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REVIEW

Perspectives on Precision Medicine Approaches to NAFLD Diagnosis and Management

Amedeo Lonardo · Juan Pablo Arab · Marco Arrese

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ABSTRACT

Precision medicine defines the attempt to identify the most effective approaches for specific subsets of patients based on their genetic background, clinical features, and environmental factors. Nonalcoholic fatty liver disease (NAFLD) encompasses the alcohol-like spectrum of liver disorders (steatosis, steatohepatitis with/without fibrosis, and cirrhosis and hepatocellular carcinoma) in the nonalcoholic patient. Recently, disease renaming to MAFLD [metabolic (dysfunction)-associated fatty liver disease] and positive criteria for diagnosis have been proposed. This review article is specifically devoted to envisaging some clues that may be useful to implementing a precision medicine-oriented approach in research and clinical practice. To this end, we focus on how sex and reproductive status, genetics, intestinal microbiota diversity, endocrine and metabolic status, as well as physical activity may interact in determining NAFLD/MAFLD heterogeneity. All these factors should be considered in the individual patient with the aim of implementing an individualized therapeutic plan. The impact of considering NAFLD heterogeneity on the development of targeted therapies for NAFLD subgroups is also extensively discussed.

Keywords: Cirrhosis; Fibrosis; Metabolic syndrome; NAFLD; NASH; Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Steatosis

A. Lonardo (✉)
Department of Internal Medicine, Azienda Ospedaliero-Universitaria, Ospedale Civile di Baggiovara, 1135 Via Giardini, 41126 Modena, Italy
e-mail: a.lonardo@libero.it

J. P. Arab · M. Arrese
Departamento de Gastroenterología, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

J. P. Arab · M. Arrese
Departamento de Biología Celular y Molecular, Centro de Envejecimiento y Regeneración (CARE), Facultad de Ciencias Biológicas, Pontificia Universidad Católica de Chile, Santiago, Chile

Key Summary Points

Precision medicine tries to identify the most effective approaches for specific subsets of patients based on their genetic background, clinical features, and environmental factors.

Nonalcoholic fatty liver disease (NAFLD), now renamed metabolic (dysfunction)-associated fatty liver disease (MAFLD), encompasses the heterogenous alcohol-like spectrum of liver disorders in the nonalcoholic.

This review article aims at envisaging useful clues to implementing a precision medicine-oriented approach in NAFLD/MAFLD research and clinical practice.

We discuss how sex and reproductive status, genetics, intestinal microbiota diversity, endocrine and metabolic health, as well as physical activity may interact in determining NAFLD/MAFLD heterogeneity.

We also attempt to envision a tailored management approach based on each of the factors outlined above.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.14113481.

INTRODUCTION

Personalized medicine is part of the "4P Medicine" approach, which intends to advance clinical care to a preventive, predictive, personalized, and participatory model [1, 2]. The expression "personalized medicine" is often used interchangeably with "precision medicine" which, in its wider definition, focuses on identifying the most effective approaches for specific subsets of patients based on their genetic background, environmental factors, and lifestyle features including their social and environmental profile. Precision medicine approaches promote a deeper understanding of the disease process in any individual patient. This is believed to better predict clinical outcomes and maximize the therapeutic benefits of a given treatment while keeping adverse effects to a minimum [3]. To this end, a more accurate and refined characterization and stratification of disease is needed while assessing individual patient pathologies by applying multiple molecular tools (e.g., omics, genetic testing, microbiome assessment) and advanced imaging techniques as well as a detailed evaluation of the patient's clinical features [4]. Indeed, it has recently been proposed that precision medicine paradigms should also be applied to the hepatology arena following behind other medical disciplines including oncology and genetic diseases [5–8].

NAFLD, the acronym of nonalcoholic fatty liver disease, is a definition originally proposed by Shaffner and Thaler in the mid 1980s based on an earlier definition coined by Ludwig et al.: nonalcoholic steatohepatitis (NASH) [9]. NAFLD, of which NASH is the most rapidly progressive histological variant, is an umbrella definition which includes the gamut of fatty liver syndromes spanning simple steatosis through NAFLD–hepatocellular carcinoma (HCC), which usually occur via NASH and NAFLD-related cirrhosis [10]. As a universally widespread condition and owing to a large variety of hepatic and extrahepatic manifestations, complications, and concurrent conditions, NAFLD has been the subject of intensive research over the last 40 years [9, 11–13]. Over time, the adjective "nonalcoholic" [9], however, has been much criticized for a variety of reasons, notably including the fact that it identifies something for which it is not rather than something for which it is [14]. Following pioneer attempts, several authors have proposed to rename NAFLD, the most recent of such proposals resulting in the definition of this disease

as MAFLD, i.e., metabolic (dysfunction)-associated fatty liver disease, which aims at emphasizing the strong connections of NAFLD with diabetes and obesity in most individuals [15, 16]. Although the initiative to rename NAFLD to MAFLD has generally been welcomed by the scientific community [17–19], the suggestion to change the name has been felt to contain some elements of prematurity and a debate is presently ongoing [20, 21].

Recent advances in our knowledge of NAFLD genetics and in systems biology have fueled the potential application of precision medicine approaches to this disease [5, 6, 22]. In the present review article, we aim at providing a critical overview of selected research topics that relate to a more precise sub-phenotyping of patients with NAFLD based on sex and reproductive status, genetics, intestinal microbiota diversity, endocrine and metabolic status, as well as the degree of physical activity. Proper consideration of these factors may lead to more precise diagnostic approaches that, in turn, could be translated into improvements in efficacy and safety of both conventional and experimental therapeutic strategies.

