



Review Article

Redefinition of Fatty Liver Disease from NAFLD to MAFLD through the Lens of Drug Development and Regulatory Science

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Abstract

Metabolic (dysfunction)-associated fatty liver disease (MAFLD) affects a third of the population and is a leading cause of liver-related death. Since no effective treatments exist, novel approaches to drug development are required. Unfortunately, outdated terminology and definitions of the disease are hampering efforts to develop new drugs and treatments. An international consensus panel has put forth an influential proposal for the disease to be renamed from nonalcoholic fatty liver disease (NAFLD) to MAFLD, including a proposal for how the disease should be diagnosed. As allies with the many stakeholders in MAFLD care—including

patients, patients' advocates, clinicians, researchers, nurse and allied health groups, regional societies, and others—we are aware of the negative consequences of the NAFLD term and definition. We share the sense of urgency for change and will act in new ways to achieve our goals. Although there is much work to be done to overcome clinical inertia and reverse worrisome recent trends, the MAFLD initiative provides a firm foundation to build on. It provides a roadmap for moving forward toward more efficient care and affordable, sustainable drug and device innovation in MAFLD care. We hope it will bring promising new opportunities for a brighter future for MAFLD care and improve care and outcomes for patients of one of the globe's largest and costliest public health burdens. From this viewpoint, we have revisited this initiative through the perspectives of drug development and regulatory science.

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Abbreviations: ADAPT, age, presence of diabetes, PRO-C3, and platelet count; ALEH, Latin American Association for the Study of the Liver; CAP, controlled attenuation parameter; CRN, Clinical Research Network; EMA, European Medicines Agency; FDA, USA Food and Drug Administration; FIB-4, fibrosis 4 index; LSM, liver stiffness measurement; MAFLD, metabolic associated fatty liver disease; MENA, Middle East North Africa; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NAS, NAFLD activity score; PIIINP, N-terminal pro-peptide of type III collagen; PRO-C3, type III procollagen.

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Introduction

Despite the global shift in the burden of disease from viral hepatitis toward nonalcoholic fatty liver disease (NAFLD), high morbidity and mortality is still experienced by these

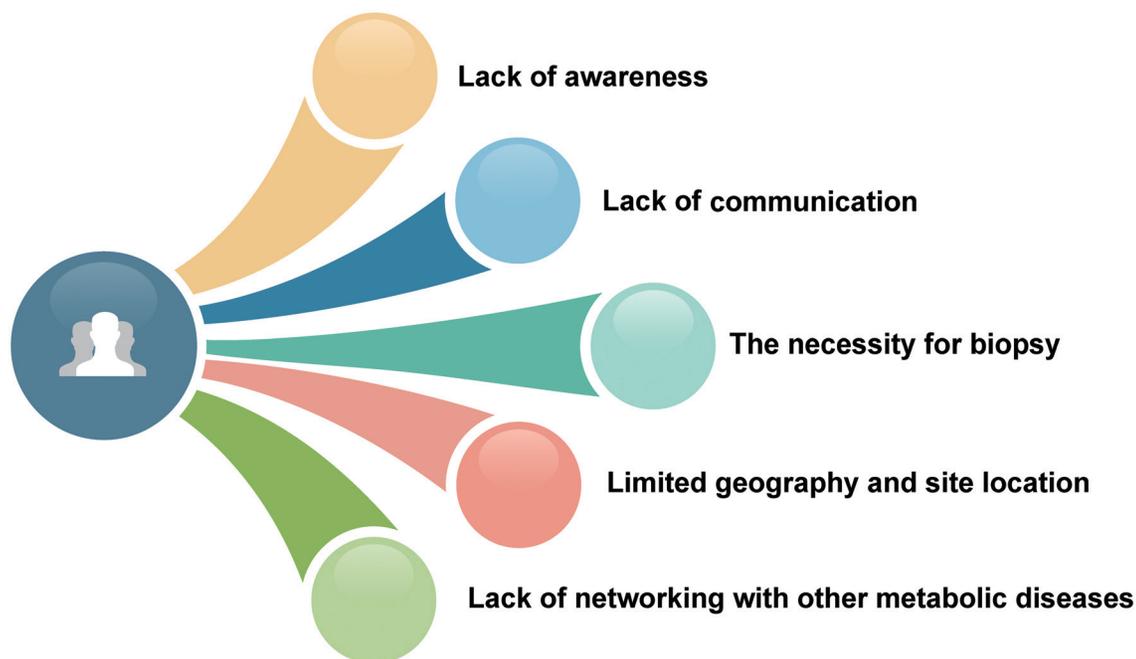


Fig. 1. Negative implications of the NAFLD term and definition on patients' recruitment and retention in clinical trials.

