MAFLD: A consensus-driven proposed nomenclature for metabolic associated fatty liver disease

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Abstract

Fatty liver associated with metabolic dysfunction is common, affects a quarter of the population, and has no approved drug therapy. While pharmacotherapies are in development, response rates appear modest. The heterogeneous pathogenesis of metabolic fatty liver diseases and inaccuracies in terminology and definitions necessitate a reappraisal of nomenclature to inform clinical trial design and drug development. A group of experts sought to integrate current understanding of patient heterogeneity captured under the acronym nonalcoholic fatty liver disease (NAFLD) and provide suggestions on terminology that more accurately reflects pathogenesis and can help in patient stratification for management. Experts reached consensus that NAFLD does not reflect current knowledge and metabolic (dysfunction) associated fatty liver disease "MAFLD" was suggested as a more appropriate overarching term. This opens the door for efforts from the research community to update the nomenclature and sub-phenotype the disease in order to accelerate the translational path to new treatments.

Introduction

Why it is time to revise the fatty liver nomenclature?

Since the term non-alcoholic fatty liver disease (NAFLD) was coined by Ludwig and colleagues in 1980 to describe fatty liver disease arising in the absence of significant alcohol intake [1], the nomenclature and criteria for a diagnosis has not been revisited. Yet, this disease has risen in prevalence, with a major impact on clinical and economic burden to society, such that nearly 1 billion people globally are affected[2]. Of concern, NAFLD is increasingly recognised and diagnosed in children and adolescents[3], and this, when paired with the intimately associated hepatic as well as cardiovascular and oncological sequlae[4, 5], places an enormous burden on individuals, families and health-care systems[6]. The estimated annual medical costs directly attributable to NAFLD exceeds €35 billion in four large European countries (The United Kingdom, France, Germany and Italy) and $100 billion in the United States[7]. While reducing disease burden through prevention seems obvious, this have not been achieved. Further, while pharmacotherapies are expected to become available in the near future, none to date has been approved. Thus far, several phase 2b and phase 3 studies either have fallen short of meeting current required histologic endpoints, or have done so with a modest margin. Muted efficacy of various compounds in development are in part a reflection of the imprecise definitions and the lack of precision medicine including consideration of heterogeneity of the disease.

Despite these alarming data, the nomenclature of the disease and the criteria for diagnosis have not been updated to reflect our expanding knowledge. The heterogeneity of the population with NAFLD with respect to its primary drivers and co-existing disease modifiers, represent an important impediment to the discovery of highly effective drug treatments. The phenotypic manifestation of fatty liver diseases likely reflects the sum of the dynamic and complex systems

level interactions of these drivers; it follows that effective treatment requires that they be targeted with precision, based on a person's phenotype and genetic background[8, 9]. However, trial recruitment is currently based on histologic grading and staging – and that is a problem because many pathways lead to the same histologic phenotype, without dissection of the predominant pathogenic pathways [10, 11]. Perhaps not surprisingly, the response rates to current investigational agents range from 20 to 40% with a difference from placebo of 10-20% [8]. Thus, a "one size fits all approach" would seem inappropriate when dealing with a very heterogeneous liver disease.

From the patient's perspective, the term 'non-alcoholic fatty liver disease' not only trivialises the problem by including terms such as 'non', but is also pejorative as it introduces words such as 'alcoholic' potentially placing the blame on the patient as having caused their condition. It also implies that the treatment must entirely lie in the patient's hand. This has enormous implications on how industry and policy makers choose to allocate resources for tackling the syndrome, which clearly is a major cause of death. Lessons can be learnt from cardiologists, diabetologists, neurologists and oncologists who have successfully distanced the disease they are trying to treat from the underlying obesity, smoking, alcohol abuse and drug abuse. Some of these factors have high genetic predisposition. In support of this idea, a meeting organised by the European Liver Patient's Association (ELPA) with the European Commission in 2018 suggested that a change in nomenclature was one of their key requirements.

As a first step to tackle this challenge, revising the nomenclature and definitions of the disease is critical. Recently, concerns over the inaccuracies of the nomenclature of fatty liver disease have been raised by individual experts [12-14]. In prior work, we called for a consensus to consider these aspects [15] and in this review, an international panel sought to integrate epidemiological knowledge about disease progression that includes steatosis and steatohepatitis associated with metabolic dysfunction, with information about risk prediction derived from genetic and

phenotyping studies. We suggest a new nomenclature based on consensus voting by participants to describe the disease that will allow us to properly sub-phenotype and stratify patients, via the application of more precise genetic, anthropometric and metabolic phenotyping approaches. In turn, detailed phenotyping will translate into individualised risk prediction and prevention strategies, and improvements in clinical trial design.

Methods

Following discussions, an initial concept sheet was circulated to the panel of contributors. This revealed widespread agreement and consensus that it was time to revisit the nomenclature of metabolic fatty liver disease as a critical initial step for improved patient sub-phenotyping, clinical trials design and ultimately, for personalisation of medicine.