RATIONALE AND METHODS

The historical backdrop of the difficulties in identifying the best nomenclature to designate NAFLD (reviewed in [14]) reflects itself in disappointing therapeutic results. Decades of intensive research have indeed led to an improved understanding of disease epidemiology and pathogenesis [9, 23–25] but this has not yet translated into success in identifying effective drug treatments. In fact, a significant portion of investigational drugs have failed in showing efficacy even in late phase randomized controlled trials (RCTs) [26, 27]. While myriads of explanations may, in principle, account for this therapeutic failure, it should constantly be kept in mind that the pathogenesis of disease is multilayered and extraordinarily composite [28, 29], which may explain the variability, in the individual patient, of NAFLD clinical course and outcomes, from a benign to a progressive and deadly disease, and from hepatic to extrahepatic manifestations and complications.

The recent proposal to rename NAFLD to MAFLD [15, 16] has fueled expectations that this change in nomenclature may help, or at least contribute, to better identifying more homogeneous patient subgroups to be included in future clinical trials [15]. However, while consensus is growing, evidence remains lacking. In the meanwhile, we consider that patients with NAFLD included in clinical trials should be evaluated with the most in-depth approach possible aimed at trying to define more homogenous subgroups of patients that may better respond to novel investigational drugs.

Epistemology defines the logical foundations of scientific thinking. From the epistemological point of view, there are two main approaches: the inductive theory and the deductive theory [30]. The inductive method is based on the systematic observation and classification of findings. These are critically examined and, based on whether they are consistent/inconsistent with the interpretative hypothesis, they will lead to either accepting or rejecting the hypothesis [30]. Stated in short, this approach implies that "observing and thinking" (*observatio and ratio* in Latin) is sufficient to reach a medical diagnosis. In contrast, the deductive method is based on a hypothesis-driven approach which will inform the diagnostic flowchart aiming to either prove or reject the originary hypothesis. In short, the deductive method may be likened to an electric torch that the clinician directs in order to shed light on the most obscure spots she/he wants to focus on [30]. These general principles of medical epistemology may also be applied to NAFLD, an arena in which individual variability in response to metabolic stress and in liver tissue repair are acknowledged determinants of heterogeneity in disease pathobiology and susceptibility to hepatic fibrosis due to the multiphasic pathogenesis of NAFLD/NASH [28, 31, 32]. Severity of hepatic fibrosis, in its turn, is a key player in the course of hepatic and extrahepatic diseases given that liver-related events predominantly affect patients with NAFLD-cirrhosis, whereas those with bridging fibrosis will mainly develop non-hepatic cancers

and vascular events [33, 34]. This implies that information obtained from liver biopsy is key in predicting the outcome of the individual patient. However, given the limitations of liver biopsy, non-invasive techniques may also fruitfully be applied to this end [35]. Therefore, what we need is an electric torch systematically exploring (either invasively or non-invasively) all the "dark spots" of NAFLD variability.

Similar to other complex disorders, such as type 2 diabetes (T2D), arterial hypertension, and cancer, our therapeutic approach to NAFLD should best be strongly personalized and based on the individual features of disease and on its expected outcomes (i.e., the natural history of disease).

In order to prioritize the vast biomedical literature published on this topic, in January 2021, PubMed was consulted using the following search terms: "NAFLD", "nonalcoholic fatty liver disease", "NASH", "steatosis", "fatty liver", "precision medicine", "steatohepatitis", "metabolic syndrome", "MAFLD". Guidelines, original articles, review articles, editorials, and their reference lists were considered. There were no language restrictions nor specific exclusion criteria. Inclusion of proposed articles was based on unanimous agreement among the authors. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

COMPLIANCE WITH ETHICS GUIDELINES

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

DIAGNOSIS

Further to standard assessment, which includes the use of biomarkers and imaging techniques as the initial step [36–39], the NAFLD diagnostic process should include a more accurate definition of a series of parameters mirroring the extent and severity of hepatic and extrahepatic involvement [40, 41]. The recently proposed "LDE system" [42, 43] is an example of a possible synthetic descriptor of variables related to the liver (L), to the determinants of disease specific to the individual patient (D), and to the extension of extrahepatic involvement (E) that is typical of a systemic disorder such as NAFLD [44].

L—Estimation of liver disease severity in patients with NAFLD is currently focused on the assessment of the presence and degree of liver fibrosis as this feature is the main determinant of mortality among these patients and accurately predicts both all-cause and disease-specific mortality in patients with NAFLD [24, 45]. A large variety of biomarkers, algorithms, and imaging techniques collectively grouped under the heading of "non-invasive diagnostic tools" are available to estimate the degree of liver fibrosis in NAFLD [46]. Table 1 summarizes advantages and limitations of each approach that have been extensively reviewed elsewhere [35]. In addition, recent studies have pinpointed that thresholds of non-invasive fibrosis scores, such as Hepamet, FIB-4, and NFS, can be modified according to the ethnicity of patients with NAFLD with the aim of reaching maximal diagnostic accuracy [47]. In addition, liver fibrosis biomarkers such as aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio (ARR), AST to platelet ratio index (APRI), Fibrosis-4 (FiB-4), Forns index, NAFLD fibrosis score (NFS), BARD (body mass index (BMI), AAR, diabetes) score, and Hepamet fibrosis score (HFS) can rule out advanced fibrosis and are positively correlated with cardiovascular risk (CVR) scores in patients with NAFLD [48]. The role of the HFS should best be further explored in prospective studies as well as when combined with other diagnostic methods [49].

