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# The paradigm shift from NAFLD to MAFLD: A global primary care viewpoint

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## Introduction

Half of the global overweight/obese adults population have metabolic-dysfunction-associated fatty liver disease (MAFLD)[1], with prevalence rising, even among non-obese individuals [2,3]. This increase is observed globally and mostly in low- and low-middle-income countries of Africa, Asia and South America and represents, a great worldwide burden on health care expenditures [4-7]. Lifestyle changes and healthy diet are still the cornerstone in the clinical management of these patients, since approved medications are presently lacking [4,8].

In clinical settings, most of patients with fatty liver disease are first identified and subsequently followed up in the community by primary care practitioners (PCPs)[9]. There is unequivocal evidence of the health-promoting influence of primary care and its role in prevention of illness and death [10]. In addition, in contrast to specialty care, primary care is characterised with a more equitable distribution as health care service for all populations[10]. In this context, primary care is central and may therefore help or hinder optimal chronic disease care. For PCPs, to provide effective and high quality care, it is crucial to integrate novel knowledge, skills, and favorable attitudes towards care that focuses on system reform and interactive patients and primary care team relationships [11].

In 2020, a group of international experts reached a consensus to comprehensively revisit the current definition of the fatty liver disease, including updating the nomenclature from non-alcoholic fatty liver disease (NAFLD) to metabolic-dysfunction-associated fatty liver disease (MAFLD) and more importantly introducing a simple set of "positive" diagnostic criteria for both adults and children [12-15]. The diagnosis of MAFLD is made if a patient has hepatic steatosis and is overweight or obese, has type 2 diabetes mellitus, or two or more of the following: central obesity by ethnic-specific waist circumference cutoffs; Blood pressure ≥135/85 mmHg or specific drug treatment; Plasma triglycerides ≥150 mg/dL or specific drug treatment; Plasma HDL-cholesterol <40 mg/dL for men and <50 mg/dL for women or specific drug treatment; Fasting

plasma glucose ≥100 mg/dL, 2-h post-load glucose ≥140 mg/dL, or hemoglobin $A_{1c}$ ≥5.7%; Homeostasis model assessment of insulin resistance ≥2.5; Plasma high-sensitivity C-reactive protein >2 mg/L. This call received a substantial support from hepatologists across the globe, hepatology scientific societies, nursing and allied health leaders, pharma and regulatory science experts, and patient associations [4,5,16-23]. Nonetheless, the new nomenclature has also triggered controversy[24], suggesting the need for a consensus-driven redefinition of NAFLD [25].

The high prevalence of fatty liver disease and its strong association with conditions traditionally managed in primary care like obesity, diabetes mellitus, hypertension and hyperlipidaemia, positions general practitioners/family doctors to lead the charge of providing high-quality treatment at the scale that is needed to combat the fatty liver epidemic. Therefore, it is crucial to understand PCPs perspectives regarding the proposed redefinition of fatty liver disease as well as the implications on primary care of patients. In fact, the way PCPs envisage the utility of this change will play a significant role in global consensus building. Thus, the aim of this paper is for an international team of experts in primary care to provide perspective regarding the proposed redefinition of MAFLD. We think that the main role of PCPs is raising awareness, diagnose cases, follow up and detection of complications. The role of PCPs is essential in detection and management of extrahepatic associations as well as screening and surveillance of HCC.

Currently, numerous systemic barriers exist for PCPs who are managing fatty liver disease. These include the diagnosis and screening, efficient referral pathway, restrictive policies, disease awareness and continuum of care. We believe that the transformational change from NAFLD to MAFLD can help to overcome some of these barriers and promote widespread active case findings of MAFLD and improvement of care.

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**Diagnosis and screening barriers**

NAFLD is woefully underdiagnosed in primary care, with multi-national and U.S. studies demonstrating the prevalence of recorded NAFLD diagnoses at 2% and 5% respectively, far below the estimated population prevalence of 25-30% [26,27]. Even in the presence of metabolic syndrome comorbidities and ultrasonographic or image testing reports of hepatic steatosis, NAFLD goes undiagnosed [28,29]. Reasons for these diagnostic errors are complex, with survey studies showing that NAFLD is not perceived as a priority in primary care, and there is a large knowledge deficit regarding NAFLD diagnosis and management. These phenomena result in substantial disconnect between current guidelines and real-world clinical practice [30,31]. Alarmingly, a recent study demonstrated that 71% of primary care patients had a non-invasive fibrosis score (Fibrosis-4 Index (FIB-4) and NAFLD Fibrosis Score (NFS)) in the indeterminate-risk or high-risk category for advanced fibrosis, reinforcing the clinical significance of knowledge deficits regarding diagnosis, although being the major determinant of complications [32]. Primary care uptake might be hampered by the limited involvement of primary care physicians in the development of clinical practice guidelines.