Subsequently, a manuscript was drafted, circulated to the panel, and feedback incorporated over several rounds of revision. To reach consensus on a nomenclature, the Delphi method was adopted in two rounds. This method is a recommended iterative process for use in the healthcare setting as a reliable means to solicit and distil the judgments of experts and to determine consensus via a systematic progression of repeated rounds of voting[16]. A "closed" electronic survey URL was sent to participants providing a unique link that could only be used once. Survey data were collected and managed using REDCap (Research Electronic Data Capture). In the first round of surveys members suggested one or more terms to describe metabolic fatty liver disease. In a second round (based on a summary of the experts' suggestions), participants were asked to vote on the suggested terminology. To ensure a robust and transparent process, anonymity of the participants was maintained.

Metabolic associated fatty liver disease: a heterogeneous phenotype

We now recognise that metabolic fatty liver disease is a phenotype with complex and disparate causes; the current terminology (NAFLD) represents an umbrella term for the multiple

underlying sub-types [17, 18]. This is evidenced by the wide spectrum of disease severity and natural history, as well as the substantial inter-patient variability across the spectrum. Although hepatic steatosis is highly prevalent, only a minority exhibit inflammatory injury at any time; more importantly, an individual can oscillate between steatosis and steatohepatitis even over a short timeframe [19]. In addition, while there is convincing evidence that liver-related complications (i.e., cirrhosis and cancer) are more likely in those with steatohepatitis, progression is far from inevitable[19-21]. Further, there is growing evidence that hepatocellular carcinoma (HCC) can develop in a fatty liver in the absence of cirrhosis[22]. Even among those with steatohepatitis, there appear to be individuals with apparent rapid-fibrosis progression and those with inherently slow-fibrosis progression [23]. Finally, disease evolution can be modified by exogenous interventions (for instance, life-style changes)[24], superimposed disease states (e.g., type 2 diabetes mellitus)[25], inherited predisposition[26], and can even "spontaneously" regress, as has been demonstrated in placebo group participants in treatment trials and by observational dual-biopsy studies in secondary/tertiary care settings [23, 27, 28]. Adding to the complexity, it is unknown if the propensity for metabolic fatty liver diseases progression can vary across the lifespan. For example, given the rapidly escalating prevalence of metabolic fatty liver disease in children and young adolescents, we still do not understand if their natural history follows a different trajectory from those who develop disease in adulthood, middle age or even old age [29].

Sources of heterogeneity

The heterogeneity in clinical presentation and disease course of fatty liver disease is likely influenced by multiple factors including age, gender, hormonal status, ethnicity, diet, alcohol intake, smoking, genetic predisposition, the microbiota and metabolic status. Thus, the final outcome will reflect the balance of these diverse inputs, each interacting with the other and modifying the ultimate manifestations and clinical course (**Figure 1**). It follows that effective

treatment will require systematic dissection of the pathways involved and likely multifaceted and personalised treatments[30, 31]. A brief summary of current knowledge about factors contributing to NAFLD heterogeneity is provided below.

Age and gender

NAFLD prevalence, the risk of hepatic and extra-hepatic complications, and the likelihood of overall and disease-specific mortality increases with advancing age [19, 21, 32, 33]. With ageing, substantial changes occur in the liver including a decline in hepatic blood flow, hepatic volume, and liver function, a reduction in bile acid synthesis and alterations in cholesterol metabolism, as well as a reduction in mitochondrial number with subsequent increases in oxidative respiration[34]. Cellular senescence has also been implicated[35, 36]. Furthermore, ageing is accompanied by changes in body composition, including a decrease in muscle mass, an increase in abdominal adiposity and ectopic fat deposition, with increases in insulin resistance and prevalence of the metabolic syndrome[37, 38]. Emerging evidence suggests that sarcopenia is associated with both NAFLD and NAFLD-related advanced fibrosis, even after adjusting for BMI and insulin-resistance[39, 40]. Presumably, ageing also captures greater exposure to the drivers, which result in steatohepatitis and fibrosis.

Equally, as recently reviewed [41], there is substantial sexual dimorphism in many aspects of fatty liver disease with regard to risk factors, prevalence, fibrosis pattern, and disease outcomes. Generally, prevalence tends to be lower in women predominantly at earlier disease stages, whereas, disease frequency increases in postmenopausal women [41]. Similarly, fatty liver prevalence is lower in post-menarchal girls than in boys[42]. Among postmenopausal women, those not on hormone replacement therapy (HRT) tend to have higher disease prevalence compared to those on HRT[43], and similarly, premenopausal women have less severe hepatic fibrosis and better survival compared to men and postmenopausal women[44, 45]. Consistently, a

longer duration of estrogen deficiency associates with a higher likelihood of fibrosis among postmenopausal women with fatty liver disease [46]. By analogy, studies of diet induced mouse models suggests that males develop more severe steatosis and liver histology compared to females [47, 48].