D—Assessment of disease determinants in individual patients is not routinely performed in clinical practice nor in RCTs despite the fact that a variety of pathogenic risk factors are well characterized. In our view, all the following features are important modifiers that are worth registering in the individual patient and should be taken into consideration in therapeutic

Table 1 Advantages and limitations of non-invasive diagnostic biomarkers and tools for detecting fibrosis in NAFLD

Biomarkers							
Biomarker	**Components**	**Validation**	**Accuracy for advanced fibrosis**	**Indeterminate cases**	**Prognostic ability**	**Advantages**	**Limitations**
APRI, AST-platelet ratio index (APRI) [193, 194]	AST, platelets	Good	AUROC 0.70–0.79	50–60%	Fair	Easy to calculate Clinical information for the score is often available	Large number of individuals fall in the indeterminate range
Fibrosis-4 (FIB-4) [195, 196]	AST, ALT, platelets, age	Very good	AUROC 0.80–0.85	20–30%	Very good	Easy to calculate Clinical information for the score is often available	Large number of individuals fall in the indeterminate range Various cutoffs used in studies Limited usefulness in the general population
NAFLD fibrosis score (NFS) [197]	Age, BMI, IFG/diabetes, AST, ALT, platelets, albumin	Very good	AUROC 0.80–0.85	20–35%	Good	Easy to calculate Clinical information for the score is often available	Large number of individuals fall in the indeterminate range Different cutoff values needed for younger or older participants Limited usefulness in the general population

Table 1 continued

Biomarkers							
Biomarker	**Components**	**Validation**	**Accuracy for advanced fibrosis**	**Indeterminate cases**	**Prognostic ability**	**Advantages**	**Limitations**
Hepamet fibrosis score [198]	Age, sex, diabetes, glycemia, insulin, HOMA, AST, albumin, platelets	Fair	AUROC 0.78–0.92	20%	Good	Easy to calculate Clinical information for the score is often available Less subjects in the indeterminate range compared to FIB-4 and NFS	More validation needed, especially in non-European population Limited usefulness in the general population Insulin is not always available
Fibrotest/ Fibrosure [199, 200]	Age, sex, bilirubin, GGT, α2M, haptoglobin, Apo-A1	Good	AUROC 0.80–0.85	0–35%	Very good	Increased accuracy compared to non-commercial serum tests	More validation needed Not as widely available as non-patented scores and more expensive
Hepascore [201]	Age, sex, bilirubin, GGT, α2M, HA	Good	AUROC 0.85–0.89	0–30%	Very good	Increased accuracy compared to non-commercial serum tests	More validation needed Not as widely available as non-patented scores and more expensive

Table 1 continued

Biomarkers							
Biomarker	**Components**	**Validation**	**Accuracy for advanced fibrosis**	**Indeterminate cases**	**Prognostic ability**	**Advantages**	**Limitations**
Fibrospect [202]	α2M, HA, TIMP-1	Low	AUROC 0.85–0.89	0–40%	NA	Increased accuracy compared to non-commercial serum tests	More validation needed Not as widely available as non-patented scores and more expensive
FibroMeter (SNAFFLED) [203]	Age, sex, weight, platelets, ALT, AST, ferritin, glucose	Fair	AUROC 0.75–0.79	0–35%	NA	Increased accuracy compared to non-commercial serum tests	More validation needed Not as widely available as non-patented scores and more expensive
Enhanced liver fibrosis score [204]	HA, TIMP-1, PNPIII	Good	AUROC 0.85–0.99	0–40%	Very good	Increased accuracy compared to non-commercial serum tests	Not as widely available as non-patented scores and more expensive
NIS4 [205]	miR-34a-5p, alpha-2 macroglobulin, YKL-40, and glycated hemoglobin	Fair	AUROC 0.73–0.85	0–30%	NA	Does not require adjustment for age, sex, BMI, or aminotransferase concentrations	Not as widely available as non-patented scores and more expensive More validation is needed

Table 1 continued

Imaging techniques							
Imaging tool	**Components**	**Validation**	**Accuracy for advanced fibrosis**	**Unreliable result rate**	**Prognostic ability**	**Advantages**	**Limitations**
Vibration-controlled transient elastography (VCTE) [206]	NA	Very good	AUROC for F ≥ 2 = 0.79 and F4 = 0.93	1–9%	Excellent	Performed in liver clinic Simultaneously quantify fat (CAP) Integrated quality control Larger area of liver assessed No prior experience with ultrasound required Portable options available	Failure if narrow rib spaces Failure if large ascites Only measures CAP and LSM Less cost-effective if also need ultrasound
Shear wave elastography (SWE) [207]	NA	Good	AUROC for F4 = 0.9 approx.	16–24%	NA	Not impacted by rib spaces Ok with large ascites Evaluates other features of portal hypertension Cost-effective if also ultrasound need	Performed in radiology Does not quantify fat Quality control not integrated Smaller area of liver assessed Lack of portability Requires ultrasound expertise

Table 1 continued

Imaging techniques							
Imaging tool	**Components**	**Validation**	**Accuracy for advanced fibrosis**	**Unreliable result rate**	**Prognostic ability**	**Advantages**	**Limitations**
Acoustic radiation force impulse (ARFI) [208]	NA	Good	AUROC for F4 = 0.9 approx.	1–13%	NA	Not impacted by rib spaces Ok with large ascites Evaluates other features of portal hypertension Cost-effective if also need ultrasound	Performed in radiology Does not quantify fat Quality control not integrated Smaller area of liver assessed Lack of portability Requires ultrasound expertise
Magnetic resonance elastography (MRE) [209]	NA	Good	AUROC for $F \geq 2$ = 0.93 and F4 = 0.94	Negligible	Excellent	Overall best performance Ok with large ascites Can be easily performed with other techniques to quantify liver fat Largest area of the liver assessed	Performed in radiology Performed at a limited number of centers Quality control not integrated Lack of portability Cost

ALT alanine aminotransferase, *Apo-A1* apolipoprotein-A1, *AST* aspartate aminotransferase, *AUROC* area under the curve, *BMI* body mass index, *HA* hyaluronic acid, *IFG* impaired fasting glucose, *α2-M* α2-macroglobulin, *NA* not applicable, *NAFLD* non-alcoholic fatty liver disease, *PNPIII* procollagen N-terminal peptide III, *PTI* prothrombin index, *TIMP-1* tissue inhibitor of matrix metalloproteinase 1

studies: (i) sex and reproductive status, (ii) genetics, (iii) intestinal microbiota, (iv) endocrine assessment, (v) metabolic assessment, and (vi) physical activity. Existing data on the role of these factors in NAFLD are summarized in "Sex, Gender, and Reproductive Status".

