MAFLD in adults
⇒ The diagnosis of MAFLD is made if there is evidence of hepatic steatosis plus one of the following three criteria:
   ⇒ Overweight/obesity.
   ⇒ Type 2 diabetes mellitus (DM).
   ⇒ Evidence of metabolic dysregulation (≥2 metabolic risk abnormalities as follows: waist circumference ≥102/88 cm in Cacacsuian and ≥90/80 cm in Asian men and women, blood pressure ≥130/85 mm Hg or specific drug treatment, plasma triglycerides ≥150 mg/dL or specific drug treatment, plasma high-density lipoprotein cholesterol <40 mg/dL for men and <50 mg/dL for women or specific drug treatment, prediabetes, homeostasis model assessment of insulin resistance score ≥2.5 and plasma high-sensitivity C reactive protein level >2 mg/L).

Diagnostic criteria of MAFLD in children
⇒ The diagnosis of MAFLD is made if there is evidence of hepatic steatosis plus one of the following three criteria:
   ⇒ Excess adiposity.
   ⇒ Prediabetes or type 2 DM.
   ⇒ Evidence of metabolic dysregulation.

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need to *evaluate* for these other conditions rather than having these diseases excluded for a diagnosis of MAFLD to be made. For patients in real life, this allows MAFLD and alcohol-related liver disease (ARLD) or other diseases to coexist, each requiring specific therapeutic intervention. Fourth, there was consideration that the criteria must be operationalised in a universal and clinically relevant manner applicable in all health systems. We envisaged that the criteria would need to have utility both for practice and for clinical trials and would be applicable to patients who had been diagnosed with MAFLD under the prior NAFLD criteria. Finally, we hoped that any new set of criteria would turbocharge the path for new clinical trials and studies. With the benefit of hindsight, it is clear that the MAFLD definition has abundantly met its promise. We believe that the development and subsequent validation of the criteria for MAFLD has created a positive momentum for change. During the course of the ongoing discussion on the redefinition, some concerns have surfaced that we thought needs clarification.

DIAGNOSTIC VERSUS CLASSIFICATION/STRATIFICATION VERSUS INCLUSION CRITERIA

As a first step, bringing clarity to the distinction between diagnostic criteria, classification/stratification and inclusion criteria for clinical studies or trials is vital for the field. Diagnostic criteria are generally broad set of symptoms, signs and tests used in routine care. They must reflect the different features of a disease with a view to accurately identifying as many people with the condition as possible. Optimally, diagnostic criteria are easily memorised and recalled as required. Diagnostic criteria

will only be useful if practicable and simplicity of use is a critical feature for universal adoption.[6 7] Although some diagnostic tests such as Dual-energy X-ray absorptiometry have been suggested as a potential criterion for MAFLD, they are unavailable, unreliable or unaffordable in the majority of countries with a high burden of liver disease and are, hence, barriers to adoption. The lack of access to tests that are appropriate for low-resource settings makes the disease more difficult to detect and to treat, further contributing to health inequities.[8 9] This aspect has been suggested by multiple regional societies as one of their key reasons for the early endorsement of MAFLD and for its subsequent implementation to clinical practice.[7–9]

As compared with clinical diagnosis, the intent of classification or stratification systems is different. Diagnosis aims to accurately determine whether the underlying disease in an individual patient is or is not MAFLD. In contrast, a classification defines a rather homogenous set of patients for guiding prognosis and therapy. For example, the diagnosis of breast cancer is different from stratifying into subtypes such as oestrogen receptor positive, progesterone receptor positive or human epidermal growth factor receptor 2 (HER2) positive that then guides personalised management with chemotherapy, hormonal or HER2 targeted therapy. If all of these patients were lumped together, the results for each treatment modality would be suboptimal, as we are witnessing for MAFLD. In particular, stratification is extremely helpful if a patient is in need of expensive treatments or needs one that has a low safety profile. Thus, diagnosis of MAFLD is different from future attempts to stratify the disease according to polygenic risk factors, epigenetics, dysbiosis, etc. Interestingly, with the redefinition to MAFLD, studies have emerged that show a differential prognosis for patients according to the three diagnostic criteria. An outcome is that such information can be used to guide disease stratification as a promising step in the path to personalisation of care.[10] In the search for improvements, a future challenge would be to strike the right balance between simplicity and complexity for clinical practice and for clinical research and treatment.