patients. It is a leading cause of liver transplants and hepatocellular carcinoma, and it is associated with exorbitant healthcare costs. At this time, there are no approved medications for it.¹ This is sobering, given the sharp contrast with the great victories that hepatology has witnessed in the treatment of viral hepatitis or as compared to other related metabolic diseases, such as type 2 diabetes and cardiovascular diseases, which have witnessed substantial evolution over the past few decades with the introduction of multiple new drug classes to the treatment landscape.

The rising prevalence of NAFLD and the lack of treatments has prompted many pharmaceutical companies to pursue novel treatments for this disease, with a significant escalation in drug development and randomized controlled trials in NAFLD.² However, most phase 2b and phase 3 studies have shown no or a modest margin of benefit. This has led many experts to wonder why so many NAFLD clinical trials fail.^{3,4} In addition, recruiting patients for these clinical trials is difficult, with high screening failure rates. For those trials relying on histology for enrollment, it is even more challenging. This complicated situation has a serious negative impact on the process of drug development for NAFLD.

Using *NAFLD* as a definition for fatty liver disease has unique limitations. First is the limited awareness of the *NAFLD* term. Second is that inclusion of patients into clinical trials is based on histologic grading and staging, which affects patient recruitment since NAFLD is a much broader disease when imaging or elevated liver tests may signal this disease. Third, the diagnosis of the disease, which relies solely on "exclusion," has a negative impact on case definition and target population when alcohol use and alcohol use disorder is a widely prevalent pair of conditions. Lastly, healthcare providers often do not consider the impact of the heterogeneity of the fatty liver disease on diagnostics modalities and therapeutic interventions. The adoption of a one-size-fits-all approach for such a heterogeneous liver disease is likely to be defective. Patient stratifications and examination for overlap of disease states are needed to prevent suboptimal performance of the investigational targets in clinical trials (Fig. 1).

In order for advancement to be achieved in the treatment of this disease, it is crucial to integrate multiple stakeholder efforts that involve the hepatology community, advocacy groups, regulatory agencies, patients, and pharmaceutical companies. Together, they need to find novel solutions to the problems posed above and apply innovative strategies for more effective clinical trial design. Recently, an international consensus panel put forth a novel redefinition for fatty liver disease, including shifting the name of the disease from *NAFLD* to *MAFLD*, as a new and more appropriate nomenclature, and providing a positive and inclusive set of diagnostic criteria of the disease to replace the previous exclusion-based set of diagnostic criteria.⁴⁻⁶ The proposal is generating momentum, with support from numerous liver regional societies, patients' advocacy groups, and nursing experts.⁷⁻¹⁷ In addition, multiple studies have revealed the utility of these criteria in identifying patients with significant hepatic fibrosis, cardiovascular disease, and chronic kidney disease.¹⁸⁻²⁰

Here, we intend to provide the readers with a viewpoint on this change through the lens of drug development and regulatory science. We will first discuss the challenges with the definition of the disease, then the failure of nonalcoholic steatohepatitis (NASH) trials, and lastly, we will cover how the new term and definition will improve outcomes for clinical trials and patients.

NAFLD term and definition: How does it impact patient recruitment?

There is universal recognition that patient recruitment is a predeterminate of success for clinical trials. A recent analysis of registered trials showed that 19% of clinical trials were closed or terminated early because they could not accrue enough participants.²¹ Even if trials do progress, they may experience significant delays due to difficulties in recruiting enough patients. Data suggest that despite the enormous patient population of those with NASH, the average rate of enrollment for NASH studies in the USA and Europe is just 0.1 patients per site, per month.²² This impacts on huge

time and cost challenges and has important consequences.