Although the mechanisms for these effects are not completely understood, sex differences in adiposity, metabolic risk factors and body fat distribution (which tends to shift towards abdominal obesity after menopause), likely play a role [49]. A recent study in mice from ~ 100 strains included in the hybrid mouse diversity panel (HMDP) demonstrated that multiple molecular pathways and gene networks implicated in lipid metabolism, insulin-signalling and inflammation show sexual dimorphism[50]. Similarly, another study demonstrated sexual differences in liver gene expression of regulators of multiple metabolic pathways using a mice computational model. Notably, some such as peroxisome proliferator-activated receptor PPARα, farnesoid X receptor (FXR) and liver X receptor (LXR), which are highly gender dependent, are currently being investigated as therapeutic targets for steatohepatitis [51]. A further study demonstrated gender-related pathways contribute to steatosis and fibrosis in male and female mice (males mainly inflammation and females mainly alterations of redox state), despite similar endpoints[52]. Clearly, sex and menopausal status influence disease outcomes and require stratification as treatment responses can vary substantially.

Ethnicity

Population-based data show ethnic differences in the prevalence of fatty liver; a recent meta-analysis demonstrated both NAFLD prevalence and risk of NASH were highest in Hispanics, intermediate in Whites, and lowest in Blacks. However, fibrosis risk did not differ according to ethnicity [53]. Metabolic fatty liver disease is also rapidly increasing in Asian populations [54]. Previous studies have demonstrated that Asians tend to accumulate liver fat at lower body mass

index (BMI) compared to those of other races[55]. The course of disease also appears to be more severe in Asians compared to non-Asians, and they tend to have more lobular inflammation and higher grades of ballooning compared to other ethnicities [56,57]. While data regarding fibrosis are scarce in the studies above, Asians tended to have a higher risk of fibrosis, while Africans were at lower risk compared to whites; this did not reach significance, perhaps due to sample size limitations [56, 57]. However, and notably, these biopsy-based studies might suffer from selection bias. For example, a community-based study in Hong Kong suggested that while NAFLD is detected in a quarter of the population, the prevalence of advanced fibrosis is low[58].

The reasons for racial disparities in fatty liver risk are not completely understood. Plausible explanations include variations in genetic predisposition, metabolic attributes, cultural and socioeconomic factors, dietary and exercise habits, access to health care as well as environmental risks. There are substantial differences in genetic heritage across ethnic groups; variation in the risk allele of the *Patatin-like phospholipase domain-containing protein 3* (*PNPLA3*) gene that is most frequent in Hispanics (49%), followed by non-Hispanic white (23%) and African Americans (17%) has helped, at least partially, to explain some of this ethnic variability[59-61]. In addition, the risk allele of the *PNPLA3* rs738409 polymorphism was found to be more common in East Asians than Caucasians [62]. Notably, because the effect size of fatty liver-related gene variants supports the existence of differences among races, the relative contribution of specific genetic and and environmental triggers (e.g. dietary factors) or modifying risk variants, toward disease pathogenesis is likely variable among ethnic groups (**Figure 2**).

On the other hand, there are marked racial/ethnic socioeconomic disparities that are likely also reflected in differences in multiple disease risk factors. For example, there is a clear difference between European and Asian populations with regard to insulin resistance and body fat distribution, as discussed later. There are also disparities in physical activity; in 2016, a report

including 1·9 million participants across 168 countries suggested that women in Latin America, south Asia, and high-income Western countries have the highest prevalence of physical inactivity[63]. Likewise, data from the NASH Clinical Research Network (NASH CRN) reported less physical activity, increased carbohydrate consumption and lower income levels in Hispanics compared with non-Hispanic white patients with NASH [64]. A role for gut microbiota could also be implicated, as discussed below.

Light and moderate alcohol use

Since its first description, metabolic has been considered distinct from alcoholic associated liver disease based on a cut-off of daily alcohol intake of 30 g daily for men and 20 g daily for women. The assumption underlying the cut off has been that alcohol intake below these thresholds does not induce hepatic steatosis or have deleterious impacts on liver disease progression and outcomes [65] .

Due to the high prevalence of adults with NAFLD who drink at least in moderation (~ 4 drinks/week)[66], there is now much interest in the influence of light and moderate alcohol use on the prognosis of NAFLD, with debate on the protective effects [67, 68] and perceived harms [69, 70]. More recently, there has been evidence for and against safe limits for alcohol consumption in the setting of NAFLD [71]. Some reports suggest that modest alcohol consumption, even after adjustment for previous heavy drinking, is associated with a reduction in vascular complications[67, 72] or has no impact[73]. Other studies have demonstrated that moderate drinking (2 drinks a day for women and 3 drinks a day for men) is associated with a reduced prevalence of NASH and advanced fibrosis[74]. In contrast some studies highlight that even low alcohol intake in those with a fatty liver is associated not only with increased risk of disease progression, but also for advanced liver disease and cancer [75, 76,77, 78] and decreased rates of improvement in steatosis and NASH [79]. The effect of alcohol use on liver disease evolution

likely has a dose-response, rather than a J-shaped association[80, 81], with a synergistic detrimental effect with the presence of metabolic syndrome [75, 77] as has recently been reviewed [74].