Inclusion criteria on the other hand are standardised definitions primarily intended to create well-defined, relatively homogenous cohorts for research. They are not intended to capture the entire universe of possible patients, but rather to capture the majority of patients with key shared features of the condition. The 'distance' between diagnostic and inclusion criteria on this continuum depends on the study designer and is informed by various factors, including disease prevalence, geography and prevalence of 'mimickers', among other factors.[5] By default, inclusion criteria have the potential to restrict the external validity of studies as interventions may perform differently in study participants who fulfil the inclusion criteria for a trial than the broader group diagnosed with the same disease, that is, those that share some but not other disease manifestations considered in the inclusion criteria. For example, a trial of tamoxifen

will show minimal benefit in patients with breast cancer who are not hormone receptor positive. In our field, it also implies that not every MAFLD patient (eg, those with increased alcohol consumption, coexisting liver disease or even more simply lean vs obese, diabetic vs non-diabetic) would be appropriate for inclusion in every clinical trial or study.[11] Alcohol consumption as an entry criterion will depend on the mechanism of the therapy under investigation and the label sought.

MAFLD: LIVING UNDER THE SHADOW OF ALCOHOL FOR 40 YEARS

'NAFLD' is diagnosed in the presence of fatty liver without 'significant' amounts of alcohol consumption in the absence of other causes of hepatic steatosis, as per the American Association for the Study of Liver Diseases (AASLD) guidelines.[12] This exclusion-type diagnosis stemmed from the initial observation that these patients shared many features on liver histology to those with alcohol-related liver disease (ALRD), but who on close questioning denied alcohol intake. Unfortunately, since the name persisted, fatty liver disease due to metabolic dysregulation has remained under the shadow of alcohol. Current confusion around many aspects of MAFLD is an outcome of this historical fact.

To put it simply, how can alcohol consumption be considered in MAFLD? Does it have anything to do with the diagnosis? Is it implicated in the underlying pathogenesis? Or is it just one of a multitude of other modifiers such as ethnicity, age, sex, diet, physical activity, coffee intake, smoking,…etc? We know that all these modifiers are implicated either positively or negatively in the natural history and outcomes of MAFLD, but we do not have 'non-coffee fatty liver disease'. Second, any consideration of alcohol in the current diagnosis of NAFLD is based on the 'amount of alcohol consumed'. This is in the context of the research community repeatedly telling us about the underreporting of alcohol consumption in patients with NAFLD. Some reports suggest that over a quarter of patients with NAFLD consume alcohol above the arbitrary threshold for diagnosis.[13] Other research shows that alcohol intake below the arbitrary threshold of NAFLD is associated with an increased risk of steatosis and fibrosis,[14] while epidemiological data indicate that the impact of alcohol on hepatic steatosis is much lower than that of metabolic factors. A recent report observed that only 23% of patients with excessive alcohol consumption but not MAFLD had steatosis.[15] What about the patterns of alcohol consumption (beverage type, frequency and consumption with food)? There is evidence that these aspects can be more relevant for the risk of adverse health outcomes, including cirrhosis and liver cancer.[16 17] In addition, does an alcohol diagnosis consider interindividual variability in response to alcohol consumption based on age, sex, pharmacokinetics, ethnicity or genetic susceptibility or take into account new evidence that some gut bacteria produce alcohol contributing to liver damage in patients with presumed NAFLD?[18]

A further concern if we fail to progress the disease terminology is that we would need to ask the patient his or her alcohol consumption at the first visit and then give a label of 'NAFLD'. It has even been suggested by a few that, for some patients, this can be perceived as destigmatising. We know that alcohol consumption can change over the life course, including multiple reports indicating changes during COVID-19 as just one example.[19] Furthermore, recent alcohol consumption rather than that earlier in life is associated with the risk of alcohol-related cirrhosis.[20] So does that mean a patient can have NAFLD and then if he/she drinks above the acceptable limits he/she has ALRD when reviewed a year later, and then if he/she stops drinking in another year has NAFLD again? This is patently ridiculous if the patient remains throughout with metabolic risk factors.