E—The extent of extrahepatic manifestations and complication of NAFLD exhibits an ever-enlarging spectrum of conditions spanning, for example, T2D to chronic kidney disease and colorectal cancer, just to name a few. This spectrum has extensively been reviewed elsewhere [13]. For clinical purposes, it is important to categorize each patient as being affected by metabolic derangements [50], cardiovascular disease [51], and/or non-hepatic cancer [52]. This categorization promises to contribute to a more accurate risk stratification, personalized follow-up protocols, and full consideration of polypharmacy.

Sex, Gender, and Reproductive Status

Sex and gender are major modifiers of a series of common conditions pertaining to the domain of internal medicine including heart, lung, and kidney disease [53]. Sex medicine is the first step of personalized medicine in as much as, for example, sex is one of the major determinants of drug dose level, responses, and adverse reactions [54]. NAFLD also has definite sexual dimorphic features [55]. A recent meta-analytic study found that women were more protected from the risk of developing bland steatosis than men, while being at an increased risk of fibrosis progression than men [56].

Gender defines a social attribute as opposed to sex that is a biological feature [53]. Little is known regarding the role of gender in the development and progression of NAFLD. However, it is conceivable to postulate that gender attributes, such as drinking alcohol, may contribute to the increased risk of developing HCC in men with NAFLD [57, 58].

Reproductive status is also a strong determinant of the risk of development and progression of NAFLD given that postmenopausal NAFLD tends to mimic epidemiological features such as those seen in men [59–61].

On this background, experts have recommended that sex and reproductive status should receive adequate consideration when planning NAFLD research [59, 62, 63].

Genetics

The risk of developing NAFLD and related complications has been clearly related to genetic factors. Genome-wide association studies (GWAS) have consistently shown associations between a set of genetic variants and NAFLD development and severity [64]. The main genes uncovered by these studies are *PNPLA3*, *TM6SF2*, *MBOAT7*, *GCKR*, and *HSD17B13* (Table 2), with the *PNLA3* I148 variant (rs738409) being the most extensively characterized [65]. Of note, having this variant carries an approximately doubled risk of developing NAFLD and, of concern, a tripled risk of NASH and HCC per allele [6, 65]. Interestingly, while the *PNPLA3 gene* 148Met allele and the *TM6SF2* gene 167Lys allele are associated with an increased risk of steatosis development and progression (to NASH and cirrhosis) they seemingly protect from cardiovascular disease [66, 67]. This feature might be leveraged to conduct a stricter hepatological follow-up in carriers of these variants as opposed to "metabolic NAFLD" wherein cardiovascular assessment is strongly recommended [37, 64]. Of note, genetic variants are not present in all individuals with NAFLD and, based on current understanding, as pointed out by some authors it is uncertain whether "metabolic NAFLD" and "genetic NAFLD" are entirely equivalent [68, 69]. Although routine genotyping of patients is not yet recommended, the use of polygenic risk scores (PRS), which are based on the sum of all independent risks conferred by carrying a single nucleotide polymorphism (SNP), is being investigated as a useful tool to identify patients at risk of developing more severe disease [5] or complications, such as HCC [70].

Table 2 Genetic polymorphisms associated with the risk of development and/or progression of NAFLD/NASH

Gene	Variant	Impact on protein	Effect of the variant	Allele frequency				Effect size	Effect of the variant
				Europeans	Hispanics	Asians	Africans		
PNPLA3	rs738409C>G	I148M	Complex: loss plus gain of function	0.23	0.57	0.38	0.14	+++	Complex: loss plus gain of function
TM6SF2	rs58542926C>T	E167K	Loss of function	0.08	0.03	0.07	0.04	+++	Loss of function
GCKR	rs1260326T>C	P446L	Loss of function	0.60	0.67	0.50	0.86	+	Loss of function
MBOAT7	rs641738C>T	Linked to 3′-UTR	Reduced expression	0.42	0.33	0.24	0.34	+	Reduced expression
HSD17B13	rs72613567T>TA	Alternate splicing	Loss of function	0.27	0.09	0.34	0.06	++	Loss of function
	rs62305723G>A	P260S		0.07	0.02		0.01		
IL28B (IFNL3/4)	rs368234815TT>dG	Alternate protein translation site	Alternative protein	0.27	0.09	0.34	0.06	+	Alternative protein
MERTK	rs4374383G>A	Noncoding variant	Reduced expression	0.37	0.37	0.73	0.47	+	Reduced expression

NAFLD non-alcoholic fatty liver disease, *NASH* non-alcoholic steatohepatitis
Adapted from ref. [64]

Intestinal Microbiota

Gut–liver axis signaling pathways, such as microbiota-related mechanisms (i.e., dysbiosis, production of endogenous ethanol, and choline deficiency) play a major role in the pathogenesis of NAFLD and NASH [71]. This may occur either directly or indirectly (i.e., via altered metabolism of bile acids) and is deemed to be a key element of personalized medicine [44, 72, 73]. Indeed, lifestyle changes are closely linked with modulation of the intestinal microbiota, which may potentially account for the inter-individual variability of patients with NAFLD [72]. Both experimental and clinical data show the relevance of diet–microbiota interaction in determining metabolic abnormalities. For example, germ-free mice exhibit less pronounced steatosis and do not become obese when fed a western-type diet [74]. Obesity is strongly associated with altered gut microbiota [72], and a diet rich in vegetables and fiber (i.e., rural African diet) is associated with a high Bacteroidetes to Firmicutes ratio [75], which is maintained even in the presence of a high-fat diet [72, 76].