Dietary intake, gut microbiota and bile acids

For metabolic homeostasis, the neuroendocrine axis, dietary intake, muscle mass, physical activity, and the enterohepatic circulation, gut microbiota, bile acids and their related metabolites are intimately implicated in fatty liver pathogenesis (**Supplementary Figure 1**). The dietary pattern that characterizes the Western diet, including increased fat and fructose consumption that is fuelling the increase in obesity and fatty liver, is associated with a wide range of metabolic dysfunction, including insulin resistance and abnormal lipid profile[82]. In contrast, adoption of a Mediterranean dietary pattern is accompanied with a decrease in liver fat in patients with NAFLD and a decrease in cardiovascular risk[83, 84].

Microbiota composition can change rapidly and widely according to dietary patterns[83, 85] and the involvement of the gut microbiome in fatty liver and steatohepatitis in both mice and humans is well recognised [86, 87]. Emerging data suggest that the microbiome and gut microbiome-derived metabolites can predict advanced fibrosis and cirrhosis in NAFLD [88-91]. Gut microbiota are also implicated in regulating bile acids and their metabolites, which in turn regulates glucose, lipid and choline metabolism, and energy homeostasis [92]. Altered gut flora and intestinal permeability have also been shown in patients and murine models of NAFLD [93, 94]. This leads to increased circulating levels of bacterial products including lipopolysaccharide (LPS) as well as other bioactive compounds that may induce intra-hepatic activation of proinflammatory cells, hepatic stellate cells and hepatocytes via stimulation of toll-like receptors (TLRs; particularly 2, 4 and 9), a sensor for these products [95-97]. However, it remains challenging to disentangle the effects of diet and its associated consequences for liver disease, from effects mediated by diet-induced alterations to the microbiome, and to ascertain causality

under these same conditions. Notably, a role for human genetic variation and ethnicity in driving differences in microbiomes has recently been suggested [98-100] [101].

Obesity and metabolic health

Although obesity intimately associates with liver fat, not all patients with obesity develop metabolic fatty liver disease[2]. Whereas obesity can be classified as metabolically healthy obesity (MHO) and metabolically unhealthy obesity (MUO), with the former affecting about 45% of obese subjects, there is no consensus on a definition of metabolic health. Various definitions of metabolic syndrome include a combination of different metabolic components [102, 103]. Similarly, while insulin resistance is believed to play a pivotal role and is a pathophysiological feature of fatty liver[104] it has not been included in several definitions of metabolic syndrome. Notably, multiple large-scale cohort studies do not clearly support the notion that metabolically healthy obesity subgroups, at least as currently defined, are protected from cardiometabolic complications compared with those with a stable normal weight who are metabolically healthy [105-107]. Better classification based on molecular or genetic profiling could help dissect with high precision, metabolically favourable and unfavourable subtypes, with distinct metabolism, anthropometry and patterns of fat deposition, and likely differential responses to drug treatments [108]. On the other hand, ~ 30% of normal-weight individuals can be classified as metabolically obese normal weight (MONW) and they demonstrate an increased propensity for cardiometabolic risk; a fair proportion of patients with a fatty liver are also lean.

Current consensus suggests that the distribution and the overall health of fat, rather than its amount is likely the major determinant of disease risk. For example, higher amounts of visceral relative to peripheral and subcutaneous adipose tissue is associated with greater metabolic risk [109, 110] and is directly linked to liver inflammation and fibrosis, independent of insulin resistance and hepatic steatosis [109]. Sex, sex hormones (as discussed above), ethnicity and genes obviously

play important roles in determining the location and health of adipose tissue. There is for example, strong evidence that ethnicity is implicated in determining fat distribution and health [111]. Thus, abdominal and visceral adiposity are greater among Asians compared with Caucasians, and lower in Africans [112-115] as is insulin resistance despite an equal or lower BMI [116 117, 118]. Genetic variants also play a role in the regulation of fat distribution [119, 120,121], with "favourable adiposity" genes have been recently identified [103, 122, 123].

Although lipid accumulation in liver is a hallmark of NAFLD, there is emerging evidence that there is likely a variety of underlying mechanisms and routes for its development. For instance, a recent study has demonstrated that lipid composition in liver is very different in two proposed sub-types of NAFLD. In sub-type 1 based on insulin resistance, patients tend to have monounsaturated TAGs and free fatty acids enriched with ceramides in liver, while sub-type 2 based on carrying the *PNPLA3* risk genotype at rs738409, have polyunsaturated triacylglycerols (TAG)[124]. Similarly, another study suggested the existence of three NAFLD subtypes, with different metabolic phenotypes [125]. In another study, regions with steatosis demonstrated distinct lipid composition, predominantly in the form of a loss of arachidonic acid-containing intracellular phospholipids, compared to non-steatosis liver tissue[126]. A further report used RNAseq analysis identified molecular subtypes with distinct gene expression pattern clusters that are implicated in lipid metabolism, interferon signalling and immune system pathways, according to different histological scores[127]. In total, these new datasets emphasize that there are likely multiple NAFLD subtypes characterized by unique metabolomic signatures. Based on subtype, it is likely that treatment responses will vary and hence defining the metabolic landscape of an individual is likely important in clinical trial design.