Apart from the liver injury, alcohol consumption is associated with extrahepatic diseases overlapping with MAFLD such as hypertension, diabetes, cancers and atrial fibrillation. In all these other fields, alcohol consumption is considered a *risk factor* with no false dichotomisation, as we in hepatology undertake. It has also been argued that, in liver, both diseases have similar histological features and, thus, can be confusing. This is precisely the value of positive diagnostic criteria for all diseases that a person might suffer from.

Are patients with liver diseases such as viral hepatitis immune NAFLD? To the contrary, using the MAFLD criteria, a considerable proportion of these patients has MAFLD.[21] Is it logical to use the term NAFLD despite having other liver diseases or acknowledging the use of alcohol?[22–24] Is it not high time that we correct the ambiguity?

Forty years later, we ask ourselves the question, what has changed? To be sure, many knowledge voids have been filled. A primitive definition cannot serve the field anymore. If there is inertia for change, what is the value of the accumulated knowledge? Clearly, the MAFLD definition did not create the problem, but rather uncovered it in full relief. The boundaries between MAFLD and ARLD are the same as the boundaries between MAFLD and any other liver disease. Whatever the diagnostic criteria or alcohol threshold the alcohol community uses to diagnose ARLD must be applied for fatty liver disease associated with metabolic dysfunction. It behoves us that we accept the criteria set by our learnt colleagues, rather than existing in a time warp with static criteria and a sex-based difference. To move forward, we must first establish diagnostic criteria for the disease associated with metabolic dysfunction, then set the margin for when to diagnose MAFLD, ALRD or MAFLD and ALRD. Within the MAFLD population, alcohol will be one of the variables that can be managed in research settings as a continuous or dichotomised variable, or included or not included in studies.

RULING OUT OTHER CONDITIONS DOES NOT IMPLY THAT MAFLD IS A DISEASE OF EXCLUSION

It has been argued that MAFLD should remain a disease of exclusion in paediatrics as ruling out less common diseases is important. Again, we would like to clarify that ruling out other conditions is an accepted part of good clinical care for any person, young or old. For example, Hepatitis C is diagnosed positively by HCV-Ab or HCV-RNA testing, but ruling out infection with other viruses such as hepatitis B virus and HIV does not imply that HCV is a diagnosis of exclusion. As in the case with MAFLD, excluding salient other diseases is a matter of accepted good clinical care.

It should be noted that discretion needs to be exercised when 'chasing down' unusual diagnoses and secondary causes. We know that excessive testing can lead to unintended patient anxiety and harm, and the risks of over-diagnosis may be physical, psychological or economic.[25] A diagnosis by exclusion as for NAFLD can have negative cost consequences. If we want to ensure that healthcare resources are appropriately distributed, we must have a reasonably clear idea on what the disease is, and second, which diseases are worth excluding based on the investments in time and money. MAFLD is a distinct disease which can coexist with other liver diseases and, thus, necessitates its own set of inclusionary diagnostic criteria. Making a positive diagnosis for all diseases is the first step towards attaining this goal, with other diagnostic considerations being based on disease likelihood, patient factors and costs. As a relevant example in gastrointestinal disease, health providers who believe irritable bowel syndrome (IBS) is a diagnosis of exclusion order 1.6 times more tests and consume $364 more per patient. Experts on the other hand are less likely to consider IBS as a diagnosis of exclusion.[26]

CAN THE NAME OF A DISEASE BE SEPARATED FROM ITS DEFINITION?

This is an important question because diagnostic criteria are created specifically to diagnose a disease. Thus, both the name and definition are intimately connected and a disease will be poorly diagnosed unless it has been properly defined. No one would claim that if a definition allows a condition to be identified, there was no real disease before. Even for NAFLD, it started with cases in which something is defined as 'a pathology' and was subsequently given a set of medical criteria for diagnosis. In this context, the shift from NAFLD to MAFLD was first proposed. This naturally led to the second question on how MAFLD will be diagnosed if it is to be more than a name change? Extending from this, a fundamental question is does the set of proposed criteria succeed in capturing the population in whom the disease term MAFLD is used? The answer is clearly yes.