Apart from knowledge deficits, adherence to NAFLD clinical practice guidelines in routine primary care settings seems to be difficult for other reasons. These include (i) limited use or availability of complicated and expensive diagnostic tests required to diagnose NAFLD according to current guidelines; (ii) the time inconvenience of assessing alcohol consumption/dependence using different questionnaires with varying dimensions, and (iii) the complexity of algorithms theoretically designed to facilitate the management of NAFLD. In this context, according to the American Association for the Study of Liver Diseases (AASLD)[33], the diagnosis of NAFLD requires an extensive set of laboratory tests (mostly negative) and an experienced specialist, to exclude other liver diseases that requires high-level laboratory and clinical capabilities. It is clear that many of the investigations recommended in

clinical practice guidelines are not attainable for most patients, even in commonly used international cohorts such as the National Health and Nutrition Examination Survey (NHANES) cohort[13]. In addition, the economic costs for health systems and society for NAFLD, independent of its metabolic comorbidities are to be considered[34].

The complexity of the requirements for a diagnosis of NAFLD represents a substantial barrier for PCPs to begin screening or active case finding. Simplification of the diagnostic criteria for fatty liver disease suitable for a busy primary care environment are needed to enable treatment expansion into primary care at a larger scale[35]. These criteria need to be both useful and practical, and their content should be guided by input from clinicians involved in the daily care of these patients, particularly PCPs.

Another impediment is the amount of time required to obtain a detailed and accurate alcohol history, whereby patient management may be misdirected based on this dichotomization into alcoholic or non-alcoholic[13]. In addition, the low availability and utilization of sensitive direct alcohol markers (e.g. phosphatidyl ethanol) in primary, secondary and tertiary care settings in different regions of the world, makes interviews or questionnaires the only tool for discriminating between alcoholic and non-alcoholic fatty liver disease. However, there is often a high variability in reported and measured levels of alcohol (especially between male and female). Notably, a recent study of 834 Portuguese adults demonstrated that while fatty liver was detected in 37.8%, only 17.0% were diagnosed as NAFLD. Although these patients have some evidence of metabolic dysfunction, the threshold of alcohol intake falsely reduced the prevalence of NAFLD, thereby raising concerns on the utility of the current diagnostic approach in real world health care [36]. Additionally, the recommendations for the cut-off of alcohol consumption in NAFLD guidelines are based on the lowest-level evidence (primarily expert opinion) and on an arbitrary threshold. Notably, a recent study identified that alcohol consumption is associated with hepatic steatosis even in subjects with presumed

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NAFLD [37]. In addition, alcohol intake within the current defined safe limits can still lead to NAFLD progression [13,38,39] and increased risk of hepatocellular carcinoma (HCC) [40,41]. To complicate the matter, the current cut-off of alcohol intake does not take into consideration the substantial inter-individual variability in response to alcohol consumption, based on a myriad of variables, including: body mass index, alcohol producing gut bacteria [42] and the shared genetic basis between alcoholic and NAFLD [43,44]. To address these challenges, the removal of alcohol could simplify the diagnosis of NAFLD[12]. Furthermore, it will facilitate the evaluation of the contribution of different alcohol intake levels for the risk and progression of the disease. Notably, although the amount of alcohol intake is not a prerequisite for the diagnosis or exclusion of MAFLD, it is still important to screen for harmful alcohol consumption in these patients[12]. Similarly, testing for other causes of liver diseases, such as viral hepatitis might be required based o clinical judgment.

**Barrier to optimal referral pathway**

Specialty referrals are the intersection of care where patients, PCPs, and specialty physicians work to address the patients' medical problems. The referral process begins with the patient and/or PCP's decision to involve specialized medical services and takes into account multiple aspects. An integrated health-care referral pathway should improve the coordination of care. To achieve the goal of improving the quality of care delivered, we need to find the right balance between avoiding underdiagnosis as well as over-referral.