Lean NAFLD

Currently, lean NAFLD, or NAFLD in lean individuals, is defined as hepatic steatosis with a BMI <25 kg/m^2 (or <23 kg/m^2 in Asians) in the absence of 'significant' alcohol intake.[128] Though first described in Asian populations, it is recognised that between 5% and 45% of patients with NAFLD are lean; even among Europeans, about 20% of patients are considered lean [129]. Although those with lean NAFLD have a better metabolic and histological profile compared to their counterpart obese subjects, their natural history is poorly defined, with some data suggesting they may have a worse outcome and accelerated disease progression[130, 131], while others suggest no difference or even better outcomes [132, 133]. More recent data proposes that lean NAFLD comprises a distinct pathophysiological entity from that in obese subjects, which extends beyond just simple differences in BMI. In that study, lean patients had distinct metabolic and gut microbiota profiles compared to their obese counterparts and lean healthy controls. Specifically, they had intact metabolic adaptation in response to an obesogenic environment via increased bile acids and FXR activity that likely helped them to maintain an obesity-resistant phenotype. Notably, either this adaptation tends to be lost with advancement of disease or the failure to adapt promotes disease progression. Other intriguing aspects from a subset of the patients suggests that they have a distinct gut microbiota profile, with enrichment of species implicated in the generation of liver fat, and a genetic profile with an increased prevalence of the *TM6SF2* risk allele[134], as also observed by another study[135]. Further studies will be required to explore whether the metabolic adaptation observed in lean NAFLD is seen in other subtypes of patients.

Familial Risk

Data from well-characterized cohorts of twins who underwent imaging to quantify liver fat and fibrosis has shown that both are heritable traits[136]. Furthermore, retrospective family-based studies show that there is familial aggregation of NAFLD and cirrhosis[137]. Consistently, a

recent prospective study including probands with NAFLD-cirrhosis and their first-degree relatives indicated that the risk of advanced fibrosis among first-degree relatives of patients with cirrhosis is 18%[138]. This is substantially higher than the risk of cirrhosis in the general population and points towards further sub-stratification of the population by family history of cirrhosis due to NAFLD.

Genetic variation

Genome-wide association and large candidate studies have identified multiple loci associated with NAFLD and NASH. While in depth discussion is beyond our scope, the topic has recently been reviewed [139, 140]. At least five common variants in different genes have been associated with NAFLD, namely *PNPLA3*, transmembrane 6 superfamily member 2 (*TM6SF2*), glucokinase regulator (*GCKR*), *MBOAT7*, and hydroxysteroid 17-beta dehydrogenase-13 (*HSD17B13*)[140]. Multiple other genes have reported associations, including polymorphisms in inflammatory, immune and metabolism-related, oxidative stress, adipokine, and myokine-related genes[139-144]. It is noteworthy however that all known variants explain only a small proportion of NAFLD, suggesting the existence of heritability factors that are yet to be defined [145]. Exploring the role of other types of genetic variation, gene-gene and gene-environment interactions, epigenetics, common variants that do not reach genome-wide significance, and rare and less common variants will help dissect the missing heritability[146,140, 147]. For example, a gene-environment interaction has been proposed for the *PNPLA3* variant with dietary patterns [148], increased intake of sugars [149], omega-6 poly-unsaturated fatty acids intake [150], obesity, and insulin resistance [151].

Of interest, described NAFLD-related variants show divergent metabolic effects. Multiple reports indicate an association of a genetic variant of *TM6SF2* (encoding p.Glu167Lys) with lower serum lipid levels and lower risk of coronary artery disease, but with increased risk of

fatty liver and advanced fibrosis [152-154], even in those with viral hepatitis[155]. Although early reports suggested that *PNPLA3* rs738409 has no association with the metabolic profile[156], more recent larger studies and a Phenome-wide association study (PheWAS) study indicate that it has similar metabolic effects to *TM6SF2* rs58542926 [157,158]. An association of *PNPLA3* rs738409 and *TM6SF2* rs58542926 with type 2 diabetes has also been demonstrated beside the known association of *GCKR* rs1260326 with diabetes [159]. Variants in *HSD17B13* and *MBOAT7* do not to date appear to have an effect on serum lipids, glycaemia or risk of coronary heart disease [160-163].

Epigenetic factors

Reversible epigenetic changes represent a plausible bridge between genes and the environment; their dysregulation is implicated in several diseases, including NAFLD [140]. Numerous microRNAs (miRNAs) have been linked to NAFLD. A recent meta-analysis demonstrated that in particular, miRNA-122, miRNA-34a and miRNA-192 could be biomarkers of fatty liver disease [164, 165]. miRNA-122 and miRNA-192 showed upregulation in NAFLD compared to healthy controls while miRNA-34a was upregulated in NAFLD and correlated with disease severity[164, 165].