There has been a recent argument that the proportion (0%–4%) of lean patients with fatty liver but without MAFLD (ie, with no metabolic dysfunction) is a limitation of the MAFLD definition. Apart from the fact that these patients could have another aetiology such as under-reported alcohol or drug intake, the evidence suggests that fibrosis, cardiovascular disease and mortality risk of this population is not different from the general population.[27] It is only when these individuals progress further along the disease path acquiring additional metabolic risk factors that they have a different outcome from the general population. Therefore, it is a fallacy to consider that a name can be dissected away from its definition.

GENETIC MAFLD: IS THIS A SUBTYPE?

Another aspect that needs clarification is the suggestion of having a subtype called 'genetic'. Regardless of controversies on the name and the definition, a simple interrogation demonstrates that this concept is flawed. As we all know, MAFLD is a complex disease, the outcome of the interaction of polygenic predisposition in concert with influences from the physical and social environment.[28] It is not a 'simple' single gene disease with Mendelian patterns of inheritance or one caused by mutations in a single gene.[29]

This fallacy was given wings when initial reports showed that the *PNPLA3* polymorphism might not be associated with diabetes or serum lipid concentrations. However, the reality is that the association of *PNPLA3* with metabolic traits is far more complex than originally considered.[28] Although initial studies did not detect a relationship between the p.I148M mutation and serum glucose or lipid concentrations, multiple recent larger and more robust studies demonstrate that both *PNPLA3* rs738409 and *TM6SF2* rs58542926 are associated with lower lipid levels and a lower risk of cardiovascular disease, but an increased risk of fatty liver and type 2 diabetes mellitus.[30–32] Another study provided evidence that the presence of metabolic dysfunction, including but not limited to adiposity, is a prerequisite for the deleterious impacts of the *PNPLA3* rs738409 and *TM6SF2* rs58542926 risk alleles on hepatic fat.[33]

Importantly, the presence of the variant risk genotype does not mandate the occurrence or progression of liver disease and studies have demonstrated that genetic risk can be mitigated by lifestyle intervention. What is the role of epigenetics?[34] A twin study has demonstrated that although monozygotic twins share almost identical genomes and similar epigenomes in early life, their epigenomes differ widely later in life.[35] A meta-analysis of twin studies has suggested an almost equal contribution of genes and the environment to the heritability of human complex traits.[36] Furthermore, the aforementioned variants have been implicated in modulating the risk of steatosis and liver injury from other liver diseases including alcohol and viral hepatitis.[37–39] Does this mean that we need a subtype of ALRD or viral hepatitis called the 'genetic' subtype? Do patients with the *PNPLA3* risk genotype have ARLD-induced steatosis or liver injury without consuming alcohol? Is the genetic influence not

Table 1 Changing diagnostic criteria for diabetes, hypertension and high cholesterol

	Prior 1993	1993	1998	2001	2003	2007	2010	Post 2017
Diabetes[55 56]	FPG: 140mg/dL		FPG: 126mg/dL		100mg/dL (FPG)	FPG: 126mg/dL A1c: 7.0%	FPG: 126mg/dL (7.0mmol/L) A1c: 6.5%	
Prediabetes	None		FPG: 110mg/dL				FPG: 100mg/dL	Eliminated
Hypertension[57]	160/95mm Hg	140/90mm Hg					140/90mm Hg	
Prehypertension	None						130/80mm Hg	
High-normal BP								120–129/<80mm Hg
Grade 1 hypertension								130–139/80–89mm Hg
Grade 2 hypertension								>140/>190mm Hg
High LDL cholesterol[58]	190mg/dL			160mg/dL			160mg/dL	
Borderline high	160mg/dL			130mg/dL			130mg/dL	

BP, blood pressure; FPG, Fasting Plasma Glucose; LDL, low-density lipoproteins.

just a disease modifier, even more so in the context of polygenic or omnigenic risk?

DOES THE CHANGE TO MAFLD IMPACT THE PERFORMANCE OF NON-INVASIVE SCORES?