At least four major barriers arising out of the previous nomenclature *NAFLD/NASH* are identified to contribute to this low recruitment rate: (1) patients' low awareness of NASH and physician underestimation of patient population; (2) necessity of a liver biopsy, which has to show specific histological characteristic to diagnose NASH; (3) impact of the *NAFLD*-related stigma, which detracts from the expansion of recruitment centers geographically; and (4) impact on building networks with other metabolic diseases with a high risk of NASH. One way to achieve the required trial enrollment numbers is to be strategic, creative, and thorough in effecting a paradigm shift that will change current approaches.

Low awareness of NASH

Of the challenges that pharmaceutical companies face in enrolling patients into NASH studies, the biggest is the lack of awareness of the disease, even among patients most at risk, those with metabolic abnormalities, such as type 2 diabetes, obesity, and hypertension.^{23–26} Patients do not perceive the disease as a health challenge. A recent study showed that more than 80% of patients indicated they would not be concerned if they were diagnosed with *NAFLD* and would undertake no actions. For comparison, more than 90% of these patients indicated they would be very concerned if they were diagnosed with either hepatitis C or diabetes.²⁷ Worryingly, many physicians are also skeptical about the significance of *NAFLD*, and they do not perceive it as a priority in primary care,²⁸ which leads to underdiagnosing *NAFLD* in real-world settings.^{29,30} This suggests that healthcare providers find the current term for the disease hard to articulate or explain to patients, partly because it has a certain stigma.¹² In order to overcome this stigma and uneasiness in discussing the disease, over 30 patient advocacy groups across different disciplines—including liver, renal, diabetes, and obesity—have expressed their support to the *MAFLD* proposal to overcome these limitations.

NASH and the necessity for biopsy and histology scoring

A major barrier that hinders drug development and effective management of *NAFLD* is the necessity for liver histology, obtained through liver biopsy, for the diagnosis of NASH and to determine response to different therapeutic agents. This contrasts with type 2 diabetes, for example, where a simple blood test (i.e. HbA1c) is used to establish the diagnosis and assess treatment response.

Beside the technical problems with liver biopsy, including the relatively small tissue size and possibility for sampling error, the procedure is unpleasant for the patient, costly, and carries a risk of rare but potentially life-threatening complications. All of these challenges limit the use of liver biopsy as a tool for mass screening of patients.

Histology scoring of *NAFLD* involves the quantification of a qualitative assessment of the histology sample. For example, the scoring of balloon cells in the widely used NASH Clinical Research Network (CRN) system uses a 2-point score (as opposed to a 3-point score for steatosis or steatohepatitis) that does not specify the area (e.g., number of high-power fields) that need to be examined for the evaluation.³¹ Perhaps unsurprisingly, when the utility of NASH histology scoring in practice was recently evaluated in the EMMINENCE trial, both the inter- and intra-expert reader correlations were low. Inter-reader kappa scores ranged from 0.37 to 0.61, and intra-reader-weighted kappa scores ranged from 0.23 to 0.88. In addition, nearly half (46%) of patients whose quali-

fying histology scores were judged by at least one of three other readers did not meet the study histologic entry criteria as originally determined by a single reader. As the authors note, such inconsistencies in histologic reading diminish the apparent efficacy for a therapeutic drug.³²

It has been reported that only a minority (less than 25%) of academic gastroenterologists and hepatologists in the USA routinely perform liver biopsies in patients with presumed NASH.³³ A 2020 study in Germany showed that the biopsy rate of patients with *NAFLD* presenting at outpatient unit was low (13.6%).³⁴ Similarly, two recent studies in Egypt showed that over 95% of patients will decline liver biopsy to assess for NASH if they are asked, as they believe the disease is not serious.²⁷ Over 90% of physicians indicated that the acceptance rate for liver biopsy is substantially lower in patients with *NAFLD* as compared to that in patients with hepatitis C.³⁵ This indicates that the low acceptance rate for liver biopsy is a widespread phenomenon, regardless of the cultural background of the patient.