Data on the role of long non-coding RNAs (lncRNAs) and other type of non-coding RNAs in NAFLD is limited. Some data suggests alterations in lncRNAs in NASH, such as a hepatic-specific lnc18q22.2 [166], a brown fat-enriched lncRNA 1 (Blnc1), [167] and metastasis-associated lung adenocarcinoma transcript 1 (MALAT1)[168]. A study using genome scanning with next generation sequencing has identified other candidates[169]. The role of lncRNAs in steatohepatitis remains to be further elucidated in larger cohorts.

Several studies show wide alterations in the methylation signature of hepatic as well as peripheral blood-derived DNA, including regulatory loci for key metabolic, inflammatory, and

fibrotic pathways, in patients with NAFLD. Some of these signatures appear to reverse following bariatric surgery [170, 171,172]. There is also evidence that DNA methylation can be a biomarker for fibrosis stratification in NAFLD [173] and that it regulates the expression of *PNPLA3* [174]. For example, hypermethylation of the PPARγ promoter can be used to identify patients with advanced fibrosis[173]. More recently, a series of studies have shown evidence of methylation of the key mitochondrial urea cycle enzymes carbamoyl phosphate synthase-1 and ornithine transcarbamylase enzymes resulting in a reduction in their function and hyperammonemia in NAFLD patients[175]. Hyperammonemia activates stellate cells and is associated with progression of fibrosis in NAFLD[176, 177]; treatment of hyperammonemia using ornithine phenylacetate prevented progression of fibrosis in an animal model, suggesting a potential novel metabolic therapeutic strategy[178].

Importantly, epigenetic mechanisms play a crucial role in foetal metabolic programming of liver fat [179, 180], with growing evidence that the earliest origins of NAFLD extend to *in utero* experiences. Data from animals suggest that a maternal diet high in fat triggers widespread epigenetic alterations in foetal hepatic DNA, accompanied by metabolic maladaptation that favours an increase in the risk of developing NAFLD in the offspring[181, 182]. Even paternal diet patterns and prediabetes increase the risk of diabetes in offspring [183]. Notably, these changes can be transmitted over generations, but can also be altered by exercise and lifestyle interventions [184-186]. Although data in humans are still limited, maternal obesity and patterns of infant nutrition are risk factors for the development of NAFLD in adolescence and adulthood. For instance, normal pre-gestational BMI and breast-feeding for more than 6 months reduces the risk of developing NAFLD in the mother during mid-life [187] and during adolescence in offspring [188]. Similarly, an increase in methylation of the peroxisome proliferator-activated receptor γ coactivator 1 (PGC1) gene that controls several aspects of

energy metabolism in liver [189] and in newborns, is correlated with increased maternal pre-gestational BMI [190].

Why do we need to consider NAFLD heterogeneity in clinical practice?

Impact on the performance of non-invasive assessment of fibrosis

Non-invasive fibrosis scores are commonly used to identify or exclude significant or advanced fibrosis in patients with fatty liver disease. However, a recent study suggested that the performance of scores such as the NAFLD fibrosis score (NFS) and fibrosis 4 (FIB-4) may vary across the life span, with lower specificity among older adults and lower accuracy in young adults[191]. The performance of non-invasive scores and the used Transient Elastography liver stiffness cut offs in different ethnic populations and in special subpopulations such as diabetic and obese individuals also need to be considered. For example, it has been shown that blood biomarkers are less accurate in South Asians compared to Europeans, regardless of metabolic indices [192]. As it is likely that blood-based biomarkers or imaging techniques will supplant liver biopsy for the diagnosis of disease in patients who would benefit from drug treatment, equally it implies that any future marker should be validated in more precisely defined cohorts. Thus, the consensus group suggests that the factors that shape the heterogeneity of NAFLD be considered when devising and applying risk-stratification scores and algorithms. This approach will continue to evolve as new contributors to disease variability are identified.

Impact on the development of clinically-relevant animal models

The complexity of human NASH is paralleled by the heterogeneity of animal models and the inability of these models to replicate the gamut of disease [193]. This represents both a barrier to the development of novel therapeutics but also an opportunity to better understand steatohepatitis pathogenesis based on different drivers of disease. Considering that NAFLD as

described today is not a single entity, exploring the overlapping features of preclinical models with subtypes of NAFLD may help in overcoming these challenges. For instance, it has been reported that the Methionine adenosyltransferase 1A (Mat1a) deficient mouse can recapitulate a subtype of human NAFLD [125], while mice fed a high cholesterol or methionine/choline deficient diet seem to recapitulate several features of lean NAFLD[194]. Despite the range of available models, there remains a need to develop improved *in vitro* and *in vivo* model systems.