This argument is one of the misconceptions that can easily be countered with evidence. The argument goes that a change from NAFLD to MAFLD impacts the performance of non-invasive scores for steatosis and fibrosis because MAFLD allows for a realistic consideration of alcohol. Here, it worth noting that although the diagnosis of NAFLD requires exclusion of excess alcohol consumption, multiple studies show that a considerable proportion (up to a quarter) of patients with presumed 'NAFLD' actually consume alcohol excessively above the arbitrary threshold for diagnosis.[13] Even if we accept that all patients with a diagnosis of NAFLD meet the criteria for diagnosis, there is strong evidence that the performance of non-invasive scores varies substantially based on multiple common factors and confounding such as age, obesity and diabetes.[40] In practice, including in guidelines,[41] we do not interpret non-invasive tests based on age-specific, diabetes-specific and sex-specific criteria. If we can use it in these groups, what is the difference in MAFLD?

It has been suggested by multiple studies that up to one third of patients with ARLD have at least two components of metabolic syndrome (ie, they are likely to have MAFLD and ARLD). Additional studies have shown that the diagnostic accuracy of non-invasive scores such as transient elastography, Enhanced Liver Fibrosis Test and ADAPT in ALD is not impacted by obesity and diabetes (if this can be used as a proxy of MAFLD/the group of dual aetiologies).[42 43] Similar findings have been observed in other studies on this particular group comprising both alcohol and fatty liver disease.[44] More importantly, various studies have validated these scores in actual MAFLD cohorts, as recently reviewed.[3 45] For example, a study used the National Health and Nutrition Examination Survey (NHANES) III cohort showed that the performance of scores in MAFLD is not impacted by alcohol consumption stratification.[46]

APPROACH TO CLINICAL TRIALS AND REGULATORY APPROVAL

One of the principles embedded in the MAFLD diagnostic criteria is ensuring that patients treated in clinical trials for NAFLD would still meet the criteria for an MAFLD diagnosis. Patients diagnosed within NAFLD criteria would we argue, universally meet the criteria of having MAFLD. For the sake of homogeneity, exclusion criteria have been applied to NAFLD trials that would equally apply to MAFLD. For example, inclusion for the REGENERATE required at least one accompanying comorbidity (obesity (body mass index ≥30 kg/m^2) or type 2 diabetes),[47] while inclusion for Resmetirom (MGL-3196) trial included metabolic syndrome,[48] requirements

that would automatically justify the MAFLD label. Indeed, it is better to change now before we have an approved drug, rather than changing latter. Going forward, clinical trial designs must specify and provide the rationale for the subtype of the MAFLD population being studied, so that optimal drug responses are ensured based on their mechanism of action. Such criteria will allow for the conduct of clinical trials that truly move the field. This is imminently possible with the use of basket or umbrella trial designs that could for example allow certain levels of alcohol intake in some cohorts that reflect the populations we see in real-world settings.[49]

NOT ONLY WILL KNOWLEDGE BE PRESERVED, BUT IT WILL INCREASE

Will the change to MAFLD result in a loss of preceding knowledge? We argue that not only will knowledge be persevered but that it will increase. We know that there is a high overlap between NAFLD as previously defined, and MAFLD. A recent study in a veterans population in primary care settings demonstrated 100% concordance between the two definitions.[50] In addition, a meta-analysis including data from 17 studies comprising 9 808 677 individuals showed that the prevalence of MAFLD was comparable to the prevalence of NAFLD. Only 4.0% of patients with NAFLD did not meet the MAFLD criteria.[51] It stands to reason that knowledge generated under the NAFLD term will be transmitted to the new MAFLD term. Was any knowledge lost when acute coronary syndrome as a term was introduced?