The highly lipogenic sugar fructose, deemed to be a major risk factor of the development of NAFLD [77, 78], is a key player in intestinal dysbiosis, increased gut permeability, portal blood endotoxemia, and again in determining an altered Bacteroidetes to Firmicutes ratio, which characterizes NASH. Finally, progress in harnessing intestinal microbiota as a potential diagnostic tool in NAFLD/NASH as well as NASH-related HCC is being made [71, 79]. Data on the existence of distinct microbiota signatures associated with significant fibrosis [80, 81] is of particular interest in this regard. Thus, it is likely that in the near future simplified assessment of intestinal microbiota composition may help in better characterizing patients with NAFLD/MAFLD.

Endocrine Assessment

In clinical practice and in RCTs, the amplitude of the diagnostic protocol aimed at ruling out competing causes of liver disease remains poorly defined in patients with NAFLD. However, "endocrine-related NAFLD and NASH" forms do exist and have been discussed elsewhere [82, 83]. Based on the finding that hypothyroidism-induced NAFLD (HIN) is commonly seen in clinical practice and on the high prevalence of hypothyroidism in general population studies, it has been proposed that thyroid status should be assessed through the routine evaluation of thyroid-stimulating hormone (TSH) [42, 84–86].

So distinctive is the pathogenesis of liver disease in these cases and given the potential for total reversibility of disease with thyroid hormone replacement therapy that HIN has been proposed as a distinct disease entity [87, 88].

In the clinic, clues from signs and symptoms of androgen excess and ovarian dysfunction (e.g., menstrual irregularities) may suggest the presence of polycystic ovary syndrome (PCOS) [89], a condition which is deemed to be strongly associated with progressive forms of NAFLD [90, 91].

Other well-defined forms of NAFLD/NASH secondary to specific endocrine disorders include growth hormone (GH) deficiency [92, 93], which is deemed to mirror the failure of low GH levels to inhibit hepatic de novo lipogenesis [94]. Phenotypically, in adults, GH deficiency exhibits NAFLD, NASH (whose histology will significantly improve following administration of GH to GH-deficient adults), and NASH-cirrhosis associated with visceral obesity, dyslipidemia, and premature atherosclerosis [95].

Data regarding glucocorticoid excess appear to be less robust: on the basis of computerized tomography findings, Rockall et al. found steatosis in 20% of patients with Cushing's syndrome [96]. It has been speculated that an excess of cortisol, by inhibiting systemic low-grade chronic inflammation mainly mediated by interleukin-6, could account for this protective effect from developing NAFLD [97]. Auer et al. found that NAFLD, assessed with a surrogate index, fatty liver index (FLI), in 33 patients with biochemically controlled Cushing's disease was not more common than that found among 79 individuals with non-functioning pituitary adenomas [98].

In conclusion, while screening for TSH alterations seems justified in the standard evaluation of NAFLD given the common occurrence of HIN, PCOS may be suggested by clinical findings. Finally, evaluation of GH deficiency and hyperadrenalism should be reserved for selected cases based on clinical suspicion.

Cardio-Metabolic Assessment

A first-level assessment of common anthropometric indices (such as BMI and waist circumference) should routinely be evaluated to differentiate the various subtypes of NAFLD, such as NAFLD in the obese (high BMI), in the visceral obese (high waist circumference with/without high BMI), or in the non-obese (normal BMI and waist circumference). Also, blood pressure should be recorded together with the use of antihypertensives, given that high blood pressure is a risk factor for the progression of liver fibrosis [99].

The dangerous association of impaired glucose disposal and NAFLD is widely acknowledged [100, 101]. For example, a recent study found that fatty liver, when associated with dysglycemia, had the potential to progress to chronic kidney disease (CKD) as defined by reduced estimated glomerular filtration rate (eGFR) [102]. Similar to obesity, the various grades of normal, impaired, and frankly altered gluco-tolerance should be evaluated and recorded with appropriate static and dynamic testing [103].

The diagnosis of MAFLD, as opposed to NAFLD, may partially obviate the need to specify if the patient has diabesity or not, but whether the risk of progression is the same among those who have diabetes and among those who are obese remains to be proven.

Types and severity of lipid metabolism disorders should be registered [104]. A study has reported that hypertriglyceridemia was a risk factor for cirrhosis in overweight Swedish individuals [105], a finding that may suggest unrecognized T2D as the culprit. It has also been reported that an atherogenic lipoprotein profile is related to NAFLD severity and progression to cirrhosis [106]. In addition, the pathogenic role of cholesterol in the pathogenesis of NASH is well characterized [107, 108] and accumulating epidemiological data support the beneficial effects of statins in this setting [109–111]; however, evidence is observational and well-conducted RCTs remain to be performed.

It is widely acknowledged that NAFLD is closely associated with an increased risk of conditions of the cardiovascular system. These comprise both anatomic abnormalities and perturbed heart function [112, 113], notably including an increased risk of atrial fibrillation [112]. The venous system may also be involved, and it has indeed been reported that patients with NAFLD are prone to the risk of venous thromboembolism [112].

Finally, although in the absence of clear-cut data suggesting that venesection cures NAFLD/NASH [114] and given that in NAFLD hepatic iron overload is strictly associated with insulin sensitivity [115], it may be logical to record the levels of ferritin and to further investigate all patients with percent saturation of transferring above the cutoff limits [116].