Patients enrolled in phase 3 clinical trials for NASH are usually required to have a *NAFLD* activity score (NAS) of 4 or higher and a fibrosis stage of F2 or higher by liver biopsy according to the NASH CRN. However, approximately half of the screened individuals fail to meet these eligibility criteria.^{36,37} In the FLINT and REGENERATE trials for individuals with non-cirrhotic NASH histology, this was the most important selection criterion, with 71% of pre-selected study candidates being excluded because they did not have a *NAFLD* NAS of 4 or higher and 63% of pre-selected study candidates being excluded because they did not have a fibrosis stage of F2 or higher.^{38,39}

In addition, the current histological endpoints of NASH clinical trials require both resolution of NASH without worsening of fibrosis and improvement of fibrosis without worsening of NASH during the treatment phase.⁴⁰ This implies the need for two liver biopsies within a 48- to 72-week period. Given the exclusion criteria of *NAFLD*, liver biopsy is also performed to rule out other differential diagnoses just to make the diagnosis of *NAFLD*.

Histological baseline criteria and the need for two liver biopsies represent the major hurdles for the recruitment of patients in clinical trials and could lead to selection bias, as individuals who make it through the hurdles might be not representative of the total *NAFLD* patient population. It is, therefore, crucial to identify efficient noninvasive parameters. Although we have many good markers for fibrosis, fat, and inflammation, and imaging modalities for fibrosis, it may take two, three, or four studies to focus on an implied histological diagnosis.^{41–43} We have many noninvasive markers for NASH, yet none are accepted by the USA Food and Drug Administration (FDA) or European Medicines Agency (EMA) for phase 2b and 3 trials, which still require two liver biopsies.⁴³ In addition, it is still a nonvalidated surrogate endpoint that is "likely" to anticipate clinical benefit (i.e. how a patient feels, functions, and survive). The implication being that registrational studies still need to have the phase 3/phase 4 design, which adds further complexity.

Fibrosis is the major determinant of liver-related complications and mortality.⁴⁴ Fibroblast activity drives fibrosis progression, organ function loss, and comorbidities.⁴⁵ The fibroblast is the principle promoter of extracellular matrix, which is expanded in all fibrotic disorders.⁴⁶ The fibrotic extracellular matrix consists mainly of collagens, which are produced by activated fibroblasts. This is important, independent of insults, as there are serological biomarkers that may quantify the overall fibrotic activity, which drives progression, independent of insult, and can objectively quantify the level of activity. All of this may be associated with outcome, response to treatment, and thus the quality of life of patients. For example, type III collagen, either quantified by N-terminal pro-peptide of type III collagen (PIIINP)

Table 1. Some medications tested in phase 3 clinical trials for NASH

Medications	Conditions for treatment	Current status in phase III trials
Obeticholic acid	Fibrosis due to NASH	Active; not recruiting
Selonsertib	NASH and fibrosis	Terminated
Cenicriviroc	NASH	Terminated
Elafibranor	NASH with fibrosis	Terminated
Rimonabant	NASH without diabetes	Terminated
Pentoxifylline	NASH	Completed
Resmetirom	NASH and fibrosis	Recruiting

Data was retrieved from <https://clinicaltrials.gov/> on February 16, 2021 by searching condition or disease and "nonalcoholic steatohepatitis."

or type III procollagen (PRO-C3),⁴⁷ have been directly associated with fibroblast activity, which predicts fibrosis progression,⁴⁸ response to therapy,⁴⁹ and relation to fibrosis stage in algorithms such as the ADAPT score (Age, presence of Diabetes, PRO-C3 [a marker of type III collagen formation], and platelet count).⁴¹ Elevated levels of type III collagen formation is the common denominator in most fibrotic diseases and have been reported in hepatitis B,⁵⁰ hepatitis C,⁵¹ MAFLD,⁴¹⁻⁴³ idiopathic pulmonary fibrosis,⁵² systemic sclerosis,⁵³ and chronic kidney disease.⁵⁴

Limited geography and site location

To access the required number of patients for developing large clinical trials, recruitment outside of traditional Western markets would be required. Despite its large population and having the highest prevalence of NAFLD worldwide,^{1,11} the Middle East North Africa (MENA) region has not been considered in most NAFLD clinical trials. The disease remains substantially underdiagnosed in the region, due to the severe social stigma associated with the word *alcohol* in the NAFLD term.¹¹⁻¹³