Is hepatology the first field to change diagnostic criteria? Virtually all common and rare diseases have undergone changes in diagnostic criteria and targets for therapy with advancements in knowledge (table 1). One wonders what the value of accumulating knowledge is, if it does not inform change. The fear of change merely creates inertia for progress. It is akin to changing from Windows 6 to 11, meeting the current needs of our patients. In this context, early reports demonstrated improved patient and physician awareness with the introduction of MAFLD.[52 53] Similarly, patients diagnosed according to the new criteria for multiple sclerosis displayed a lower risk of reaching disability.[50] In the field of drug development, one example is the change in diagnostic criteria for eosinophilic esophagitis implemented in 2018 that removed the proton pump inhibitor (PPI) use requirement for a diagnosis of coexisting eosinophilic esophagitis and gastrooesophageal reflux disease. Previous requirement for PPI trial stemmed from the belief that both entities were mutually exclusive.[54] Multiple clinical trials were ongoing at the time of change,[54] and in May 2022, the Food and Drug Administration (FDA) approved Dupixent (dupilumab) as the first treatment for eosinophilic esophagitis. The case for MAFLD is no different. Try it and reap the benefits for patients, patient groups and for hepatology. The future of the field is bright, if only we can ponder the evidence.

REFERENCES

1 Tresker S. A typology of clinical conditions. *Stud Hist Philos Biol Biomed Sci* 2020;83:101291.
2 Eslam M, Sanyal AJ, George J, *et al*. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. *Gastroenterology* 2020;158:1999–2014.
3 Alharthi J, Gastaldelli A, Cua IH, *et al*. Metabolic dysfunction-associated fatty liver disease: a year in review. *Curr Opin Gastroenterol* 2022;38:251–60.
4 Eslam M, Alkhouri N, Vajro P, *et al*. Defining paediatric metabolic (Dysfunction)-associated fatty liver disease: an international expert consensus statement. *Lancet Gastroenterol Hepatol* 2021;6:864–73.
5 Eslam M, Newsome PN, Sarin SK, *et al*. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. *J Hepatol* 2020;73:202–9.
6 Méndez-Sánchez N, Bugianesi E, Gish RG, *et al*. Global multi-stakeholder endorsement of the MAFLD definition. *Lancet Gastroenterol Hepatol* 2022;7:388–90.
7 Spearman CW, Desalegn H, Ocama P, *et al*. The sub-Saharan Africa position statement on the redefinition of fatty liver disease: from NAFLD to MAFLD. *J Hepatol* 2021;74:1256–8.
8 Mendez-Sanchez N, Arrese M, Gadano A, *et al*. The Latin American Association for the study of the liver (ALEH) position statement on the redefinition of fatty liver disease. *Lancet Gastroenterol Hepatol* 2021;6:65–72.
9 Xu X, Nan Y. "Reply to: correspondence on "the Chinese society of Hepatology position statement on the redefinition of fatty liver disease"" *J Hepatol* 2022;76:S0168-8278(21)02170-X:484–5.:.
10 Huang J, Ou W, Wang M, *et al*. MAFLD criteria guide the subtyping of patients with fatty liver disease. *Risk Manag Healthc Policy* 2021;14:491–501.
11 Eslam M, El-Serag HB, Francque S, *et al*. Metabolic (Dysfunction)-Associated fatty liver disease in individuals of normal weight. *Nature Reviews Gastroenterology & Hepatology* 2022;19:638–51.
12 Chalasani N, Younossi Z, Lavine JE, *et al*. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the study of liver diseases. *Hepatology* 2018;67:328–57.
13 Staufer K, Huber-Schönauer U, Strebinger G, *et al*. Ethyl glucuronide in hair detects a high rate of harmful alcohol consumption in presumed non-alcoholic fatty liver disease. *J Hepatol* 2022;77:918–30.
14 Eslam M, Sanyal AJ, George J. Toward more accurate nomenclature for fatty liver diseases. *Gastroenterology* 2019;157:590–3.
15 van Kleef LA, de Knegt RJ, Brouwer WP. Metabolic dysfunction-associated fatty liver disease and excessive alcohol consumption are both independent risk factors for mortality. *Hepatology* 2023;77:942–8.
16 Jani BD, McQueenie R, Nicholl BI, *et al*. Association between patterns of alcohol consumption (beverage type, frequency and consumption with food) and risk of adverse health outcomes: a prospective cohort study. *BMC Med* 2021;19:8.
17 Simpson RF, Hermon C, Liu B, *et al*. Alcohol drinking patterns and liver cirrhosis risk: analysis of the prospective UK million women study. *Lancet Public Health* 2019;4:e41–8.