Impact on clinical trials design and the ability to find treatments

The growing magnitude of NAFLD and the lack of effective drug treatments is reflected in intense clinical trial activity that has jumped from just eight in 2013 to over 300 ongoing in 2018[195]. Unfortunately, response rates remains modest, with <20-30% of participants demonstrating NASH resolution and fibrosis regression. This low response can be attributed to many factors, including heterogeneity in population selection, lack of stratification based on the underlying dominant driver mechanisms, and the Hawthorne (placebo) effect [8]. Therefore, the standard clinical trial design that does not take into consideration disease heterogeneity may not be the best option for studying a complex disease. Thus, future clinical trials will likely target patients with specific characteristics (sex, hormonal status, genetic predisposition, metabolic and microbiota signatures and the presence or absence of comorbid conditions) once the relationships between the characteristics and the treatment targets are understood. Such trial design will likely include rational combination approaches [31].

Considering alternative innovative trial designs might be a viable option (**Figure 3**). Recently, using overarching or master protocols designed to address multiple questions by investigating different drugs (more than one or two therapies that might even include direct comparisons of competing drugs) in different conditions (more than one patient type or disease), all within the same overall trial structure has been suggested [196]. Adaptive trial designs that provide flexibility

for altering one or more aspects of the basic features of the study design based on responses in earlier phases is also an option[197], although this will add substantial complexity to data interpretation. Notably, given the heterogeneity of NAFLD according to ethnicity and geographic region, regional stratification or performing separate trials in different geographic regions should be considered for key trials.

Is NAFLD the right name for metabolic liver disease?

How do the above considerations influence our thinking on the need to revise the definition and nomenclature for NAFLD? It is clearly the time to do this. The suggestion of this consensus focusses on four aspects.

First, NAFLD was described as a condition of "exclusion", which means that it exists only when other conditions such as viral hepatitis B and C, autoimmune diseases or alcohol intake above a particular threshold are absent. However, with advancements in our understanding of the underlying pathological processes, it is clearly a disease that must be defined by inclusion, rather than by exclusion. Further, given its high prevalence in most affluent populations, especially those consuming a westernized diet, fatty liver disease is recognized to coexist with other conditions such as viral hepatitis, autoimmune diseases and alcohol[198-200] and will have synergistic effects on disease progression [201, 202]. The nomenclature for fatty liver disease and criteria for diagnosis need to reflect this new knowledge.

Second, there remains debate about the safe limit of alcohol intake. Updating a diagnosis of NAFLD to zero or near to zero alcohol consumption as has been suggested by some is clearly impractical, as recently discussed[15]. Furthermore, there are significant methodological challenges in questionnaires used for measuring alcohol consumption including documenting prior and over life use, low amounts of intake, patient underreporting and recall bias, as well as marked variability in defining terms such as "social drinking" and "binging" in individuals

with NAFLD. Thus, linking metabolic fatty liver disease, a distinct entity, to alcohol in its name is problematic. Moreover, including the term "non-alcoholic" in the name is disappointing for abstemious patients and links this entity to the stigma of alcohol consumption. Confounding terms in the name of these diseases should be replaced as has already been done with primary biliary cirrhosis becoming primary biliary cholangitis, with sometimes redundant but more accurate and clear words, defining the entity[203]. More importantly, there is an urgent need to identify coexisting metabolic and alcohol liver disease so that they may be treated appropriately. This group of patients is distinct from those with pure or predominant alcoholic cirrhosis. Such patients are currently excluded from all NASH trials.

Third, though in clinical practice we segregate patients into those with NASH and those without, whether this is appropriate is a matter of debate. As we know, there is tremendous plasticity in metabolic liver disease over the life span and strong evidence that fibrosis is the major determinant of adverse outcomes[21]. Hence, the current classification may be misleading and perhaps metabolic dysfunction associated fatty liver disease should be considered similar to other chronic liver diseases with some degree of activity and a stage of fibrosis, without dichotomous stratification into NASH and non-NASH. From a pathological perspective, this will result in improved disease classification, at least in the context of liver biopsy[26].

Fourth, the heterogeneous nature of fatty liver diseases suggests that they cannot be considered or managed as a single condition with a "one size fits all" approach to therapy. Lack of consideration of heterogeneity impacts and detracts from our ability to precisely define the natural history of fatty liver phenotypes, to appropriately select for clinical trials that are weighted to demonstrate meaningful benefits, and to compare or pool results from the trials. For these reasons, an updated and appropriate nomenclature for the disease is the first step in the long path to deconvolution of disease heterogeneity.

Based on the above, participants agreed on the need for a revised and updated terminology; the bulk of respondents in the first round of survey suggested that the words **metabolism**, **fat** and **liver** be included in some form in the name. The final vote favouring Metabolic Associated Fatty Liver ± Disease (MAFL/MAFLD) (supported by 72.4% of participants). The second preference Metabolic Fatty Liver +/- Disease (MEFL/MEFLD) was supported by 17.2% (**Supplementary table 1**). Thus, the panel suggests we eliminate the term "NAFLD" from the lexicon and replace it with metabolic associated fatty liver "MAFLD". The term MAFLD represents the overarching umbrella of the common disease we treat and will have multiple sub-phenotypes, reflecting the dominant driver of disease. Obviously, many, if not most, patients will have overlapping contributions from other and distinct liver diseases that range from alcohol (regardless the amount) to viral hepatitis. The natural history of these latter groups is likely very different from those with pure metabolic dysfunction.