There are many preferential advantages for recruitment in the MENA region. These include the projected higher recruitment rate because of the large general population, and the productivity estimated as aggregated average number of patients per site is approximately 2-fold higher in the MENA region than developed markets in the West.⁵⁵ The MENA region has shown great capacity for drug development in the era of hepatitis C trials. Additionally, the patients in this region are typically study-naïve and are not recruited in competing clinical trials.⁵⁶ The costs of conducting a trial are usually considerably lower in the MENA region (including costs for selection of a trial site and patient enrollment compared to Western countries). The unique different ethnicities, the geographic isolation of subpopulations, and the high rate of consanguineous marriages suggest the region can contribute its distinctive gene pool of the MENA region to research.⁵⁶ Finally, the pharmaceutical market in the Middle East combined with Africa has one of the highest growth rates globally.⁵⁷ These numbers and reasons reflect that the region has a sizable population and unique opportunity not yet tapped. Overcoming the challenge of the NAFLD term would open new horizons for the market of drug development for fatty liver disease.

No link to other metabolic diseases

One of the major problems with the current NAFLD term is that it implies no link with metabolic diseases. Many stakeholders cite this as a barrier for educating healthcare provid-

ers outside of the hepatology community on NAFLD/NASH and for integrating NAFLD/NASH into public health policies and action plans on obesity and other related metabolic conditions.¹² The current NAFLD term and definition presents a barrier to diagnosis in primary care and non-hepatology settings, particularly in resource-constrained health systems.

Failure of so many NASH trials: Are current structures designed to fail?

Recent, largely negative, trials beg the question: why do so many NASH trials fail?^{3,4} (Table 1).

Apart from generic concerns in trial design, various reasons for failure are specific to the definition of the disease.

Relying on outdated case definitions

Prevention of cirrhosis and demonstrating a positive effect on well-defined liver outcomes are key clinical goals when considering a NASH drug development program. Therefore, for trials aiming to support a marketing application, it is important that patients with the greatest risk of progression to cirrhosis be enrolled. Among individual features, liver fibrosis has proven the best independent association with liver-related mortality.⁴⁴ The MAFLD new definition could identify patients at the highest risk of fibrosis, unlike the current NAFLD definition, which does not help identify the right target population.

Relying on histology rather than disease drivers

One of the main issues with the current definition of the disease is that phase 2b and 3 trial recruitment is based on histologic grading and staging.⁴ Because many pathways can lead to the same histologic stage, dissection of the predominant pathogenic pathways or the target pathway of the drug (and the stage of the disease at which it is administered) are needed.^{58,59} Unfortunately, stratifications based on NASH dichotomization do not recognize where an individual patient lies in this pathogenic continuum within liver injury. Due to the differing manifestations of NAFLD, several classes of drugs are required for NAFLD that can be tailored with personalized medicine for patients across the entire continuum of the disease.

Relying on a one-size-fits-all approach

The heterogeneous nature of fatty liver diseases suggest

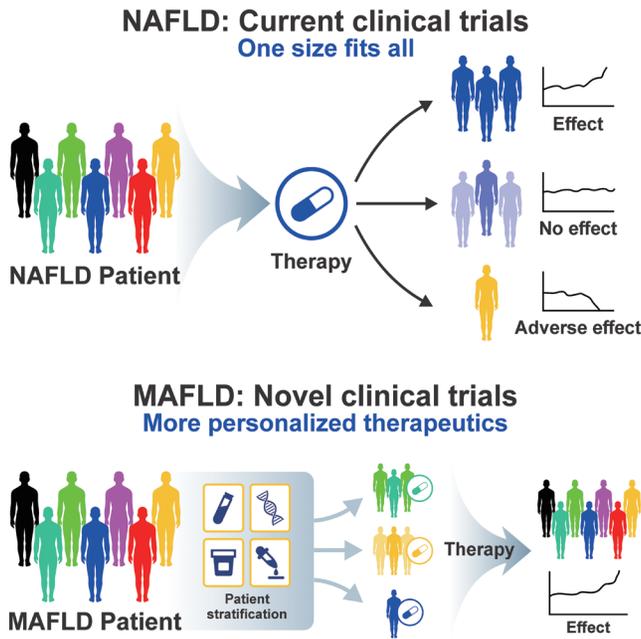


Fig. 2. One-size-fits-all approach of clinical trials in the era of NAFLD and proposed personalized trials in the era of MAFLD.