Identifying those patients with advanced disease who might benefit from early specialist intervention remains a major clinical challenge in primary care, because of the indolent asymptomatic nature of NAFLD and the varying presentations of the disease. Some patients with NAFLD are not identified until symptoms of decompensated cirrhosis necessitate hospitalization. On the other hand, it has been suggested that the vast majority of referrals of patients with NAFLD made to hepatologists could have been managed in primary care[45]. A

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fundamental problem with the NAFLD model of care is that the approach to diagnosis is basically hospital-centred (i.e. concentrated in large urban hospitals and accredited laboratories) and before long will overwhelm these specialist-based services [46].

Therefore, improving NAFLD diagnosis in primary care relies on harnessing a decentralized and demand-driven health care system, which itself focuses on efficient and effective health care delivery in primary care, especially in rural communities[47]. As diagnostic accuracy improves, developing and disseminating accessible and reliable tools to PCPs for identifying patients most likely to develop liver-related complications (e.g. fibrosis, cirrhosis, and hepatocellular carcinoma) will play a critical role in optimizing the specialty referral process[48]. Reducing inappropriate referrals represents an opportunity to reduce unnecessary investigations, inconvenience and even harm for patients, pressure on secondary care services and costs for the healthcare system; which will only continue to worsen with the rising prevalence of fatty liver disease.

**Barrier at policy level**

The notion of quality of care is complex, and quality improvement needs medical, contextual, and policy consideration[49]. Decisions to improve quality of patient care must be made with a good knowledge of the disease (medical evidence), but at the same time they must take into account patient-specific aspects of medical care (contextual evidence) and feasibility, equity, and cost effectiveness (policy evidence)[49].

At the policy level, issues of equity and cost effectiveness must be addressed. The concept of health equity has been described as overcoming differences in health care that are unfair, unjust unnecessary, and avoidable[50]. In low and middle-income countries, evidence suggests that the cause of inequalities may be a reflection of the failure of health care services to reach the most deprived areas. These health care systems are suffering from underfunding

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and fragmentation of public and private systems and poor engagement of informal workers, which together affect equity [51]. With rising income inequality, concerns have been raised that health inequalities are increasing and therefore may negatively impact the social stability of the community [52]. In this context, according to the current guidelines[33], the 'negative' diagnosis of NAFLD requires an extensive set of negative laboratory tests (i.e. full aetiology screen), which are not feasible in limited resource settings; thereby hampering extrapolation to regular patient care and aggravating health inequity[53]. For example, there are substantial variations in available diagnostic capabilities when comparing rural health centers to urban ones. Diagnostic laboratories are often poorly resourced and sparsely distributed in rural regions [54,55]. In addition, in 2019, the World Health Organization estimated that out-of-pocket expenditure exceeded 40% of total health expenditure in low income countries [56]. Improved access may be achieved by using tests that do not require advanced laboratory support.

In addition, in the context of finite healthcare resources, a goal of healthcare systems cannot be to maximize health gain without any consideration of cost. The cost-utility—including patient preferences and values, with special emphasis on equity—is critical part of improving patient care. To realize the relevance of this, various studies have illustrated that the cost-effectiveness of a diagnostic test or criteria is the most important factor for health care utilization[57,58]. This difficulty implies that the adoption of less complex diagnostic criteria and approaches particularly for such highly prevalent disease as fatty liver disease should consider all aspects of primary care delivery and expand capacity in low-income settings. A recent study suggested that one of the top five ordered laboratory tests by volume is the "basic metabolic panel" including glucose and lipid profile, similar to that incorporated in the diagnostic criteria for MAFLD[59].

Therefore, ensuring fatty liver disease care is equitable, sustainable, and efficient on all counts is impossible if the status quo is not significantly challenged to reduce the impact of

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inequalities on vulnerable populations. Simplification of diagnostic criteria, which can be incorporated into "usual care" at low cost, is likely to be the first essential step toward the goal of reducing fatty liver disease-related morbidity and mortality; especially in low-income countries.

**Barrier for awareness**

The gaps in NAFLD identification in primary care likely reflect the gaps in PCPs knowledge and awareness of relevant practice guidelines. A previous study found that nearly half (40%) of PCPs surveyed in this study were not familiar with clinical published guidelines for NAFLD management, which is translated into paradoxical screening practices [60]. Similarly multiple other studies again found substantially low rates of awareness and screening for NAFLD in their surveys of PCPs [61,62] [63]. Another study reported that 83% of PCPs wanted more education on the topic[64]. There have been calls for greater awareness of fatty liver disease among PCPs so that diagnosis is not delayed and patients can receive early and appropriate interventions, so we can bridge the gap between evidence and practice.