Physical Activity

It has long been known that, compared to non-NAFLD controls, subjects with NAFLD have significantly lower levels of physical activity [117]. Most patients with NAFLD exhibit the so-called triple-hit behavioral phenotype consisting in (i) sedentary behavior, (ii) low physical activity, and (iii) poor diet [118]. Short-term benefits of physical activity in NAFLD are well demonstrated [119] and it is likely that physically active individuals with NAFLD, similar to patients with T2D, may be protected from developing complications of their disease leading to a reduced healthcare financial burden [120]. On these grounds, it seems relevant that patients with NAFLD should always be classified along a semi-quantitative scale of sedentary behavior defined as time spent sitting or lying with low energy expenditure (e.g., assessed with TV watching time) and physical activity (along a scale of intensity and time spent on exercising per week). That information, in addition to

proper evaluation of cardiovascular status, would help to prescribe an adequate and progressive exercise program ensuring compliance. Interestingly, some studies conducted in animal models as well as in human twins point to the existence of significant inter-individual differences in the response to a given exercise program dose with regard to achievement of cardio-respiratory fitness and modification of cardio-metabolic features [121, 122], which opens the possibility of personalized exercise program prescription.

TAILORING NAFLD MANAGEMENT TO INDIVIDUAL PATIENTS

Principles of NAFLD management have been outlined in several clinical guidelines or position papers released and endorsed by either scientific societies or expert panels [36–38]. All these documents agree that lifestyle modifications remain the cornerstone of NAFLD management and are indicated in all patients [123]. Data suggest that a Mediterranean diet is one of the nutrition styles to be recommended, associated with caloric restriction oriented to achieve a 7–10% loss of basal body weight [118]. Dieting should be combined with exercise according to current recommendations issued by the American College of Sports Medicine (ACSM) and World Health Organization (WHO) taking into account basal cardiovascular risk as well as comorbidities [119, 124]. Currently, there are no approved specific medications for NAFLD/NASH but several agents are under investigation in phase 3 trials and may offer new treatment alternatives in the near future [125, 126].

Precision medicine approaches in NAFLD treatment are still in their infancy [5, 6, 22]. Indeed, more information needs to be gathered to generate tailored therapeutic plans to the different and heterogenous patient categories grouped under the acronym NAFLD. In the following paragraphs, we attempt to envision a targeted approach based on the factors outlined above.

Sex and Reproductive Status

Human metabolism is different between sexes and is critically influenced by reproductive status. Thus, these variables could be of importance when planning lifestyle interventions in patients with NAFLD [127]. Of note, emerging data from experimental models also suggest sex differences in response to dietary restrictions [128]. Therefore, while female mice respond better to caloric restriction in terms of longevity [129], non-human primates show a male-specific reduction in body weight and increase in insulin sensitivity when subjected to this dietary limitation [130]. However, information about this matter in humans is scarce because intervention studies do not routinely stratify according to sex [131]. Some studies suggest that, in general, men tend to lose more weight and exhibit more metabolic benefits than women when undergoing lifestyle intervention programs [132]. Interestingly, in one of the most cited studies assessing lifestyle interventions in NAFLD [133], men showed a greater histological improvement than women after weight loss. In this study, male sex was one of the factors predicting beneficial histological response following a relatively modest weight loss (between 7% and 10%), while in women a more substantial weight loss (more than 10%) was required to achieve a significant histological improvement [133]. Therefore, on the basis of available data, women may require additional support to achieve their goals after introduction of lifestyle changes.

With regard to reproductive status, studies on the effect of lifestyle modifications on NAFLD specifically in postmenopausal women are limited [60, 134]. A recent metanalysis of published data suggests that weight loss interventions may not need to be tailored to women's menopausal status [135].

Genetics

The robust associations of NAFLD development and progression with specific gene variants (summarized in Table 2) may allow the utilization of genotyping of any given patient to aid

diagnosis or predict disease trajectories, thus allowing for better prognostication [65]. Moreover, once precise pathophysiology is deciphered, gene-specific therapy would be possible [136]. In spite of a plethora of information regarding the influence of genetic variants on disease severity, cardiovascular risk, and risk of developing cirrhosis and HCC, translation into clinical practice is still pending because of lack of data supporting cost-effectiveness of routine genetic testing in patients with NAFLD. Of all genetic variants identified as relevant for NAFLD development and progression (Table 2), *PNPLA3* is the most studied and the p.I148M variant of the gene encoding this protein is consistently associated with a more severe disease and an increased risk of HCC. It has also been associated with both liver-related and all-cause mortality in a general US population [65]. Moreover, it has been shown that patients carrying the p.I148M variant also exhibit an antiatherogenic lipid profile and a better response to lifestyle modifications and bariatric surgery [137–139]. This information may help to implement specific measures, such as personalized cardiovascular risk management, lifestyle intervention, and tailored HCC screening programs in patients with NAFLD. Additionally, as discussed above, genetic information may be used through the use of PRS, which reflect the risk accumulation determined by harboring multiple SNPs and may assist in disease prediction. In a recent paper, Bianco et al. showed that the use of PRS, in which *PNPLA3*, *TM6SF2*, *GCKR*, and *MBOAT7* were combined, may improve HCC risk stratification in NAFLD [70]. Thus, in the near future, the challenge is to generate data showing whether decision-making based on patients' genetic information is cost-effective or not.

From the therapeutic standpoint, data from experimental models have shown that it is possible to improve all histological features of NAFLD in vivo by silencing *PNPLA3* with liver-targeted antisense oligonucleotides [140]. Therefore, in future, specific therapy may be amenable for those individuals carrying the NAFLD p.I148M variant, which would be indicated only in "genetic NAFLD" as opposed to "metabolic" disease [68].