that they cannot be conceptualized as a single entity and managed using a one-size-fits-all strategy.⁴ Not considering heterogeneity, particularly for metabolic comorbidities may affect treatment response and may interfere with the ability to aptly select patients for clinical trials and evaluate therapeutic drugs. For instance, in the CENTAUR study, cenicriviroc showed a substantial variation in achieving the histologic endpoints in the diabetic groups compared to non-diabetic groups.⁶⁰ Similarly, in the FLINT trial, the effect of obeticholic acid was negatively affected by baseline hypertriglyceridemia.⁶¹

In addition, the disease heterogeneity may also affect the performance of non-invasive fibrosis diagnostic tools such as the NAFLD fibrosis score (NFS), fibrosis 4 index (FIB-4), transient elastography liver stiffness measurement (LSM), and controlled attenuation parameter (CAP), which may vary across the lifespan and between different ethnic populations, and in special subpopulations such as patients with diabetes or those who are obese.^{62,63}

To overcome the challenges described earlier, a stratified randomization approach, may be needed. Such an approach will require new definitions of the disease to be developed that pave the way for patient stratification (Fig. 2).

MAFLD term and definition: New solutions to fatty liver disease’s challenging questions

To change the paradigm in NAFLD/NASH, a novel approach is needed. Embracing real-world evidence and interrogating multiple stakeholders for their views (particularly patients) will allow us to better identify undiagnosed patients, engage primary care providers and non-hepatologists, and create market access and networking strategies that make sense for fatty liver diseases and the patients they affect.

To overcome these challenges, in 2020, an international consortium of 32 experts from 22 countries put forth an influential proposal to update the nomenclature of fatty liver disease associated with metabolic dysfunction from NAFLD to MAFLD. They also formulated a novel set of positive di-

agnostic criteria to replace the previous negative criteria.^{4,5} We strongly believe that a transformational change from NAFLD to MAFLD,^{4,5} with the accompanied new definition of the disease, will be an important initial step in achieving this and may circumvent many challenges faced in the era of NAFLD use.

Improve case detection and identification of target population

Emerging evidence shows that the diagnostic criteria in the MAFLD definition identify patients with significant hepatic fibrosis, cardiovascular disease, or chronic kidney disease,^{18-20,64} and those who would benefit from evaluating genetic risks for fatty liver⁶⁵ better than the previous NAFLD criteria. The utility of the MAFLD criteria have also been shown in patients with other diseases such as hepatitis B,⁶⁶ hepatitis C,^{67,68} human immunodeficiency virus,⁶⁹ celiac disease,⁷⁰ Gaucher disease,⁷¹ and myotonic dystrophy type 1,⁷² which need to be excluded to diagnose NAFLD. Not being able to concomitantly diagnose NAFLD and these diseases is another disadvantage to using the NAFLD definition since alcohol and these conditions are excluded, by definition!

Enhance patient recruitment

To overcome the limitation of recruitment, new tools and strategies are needed to more efficiently recruit patients. The correction of terminology may bring MAFLD to the visibility of other metabolic diseases.¹² Shifting to the MAFLD term and definition would enable a recruitment strategy to focus on patients with high risk factors and/or diagnosis. This model allows active engagement of diverse stakeholders and the building of an innovation network that would help to identify the large pool of patients with comorbidities such as obesity, type 2 diabetes, or other cardiovascular disease risk factors, who are at a greater risk for NAFLD/NASH. A recent study showed that changing from using NAFLD to MAFLD increased awareness of the disease among primary care providers and physicians in other specialties,³⁵ which can increase trial enrollment rates. Two other studies have demonstrated improved patient awareness with the new term MAFLD.^{27,73}

Use of this new term could lead to efforts to include MAFLD in public health policies and action plans on other related conditions and to launch shared health promotion campaigns. This would allow for establishing new multidisciplinary models of care and teams for MAFLD and foster the development of cross-specialty guidelines to help implement multidisciplinary care in practice.