18 Yuan J, Chen C, Cui J, *et al*. Fatty liver disease caused by high-alcohol-producing Klebsiella pneumoniae. *Cell Metab* 2019;30:1172.
19 Pollard MS, Tucker JS, Green HD. Changes in adult alcohol use and consequences during the COVID-19 pandemic in the US. *JAMA Netw Open* 2020;3:e2022942.
20 Askgaard G, Grønbæk M, Kjær MS, *et al*. Alcohol drinking pattern and risk of alcoholic liver cirrhosis: a prospective cohort study. *J Hepatol* 2015;62:1061–7.
21 Al-Omary A, Byth K, Weltman M, *et al*. The importance and impact of recognizing metabolic Dysfunction-Associated fatty liver disease in patients with chronic hepatitis C. *J Dig Dis* 2022;23:33–43.
22 Sanyal AJ, Contos MJ, Sterling RK, *et al*. Nonalcoholic fatty liver disease in patients with hepatitis C is associated with features of the metabolic syndrome. *Am J Gastroenterol* 2003;98:2064–71.
23 Bondini S, Kallman J, Wheeler A, *et al*. Impact of non-alcoholic fatty liver disease on chronic hepatitis B. *Liver Int* 2007;27:607–11.
24 Paik JM, Henry L, Golabi P, *et al*. Presumed nonalcoholic fatty liver disease among medicare beneficiaries with HIV, 2006-2016. *Open Forum Infect Dis* 2020;7:ofz509.
25 Moynihan R, Doust J, Henry D. Preventing overdiagnosis: how to stop harming the healthy. *BMJ* 2012;344:e3502.
26 Spiegel BMR, Farid M, Esrailian E, *et al*. Is irritable bowel syndrome a diagnosis of exclusion?: a survey of primary care providers, Gastroenterologists, and IBS experts. *Am J Gastroenterol* 2010;105:848–58.
27 Tsutsumi T, Kawaguchi T, Nakano D, *et al*. Atherosclerotic cardiovascular disease in non-metabolic nonalcoholic fatty liver disease. *Hepatol Res* 2022;52:317–9.
28 Eslam M, George J. Genetic contributions to NAFLD: leveraging shared genetics to uncover systems biology. *Nat Rev Gastroenterol Hepatol* 2020;17:40–52.
29 Eslam M, George J. Genetic and epigenetic mechanisms of NASH. *Hepatol Int* 2016;10:394–406.
30 Liu DJ, Peloso GM, Yu H, *et al*. Exome-wide Association study of plasma lipids in> 300,000 individuals. *Nat Genet* 2017;49:1758–66.
31 Meffert PJ, Repp KD, Völzke H, *et al*. The PNPLA3 SNP Rs738409:G allele is associated with increased liver disease-associated mortality but reduced overall mortality in a population-based cohort. *J Hepatol* 2018;68:858–60.
32 Diogo D, Tian C, Franklin CS, *et al*. Phenome-wide Association studies across large population cohorts support drug target validation. *Nat Commun* 2018;9:4285.
33 Xia M, Zeng H, Wang S, *et al*. Insights into contribution of genetic variants towards the susceptibility of MAFLD revealed by the NMR-based lipoprotein profiling. *J Hepatol* 2021;74:974–7.
34 Bayoumi A, Grønbæk H, George J, *et al*. The epigenetic drug discovery landscape for metabolic-associated fatty liver disease. *Trends Genet* 2020;36:429–41.
35 Fraga MF, Ballestar E, Paz MF, *et al*. Epigenetic differences arise during the lifetime of monozygotic twins. *Proc Natl Acad Sci USA* 2005;102:10604–9.
36 Polderman TJC, Benyamin B, de Leeuw CA, *et al*. Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nat Genet* 2015;47:702–9.
37 Eslam M, Mangia A, Berg T, *et al*. Diverse impacts of the rs58542926 E167K variant in TM6SF2 on viral and metabolic liver disease phenotypes. *Hepatology* 2016;64:34–46.
38 Thabet K, Asimakopoulos A, Shojaei M, *et al*. MBOAT7 rs641738 increases risk of liver inflammation and transition to fibrosis in chronic hepatitis C. *Nat Commun* 2016;7:12757.
39 Thabet K, Chan HLY, Petta S, *et al*. The membrane-bound O-acyltransferase domain-containing 7 variant Rs641738 increases inflammation and fibrosis in chronic hepatitis B. *Hepatology* 2017;65:1840–50.