Conclusion

The outdated NAFLD/NASH acronyms, the criteria for diagnosis and a lack of adequate consideration of heterogeneity in risk profiles and treatment responsiveness represent barriers that hamper progress towards effective treatments. The consensus group has suggested an acronym (MAFLD) that we believe more accurately reflects current knowledge of fatty liver diseases associated with metabolic dysfunction that should replace NAFLD/NASH. In addition, we have identified gaps in current knowledge and highlight new strategies and tools to overcome the challenges (**Supplementary table 2**). A summary of suggestions is provided in **Table 1**. The group acknowledges the many investigators in the field who have made similar well-reasoned pleas for a change in nomenclature. This work also opens up for wider consultation with the public, patients, regulators and non-hepatology health care workers, the necessity for a nomenclature update. Future studies will allow us to further characterise and

sub-phenotype the disease and its drivers as a necessary prerequisite for the design of more appropriate clinical trials and for patient management and to consider the implications of the updated of nomenclature on clinical practice and public health policy (**Figure 4**).

Figures legends

Figure 1: Heterogeneity of metabolic associated fatty liver disease. The heterogeneity in clinical presentation and course of fatty liver disease is influenced by a multitude of factors including age, sex, ethnicity, alcohol intake, dietary habits, hormonal status, genetic predisposition and epigenetic factors, the microbiota and metabolic status. It is likely that there is a differential impact in the contribution of the various factors in any individual over time and among individuals that then shapes disease phenotype and course.

Figure 2: Inter-individual variation in the predominant drivers of metabolic associated fatty liver disease. Metabolic associated fatty liver disease is a complex phenotype shaped by the dynamic interaction of genetic predisposition with environmental factors and components of the metabolic syndrome. The effect size of genetic variants and the predominant drivers can exhibit marked inter-individual variation. As an example, disease in patient 1 is driven predominantly by environmental influences with less contribution from genetic predisposition; in patient 2, metabolic syndrome is the predominant driver, while disease in patient 3 is driven by genetic factors with a limited contribution from other factors. Identification of the predominant drivers in every patient can help in personalisation of medicine.

Figure 3: Innovative clinical trials for metabolic associated fatty liver disease. The substantial heterogeneity of patients with metabolic associated fatty liver disease and the limited responses to investigational targets in current clinical trials imply that innovative trial designs are required. Trial designs such as umbrella, basket and adaptive designs have been suggested to overcome the challenges. However, such designs add complexity to the trial analysis.

Figure 4: Implications of the proposed update to the metabolic associated fatty liver disease nomenclature. The growing burden of metabolic associated fatty liver disease in the

absence of effective therapies requires an updated process map to address the challenges. The first step is an update of nomenclature, as without precise terminology, neither patient care nor science can be adequately served. This update of nomenclature we expect will be a step towards further characterisation of disease heterogeneity. In turn, detailed phenotyping can guide the development of better preclinical models and identify novel therapies that are likely to be effective for particular patient subtypes, but not others. This will lead to improved clinical trial designs, allowing us to compare and pool results and thereby help reduce the impact of disease burden.

Supplementary Figure 1: Conceptual framework of metabolic dysfunction and pathogenesis of metabolic associated fatty liver disease. For metabolic homeostasis, the neuroendocrine axes elicits multiple and complex responses that orchestrate with caloric intake, muscle mass and physical activity as well as with the enterohepatic circulation, including gut microbiota, bile acids and their metabolites. These circles are interconnected at various levels. For example adiponectin signaling from adipose tissue to liver, the liver (FGF 21) to the central nervous system, the duodenum (Cholecystokinin) to the brain, etc. These various inputs are integrated in the liver. Dysfunctional homeostatic responses at any of multiple levels are implicated in the heterogeneous pathogenesis of metabolic associated fatty liver disease.

Table 1: Statements of the consensus panel

Nomenclature and definition of metabolic associated fatty liver disease (MAFLD)

- We suggest that the nomenclature of NAFLD should be updated to MAFLD.
- The diagnosis of MAFLD should be based on the presence of metabolic dysfunction not the absence of other conditions
- MAFLD can co-exist with other liver diseases
- A reference to alcohol should not be included in the MAFLD acronym.
- Patients with both MAFLD and a contribution from alcohol to their liver disease represent a large and important group that requires further investigation and characterisation.

MAFLD heterogeneity

- MAFLD is a heterogeneous entity
- Appropriate patient stratification must be considered when non-invasive fibrosis scores are developed and in clinical trial design
- Studies are required to map the landscape of MAFLD and to precisely define subtypes of the disease

Clinical trials for MAFLD

- Detailed patient stratification and tailoring clinical trial inclusion criteria based on drivers of disease will likely yield more informative and meaningful results
- Innovative designs for clinical trials and personalised combination therapy approaches will likely be required to overcome the challenges of disease heterogeneity and for optimal clinical efficacy.

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