**The change from NAFLD to MAFLD**

Based on a transformational shift from NAFLD to MAFLD, the current MAFLD care model can be streamlined. Simplification of care will potentially have multiple benefits including better allocation of resources to diagnose more patients (expanding access and coverage). Improving identification of patients at risk of disease progression and acceleration of treatment initiation (linkage to care). Reduction in complications among high-risk populations and lowering the long-term medical costs of complications, such as those associated with advanced liver disease, extrahepatic complications of MAFLD, or liver transplant (reducing burden). Improvement in patient adherence, facilitation of task-shifting/patient management by PCPs (optimising referral pathway).

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**Strengthening the role of primary health care and task sharing**

MAFLD criteria represent a pragmatic, real world approach to identify patients with fatty liver disease in primary care using simple tests. Compared with the standard NAFLD pathway of care involving specialist review and complicated laboratory-based testing, the MAFLD diagnostic model has the potential to offer a low-cost and easily accessible strategy which can be initiated in primary care and would be ideal for routine clinical use (**Figure 1**).

The beneficial effects of these criteria is projected to lead to significant improvements in referral practice which will include a reduction in the proportion of unnecessary referrals of fatty liver disease cases while at the same time improving early case identification and the detection of patient at high risk that may enable better use of effective management interventions and hence a reduced disease burden. In concert with this, numerous recent studies have consistently demonstrated that MAFLD diagnostic criteria are practical, simple and outperform the old NAFLD criteria in identifying patients at high-risk of hepatic fibrosis as well as extra-hepatic manifestations such as cardiovascular disease and chronic kidney disease, and mortality. Similar findings were observed when MAFLD criteria were applied to patients with viral hepatitis B and C[65-67 68-72]. A similar simple care system based on simple diagnostic criteria and education, with occasional support from hospital-based clinicians for other diseases has been developed and tested in various low and middle-income countries. This approach has been shown to improve population health outcomes and reduce all-cause mortality and is a cost effective strategy for achieving universal health coverage [73,74].

**Improving disease screening and diagnosis**

Screening and diagnosis need to reach larger numbers of individuals with fatty liver disease to combat the growing burden of the disease. Although, metabolic dysfunction is a well established prominent feature of fatty liver disease pathogenesis, screening for fatty liver

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disease among high-risk groups has largely been unsuccessful. This because of, among other reasons, the stigma associated with alcohol, the asymptomatic course of the disease and the reflection of nomenclature on trivialization of disease, the lack of awareness of active case finding recommendations, and low health care engagement of the most at-risk populations, as current nomenclature does not imply any link to other metabolic diseases[17,75]. In contrast, MAFLD as a term clearly places the disease in the camp with other metabolic diseases, such as diabetes, chronic kidney disease and cardiovascular disease[43,66,76]. Blood based markers of hepatic steatosis such as fatty liver index (an algorithm based on body mass index, waist circumference, triglyceride level and gamma glutamyltransferase level) could be helpful to overcome the hurdle of lack of imaging modalities in primary care. A recent study of 135,436 patients showed that fatty liver index have higher diagnostic accuracy for detection of hepatic steatosis in MAFLD. Further biomarkers with even higher accuracy will be needed[77]. This change will facilitate the adoption of multiple health behavior change interventions for primary prevention by reducing exposure to potentially harmful lifestyle and environmental risk factors and offers the best option for reducing the large and increasing burden of metabolic multimorbidities. Specifically, this alignment of nomenclature may heighten the likelihood affected patients receive weight-loss and cardiovascular risk reduction management (**Figure 2**).

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**Improve disease awareness**

With the struggling in increasing the awareness of NAFLD for decades, a recent study demonstrated that changing from using *NAFLD* to *MAFLD* increased awareness of the disease among primary care providers and physicians in other specialties[78]. Two other studies have shown improved patient awareness with the new term MAFLD[79,80]. This demonstrates the success of the MAFLD criteria in the context of routine clinical care despite moderate adoption and suggests that the results are generalizable. Capitalising on this momentum with more widespread use of the MAFLD criteria could result in even greater improvements in care of MAFLD patients[81].