40 Armstrong MJ, Schmidt-Martin D, Rowe IA, *et al*. Caution in using non-invasive scoring systems in NAFLD beyond highly selected study populations. *Am J Gastroenterol* 2017;112:653–4.
41 European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, Clinical Practice Guideline Panel, Chair,
et al. EASL clinical practice guidelines on non-invasive tests for evaluation of liver disease severity and prognosis–2021 update. *J Hepatol* 2021;75:659–89.
42 Rasmussen DN, Thiele M, Johansen S, *et al*. Prognostic performance of 7 biomarkers compared to liver biopsy in early alcohol-related liver disease. *J Hepatol* 2021;75:1017–25.
43 Madsen BS, Thiele M, Detlefsen S, *et al*. PRO-C3 and ADAPT algorithm accurately identify patients with advanced fibrosis due to alcohol-related liver disease. *Aliment Pharmacol Ther* 2021;54:699–708.
44 Rhodes FA, Cococcia S, Patel P, *et al*. Is there scope to improve the selection of patients with alcohol-related liver disease for referral to secondary care? A retrospective analysis of primary care referrals to a UK liver centre, incorporating simple blood tests. *BMJ Open* 2021;11:e047786.
45 Eslam M, Wong GL-H, Hashem AM, *et al*. A sequential algorithm combining ADAPT and liver stiffness can stage metabolic-associated fatty liver disease in hospital-based and primary care patients. *Am J Gastroenterol* 2021;116:984–93.
46 Liu Y, Liu S, Huang J, *et al*. Validation of five hepatic steatosis algorithms in metabolic-associated fatty liver disease: a population based study. *J Gastroenterol Hepatol* 2022;37:938–45.
47 Younossi ZM, Ratziu V, Loomba R, *et al*. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. *The Lancet* 2019;394:2184–96.
48 Harrison SA, Bashir MR, Guy CD, *et al*. Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *The Lancet* 2019;394:2012–24.
49 Eslam M, Ahmed A, Després J-P, *et al*. Incorporating fatty liver disease in multidisciplinary care and novel clinical trial designs for patients with metabolic diseases. *Lancet Gastroenterol Hepatol* 2021;6:743–53.
50 Thrift AP, Nguyen TH, Pham C, *et al*. The prevalence and determinants of NAFLD and MAFLD and their severity in the VA primary care setting. *Clin Gastroenterol Hepatol* 2023;21:1252–60.
51 Ayada I, van Kleef LA, Alferink LJM, *et al*. Systematically comparing epidemiological and clinical features of MAFLD and NAFLD by meta-analysis: focusing on the Non-Overlap groups. *Liver Int* 2022;42:277–87.
52 Alem SA, Gaber Y, Abdalla M, *et al*. Capturing patient experience: a qualitative study of change from NAFLD to MAFLD real-time feedback. *J Hepatol* 2021;74:1261–2.
53 Méndez-Sánchez N, Díaz-Orozco L, Córdova-Gallardo J. Redefinition of fatty liver disease from NAFLD to MAFLD raised disease awareness: Mexican experience. *J Hepatol* 2021;75:221–2.
54 Dellon ES, Liacouras CA, Molina-Infante J, *et al*. Updated International consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE conference. *Gastroenterology* 2018;155:1022–33.
55 American Diabetes Association. Standards of medical care in diabetes--2010. *Diabetes Care* 2010;33 Suppl 1:S11–61.
56 American Diabetes Association Professional Practice Committee. Classification and diagnosis of diabetes: standards of medical care in diabetes-2022. *Diabetes Care* 2022;45:S17–38.
57 Whelton PK, Carey RM, Aronow WS, *et al*. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/Apha/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol* 2018;71:e127–248.
58 Stone NJ, Robinson JG, Lichtenstein AH, *et al*. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce Atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *J Am Coll Cardiol* 2014;63:2889–934.