As recently suggested by the Latin American Association for the Study of the Liver (ALEH), Chinese Society of Hepatology and the Sub-Saharan Africa position statement,^{9,14,16} simplification of the diagnosis of MAFLD would facilitate the education of primary care providers on MAFLD and develop clear care pathways. This would encourage more effective diagnosis at the community level and the screening of high-risk individuals for MAFLD in primary care and non-hepatology settings, with more efficient and likely cost-effective referral pathways. This would be crucial particularly in resource-constrained health systems.

Such change would enable an expansion of geographic regions for recruiting sites to areas such as MENA and Africa that are not considered at the moment. Based on the conceptualized diagnostic criteria of MAFLD and the reality of the real-world patient landscape, with the high prevalence of MAFLD and alcohol intake worldwide, we may need to consider a more pragmatic approach to target patients with

MAFLD with potentially a higher threshold of alcohol intake than used in the past.

Setting definitions for MAFLD based on “positive” criteria and excluding patients with fatty liver unrelated to metabolic dysfunction (with fatty liver but not MAFLD) will render study cohorts more homogeneous, increasing the likelihood of detecting a significant impact on clinical approaches targeting MAFLD.

Improve assessment of drug efficacy

Relying on biopsies makes diagnosing NASH a difficult task for physicians and patients, and it likely complicates the assessment of drug efficacy. Recent studies have raised concerns that the suboptimal reliability of liver biopsy evaluations is having a negative impact on clinical trials.³² This is usually more profound with pathological assessment of NASH compared to fibrosis. There is tremendous plasticity in metabolic liver disease over the life span, and patients can fluctuate from steatosis to NASH and vice versa over short spans of time, with a strong evidence that fibrosis is the major determinant of adverse outcomes.⁴⁴ To use an analogy, assessment of NASH is like measuring blood glucose in diabetes, while fibrosis is like measuring HbA1c. These factors create serious obstacles for pharmaceutical companies and clinical researchers working to develop treatments for this condition.

Again, redefinition of the disease and considering the disease as a continuum that can be assessed similar to other chronic liver diseases (with some activity and a stage of fibrosis) would help. It would refocus the attention to the need for identification and approval of drugs for the whole spectrum of the disease, as currently exists to treat hypertension or diabetes.

Create novel clinical trial design

The population of patients with MAFLD is diverse and complex.⁴ The proposed change to using the term MAFLD and its new definition would allow the consideration of alternative and innovative trial designs, such as umbrella, basket, and adaptive designs that could circumvent the aforementioned challenges.

Umbrella trial designs or master protocols allow multiple questions to be assessed and different drugs to be investigated in different conditions (more than one patient subtype or disease), within the same overall trial structure.⁷⁴ Emerging evidence suggest the presence of subtypes of MAFLD based on the diagnostic criteria; for example, those who meet the overweight/obesity criterion having different characteristics from those who meet the diabetes criterion.²⁰

Basket trials include designs to evaluate a particular drug for multiple diseases that share similar features or pathways (e.g., MAFLD, cardiovascular disease, and type 2 diabetes mellitus), paving the way for clinical trials for shared metabolic diseases.

Adaptive trial designs provide flexibility to adapt one or more aspects of the basic features of the study design based on early findings,⁷⁵ for example include more patients with diabetes or hyperlipidemia, if early interim analysis shows efficacy in this group (Fig. 3).