**Optimising the care continuum for MAFLD**

Unfortunately, the fact that existing NAFLD diagnostic criteria are based on the exclusion of other liver diseases entails a great barrier for consideration of holistic and multidisciplinary management of patients with liver diseases as well fostering research exploring the interaction between fatty liver disease and other liver diseases. This could result in miss-classification, under-reporting and suboptimal care of these patients, particularly with growing evidence that patients with MAFLD and other concomitant liver diseases including viral hepatitis B and C, alcohol intake, or autoimmune hepatitis have more aggressive liver injury compared to those with each disease alone[70,82-85]. In fact, an international expert group raised the importance of consideration of MAFLD in the hepatitis C elimination effort[86]. Notably, multiple recent studies demonstrated that in patients with concomitant CHB or CHC, the MAFLD criteria are superior than the old NAFLD criteria for identifying patients with more severe liver injury including steatosis, fibrosis and elevated liver enzymes [87]. On the other hand, the shift to MAFLD will allow for a multidisciplinary clinic featuring input from primary

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care, hepatology, endocrinology and cardiology for improving both liver-related and cardiometabolic health [35].

**Conclusion**

This viewpoint illustrates how NAFLD definition represents a substantial barrier towards full implementation of the chronic care mode at the primary care level. In fact, since the PCPs play a crucial role in the early detection of fatty liver disease and the prevention of clinical progression and potential complications, their appropriate evaluation of fatty liver disease is paramount. The revolutionary simplification in diagnosis and evaluation that the MAFLD definition is providing, we believe may facilitate the implementation of effective fatty liver disease management, prevent overdiagnosis and overtreatment in secondary and tertiary care but also reduce underdiagnosis in primary care by PCPs, reaching to a balance on behalf of public health. This change will support PCPs to continue to contribute to health and wellbeing of patients in the community, based on accessibility, equity, and respect for the authenticity of the patient. We have argued that the change to the MAFLD definition has three major attributes and in particular (i) medical; improvement in the capacity to prevent, cure, and care for diseases; (ii), contextual; making clinical guidelines work in daily practice; and (iii), policy to contribute to equity on a worldwide scale. The pivotal question remains how to overcome the clinical inertia and settle any debate. A global consensus without veto players that integrates views of multi stakeholders and involves active participation of both clinicians (especially PCPs) and more importantly, synthesis of the available scientific evidence is the key going forward.

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**Figures legends**

**Figure 1: Redefining of fatty liver disease would help strengthening the role of primary health care and task shifting**

**Figure 2: Redefining of fatty liver disease would help improving disease screening and diagnosis**

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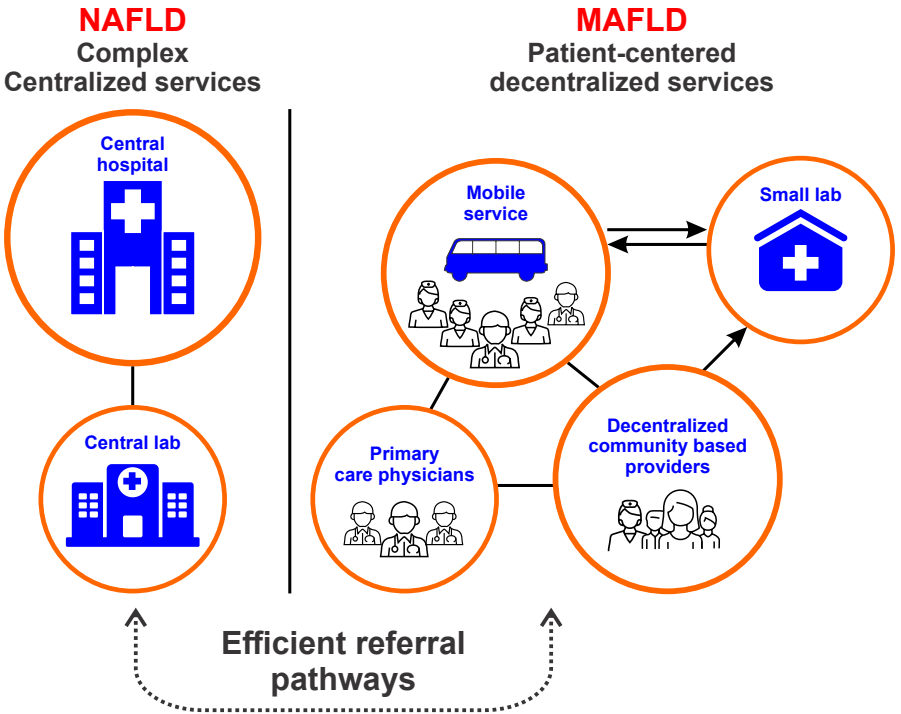
NAFLD
Complex
Centralized services
MAFLD
Patient-centered
decentralized services
Central hospital
Central lab
Mobile service
Small lab
Primary care physicians
Decentralized community based providers
Efficient referral pathways

# Redefining fatty liver disease