Manipulation of Intestinal Microbiota

The growing amount of data on intestinal microbiota in patients with NAFLD have opened the possibility to develop microbiome-based approaches to manage the disease [71, 141]. As discussed above ("Intestinal Microbiota"), "microbiome signatures" can be used for personalizing NAFLD diagnosis and staging. Moreover, these could also be useful for selecting patients to submit to therapeutic fecal microbiota transplantation (FMT) as well as biomarkers of response to therapy [142]. This is relevant considering that not all patients have either gut dysbiosis or increased intestinal permeability [143] and that it is very likely that certain subsets of patients will respond better to microbiota-targeted therapies than others. Therefore, microbiome-based biomarkers could be applied for developing more targeted management approaches such as dietary interventions, manipulation of gut microbiota through the use of probiotics, prebiotics, and/or synbiotics as well as FMT or bacteriophage therapy [71, 142]. To date, studies on the use of probiotics and synbiotics in NAFLD suggest some benefit in terms of amelioration of hepatic inflammation, steatosis, and eventually liver fibrosis [144], but data heterogeneity is significant and well-designed RCTs are lacking. Indeed, one source of heterogeneity is the diverse microbiota composition and differences in treatment regimens that affect bacterial engraftment. Interestingly, this seems to be predicted by individual baseline gut microbiota [145].

Endocrine Considerations

Thyroid Disease and Thyromimetics

As previously argued, hypothyroidism is commonly found among patients with NAFLD [84]. It is predicted that thyroid hormone replacement could fully reverse the disease or at least improve disease progression leading to better outcomes [88]. Of note, it has been proposed that HIN should be considered as a potentially curable and distinct disease entity [87]. In any case, routine evaluation of the presence of

thyroid disease should be carried out in any patient with NAFLD and treatment instituted when indicated. Levothyroxine administration has been shown to reduce serum aminotransferases and hepatic fat content in either euthyroid or subclinical hypothyroid patients with NAFLD [146, 147]. Long-term studies assessing liver disease progression and other outcomes are lacking. One interesting application of the thyroid–liver axis in NAFLD is the potential therapeutic use of liver-specific thyromimetics [88]. These drugs are agonists of the hepatic thyroid hormone receptor isoform beta (THR-β) and are devoid of systemic effects. Two drugs are under study, VK2879 and MGL-3196, also named resmetirom, with the latter showing promising results in terms of liver fat reduction in a phase 2 trial [148, 149]. Results of phase 3 clinical trials are eagerly awaited. Considering their mechanism of action, it is likely that thyromimetics may be more effective in early stages of the disease [148]. Thus, once proven effective when available, this may be a consideration for personalized prescription.

Hormonal Therapy in NAFLD Associated with PCOS, Hypogonadism, GH Deficiency, and Other Endocrine Disorders

Patients with NAFLD and concurrent endocrinopathies should be evaluated by a specialist in order to receive optimal treatment. As reported above, PCOS is independently associated with more severe liver disease, including advanced fibrosis and cirrhosis [91]. This implies that it is important to screen for PCOS in all women referred for NAFLD who have medical histories and clinical findings compatible with PCOS given that these patients require appropriate hepatological follow-up and intensive management. In particular, the use of metformin has proven effective in decreasing insulin resistance in these patients, although its efficacy on NAFLD histology remains unproven.

Male patients with hypogonadism and NAFLD could possibly benefit from testosterone administration [150, 151]. However, the long-term safety profile of this therapy, including cardiovascular outcomes, remains unclear.

GH replacement therapy is recommended in cases of symptomatic hormone deficiency, which may impact insulin sensitivity, visceral fat, and dyslipidemia [152]. However, data on its effect on human NAFLD are limited [93]. The same holds true in the case of GH excess where the impact of therapy on NAFLD remains to be evaluated [93].

Cardiometabolic Considerations

As previously pinpointed, cardiovascular disease and T2D are among major comorbidities of NAFLD. Indeed, when planning a tailored treatment scheme, these two aspects should be carefully assessed and best tackled in the context of a multidisciplinary team. Although evidence is scarce, a holistic multidisciplinary management seems to be superior to standard approaches by determining better improvements to liver and cardio-metabolic health [153].

Cardiovascular Disease

The field of precision cardiology is rapidly developing [154, 155]. Since patients with NAFLD may suffer from coronary artery disease and other cardiovascular conditions (i.e., arterial hypertension, left ventricular hypertrophy, certain arrhythmias, and valve calcification [156]), modern concepts of precision cardiology could be applied to gather data regarding risks of individual patients, thereby boosting the capacity to diagnose and estimate prognosis while planning future treatments [4, 157]. Coronary heart disease and arterial hypertension are indeed conditions that may be susceptible to a more precision-oriented approach beyond current guidelines [4]. Combined approaches using modern cardiovascular risk assessment concepts, novel biomarkers, specific genotyping of NAFLD cases, advanced imaging, and novel biomarkers may serve to stratify patients with NAFLD in terms of cardiovascular risk and allow for more personalized treatment decisions. In this regard, the proper use of statins in patients with NAFLD to prevent the development and complications of atherosclerosis in patients at a high risk is very relevant considering that these drugs are often underprescribed [156]. Of note, in the near future a precision medicine

approach to lipid-lowering therapy is also envisioned [158].

Both venous thromboembolism and atrial fibrillation are amenable to anticoagulation therapy. In the absence of any standardized indications, the use of direct oral anticoagulants should be personalized. Personal history (high risk vs. low risk of thromboembolic complications), stage of disease (cirrhotic vs. non-cirrhotic), and individual risk of bleeding complications should be carefully balanced in the individual patient [112].