The importance of renaming NAFLD to MAFLD for the pediatric population

NAFLD occurs in approximately 40% of obese children and

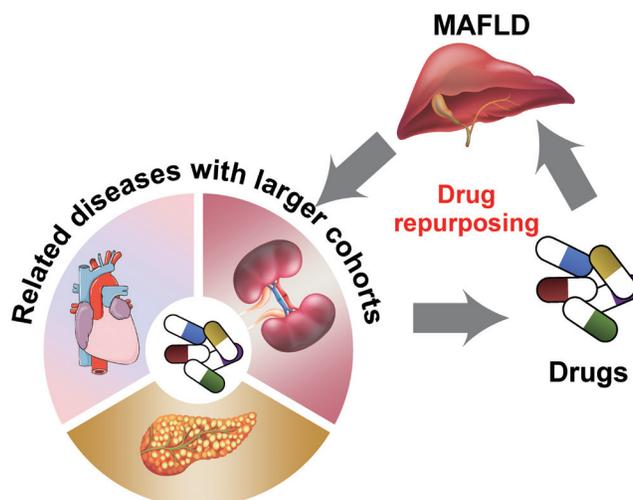


Fig. 3. Redefinition of fatty liver disease from NAFLD to MAFLD can guide drug repurposing in fatty liver disease. MAFLD is a multisystem disease with links to other metabolic disorders, such as diabetes, cardiovascular disease, and chronic kidney disease. MAFLD will bring fatty liver disease closer to other metabolic diseases and enhance understanding of the shared pathways and phenotypes between MAFLD and these related metabolic disorders that are usually investigated in larger cohorts, which can ultimately help in drug repurposing.

adolescents and in up to 10% of the general pediatric population.^{76–78} The pathophysiology of NAFLD/NASH in children is complex and multifactorial, may begin *in utero*, and is different from adult disease.^{79–82} But there are similarities to adults with NAFLD; children often have insulin resistance, central or generalized obesity, and dyslipidemia and are at increased risk of cardiovascular disease,⁸³ renal disorders,⁸⁴ and obstructive sleep apnea. As with NAFLD in adults, treatment is limited to lifestyle modification, which is rarely sustainable.

Despite the increased prevalence, its seriousness, and the unmet medical need of patients with pediatric NAFLD, very few clinical trials have been or are being conducted in this population. This starkly contrasts with the explosion of clinical trials available to adults with NAFLD/NASH. Presently on clinicaltrials.gov, there are no actively recruiting industry-sponsored interventional, multicenter, placebo-controlled clinical trials for pediatric NAFLD.

Thus, the term NAFLD may be an important contributing factor to this discrepancy, as this term is an even greater misnomer in children than in adults. First, excessive alcohol use, especially in younger children, is rarely a contributing factor or a consideration when assessing the etiology of a fatty liver, and second, inherited metabolic disorders often resemble and/or may also occur with NAFLD.⁸⁵ Using the term *nonalcoholic* when referring to a pediatric patient with a fatty liver is not only usually inaccurate, it is also likely to be a source of confusion to the family. This may be an important factor contributing to the difficulties in recruiting a pediatric NAFLD/NASH trial. When discussing a child’s diagnosis and potential trial participation, using the term MAFLD would likely be easier for the family to understand and to accept, and it may generate increased interest in clinical trial participation. Recent suggestions from experts encourage the change from NAFLD to MAFLD.⁸⁵

The prevalence of pediatric obesity is increasing at alarming rates. Using body mass index alone has become a less accurate means for distinguishing NAFLD from an underlying inherited metabolic disorder as the etiology of a fatty

liver.⁸⁵ Notably, recently, a novel set of diagnostic criteria for pediatric MAFLD was released.⁶

Conclusions

In this work, we revisited the redefinition of fatty liver disease through the perspective of drug development and regulatory science. As allies with the many stakeholders in MAFLD healthcare—including patients, patients' advocates, clinicians, researchers, nursing and allied health groups, regional societies, and others—we share the sense of urgency for change and will act in new ways to achieve our goals. Although there is much work to be done to overcome clinical inertia and reverse worrisome recent trends,⁸⁶ we believe that the MAFLD initiative provides a firm foundation to build on. It provides a roadmap for moving forward on more efficient care and affordable, sustainable drug and device innovation in MAFLD care. We hope it will bring promising new opportunities for a brighter future for MAFLD care and improve care and outcomes for patients of one of the globe's largest and costliest public health burdens.

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Conflict of interest

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Author contributions

All authors contributed to the study conception and design, data collection, and writing, revision and providing approval of the manuscript. Drafting of the manuscript (YF).

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