Type 2 Diabetes

As mentioned above, on the basis of the common association of both conditions, patients with NAFLD should be screened for T2D [100]. Additionally, given that NAFLD is a definite risk factor for incident T2D [159], a preventive approach is justified in these patients [160]. Importantly, significant liver fibrosis is an independent risk factor for T2D appearance with a hazard ratio of 2.95 (95% CI 1.19–7.31) [161]. On the basis of their higher risk of cirrhosis, patients with concurrent NAFLD and T2D should receive individualized management of T2D that seeks optimal metabolic control according to current guidelines [100, 162]. Although metformin does not seem able to improve histological endpoints in NAFLD, recent studies have shown that patients with diabetes and NASH-related cirrhosis treated with metformin do exhibit higher rates of survival and lower rates of cirrhosis decompensation and HCC development [163]. Also, particular consideration should be given to the potential benefits of antidiabetic drugs such as pioglitazone and sodium-glucose cotransporter 2 (SGLT2) inhibitors, which have been shown to be effective in patients with concurrent T2D and NAFLD [164, 165], although larger RCTs are required. Similarly, the use of the glucagon-like peptide 1 (GLP-1) receptor agonists such as liraglutide or semaglutide is very promising as there is evidence that these agents impact liver histology and can also improve cardiovascular outcomes in patients with T2D [166–169]. Finally, as T2D itself is heterogeneous in its etiology, pathogenesis, and clinical presentation, precision medicine approaches to treat and prevent the disease are being actively investigated but significant barriers to their implementation and research gaps still exist [170].

Individualizing Diet and Exercise Prescription

As mentioned above, diet and exercise are the cornerstone of NAFLD management. There are various types of diet (e.g., Mediterranean, low-fat diet, and low-carbohydrate diet) as well as different exercise modalities (e.g., high-intensity interval training, moderate-intensity aerobic exercise, and resistance exercise) that have been shown to positively influence NAFLD. Importantly, individualized prescription of diet and exercise therapy may lead to better outcomes.

The goals of dietary intervention should be aligned to patient characteristics and preferences. Weight loss is an important goal in overweight or obese patients as a dose–response relationship exists between the magnitude of weight loss and reduction in liver fat, NASH resolution, and improvement of liver fibrosis [133, 171]. Thus, a loss of at least 5% of total body weight has been associated with a decrease in hepatic steatosis, a weight loss of at least 7% has been shown to lead to NASH resolution, and a weight loss of at least 10% can result in fibrosis regression or stability [172]. Besides calorie restriction, dietary composition is also an important factor to be considered. Low-carbohydrate diets have shown to be particularly beneficial in patients with atherogenic dyslipidemia and insulin resistance and may favorably impact NAFLD [173]. In particular, the Mediterranean diet, a vegetable-based diet characterized by a high ratio of monounsaturated fatty acids to saturated fatty acids with a total fat accounting for 30–40% of daily energy consumption, has been shown to have a beneficial effect on glucidic and lipidic metabolism, resulting in improved hepatic steatosis and improved insulin sensitivity in patients with NAFLD [174, 175]. Given that the Mediterranean diet is one of the best studied, current guidelines recommend this particular dietary

style for NAFLD management [36, 123]. Studies evaluating low-calorie ketogenic diets have shown benefits in terms of reduction of hepatic fat content, but their short duration limits their interpretation. Other approaches such as intermittent fasting regimens hold potential in NAFLD management, but further studies are needed [172]. The science of precision nutrition that considers a holistic approach and allows for the prescription of comprehensive and dynamic nutrition recommendations is beginning to emerge. [176, 177]. Proper consideration of dietary habits, genetic background, health status, microbiome composition, as well as socioeconomics, psychosocial characteristics, and environmental exposures is key for successful intervention.

Exercise determines weight loss-independent benefits in NAFLD at multiple levels [118]. In addition to improving liver histology through several mechanisms [119], it improves cardiorespiratory fitness and may also decrease cardiovascular risk. Importantly, exercise training should be prescribed in a detailed and personalized manner where exercise is considered a "drug" [178]. Clearly, attention should be paid to basal cardiovascular fitness, exercise modality, intensity, frequency, and duration of training. The recent guidelines released by the WHO on sedentary behavior are useful for planning exercise prescription for healthy adults and could, in turn, be used to formulate exercise programs for patients with NAFLD [124]. The specific recommendation is to do at least 150–300 min of moderate-intensity aerobic physical activity or at least 75–150 min of vigorous-intensity aerobic physical activity on a weekly basis, adding muscle strengthening activities involving all major muscle groups 2 days a week [124]. Both aerobic and resistance training improve hepatic fat content and are associated with favorable changes in body composition [179, 180]. Also, high-intensity interval or moderate-intensity continuous aerobic exercise seem to be equally effective with respect to liver fat reduction [181, 182]. Thus, a personalized indication of exercise should consider age, sex, muscle mass, and cardiovascular comorbidities in order to select a safe and effective exercise program.

In recent years, with the emergence of precision exercise medicine [121], the existence of inter-individual differences in the response to a given dose of exercise has also been taken into consideration. However, variables determining such differences remain ill defined and more research assessing physiological responses to interventions in humans is needed [183]. Efforts to find biomarkers to detect those individuals who will benefit more with exercise, such as the META-PREDICT study, have been disappointing so far [184].

Finally, as mentioned above, paying attention to psychosocial factors of any given patient is also relevant as these might influence motivation to both adopt and sustain an exercise program. In this regard, proper support to patients' efforts (i.e., health coaching and motivational interventions) is key to successful adherence to any exercise program aimed at naturalizing physical activity in daily life.

SUMMARY AND OUTLOOK

The idea of applying precision medicine concepts to NAFLD/NASH management is gaining momentum. As various disease sub-phenotypes with potentially distinct natural history and prognosis and, eventually, different response to therapy, are grouped under the term NAFLD, proper weighing of the differential contribution of different factors to the pathogenesis and clinical expression of NAFLD could help to tailor disease management. Gathering and layering of all pertinent clinical, genetic (i.e., genotyping of major genetic variants or use of PRS), microbiome-related, and cardio-metabolic data should contribute to better defining disease trajectory, risk of progression, and likelihood of response to different therapeutic options in any given patient with NAFLD. Also, in the future, the use of high-throughput omics (i.e., lipidomics proteomics, metabolomics, and glycomics) investigations will help to generate comprehensive biochemical snapshots allowing one to discriminate between patient subgroups [185, 186]. Also, artificial intelligence tools to integrate and analyze big data as well as to develop algorithms combining the information

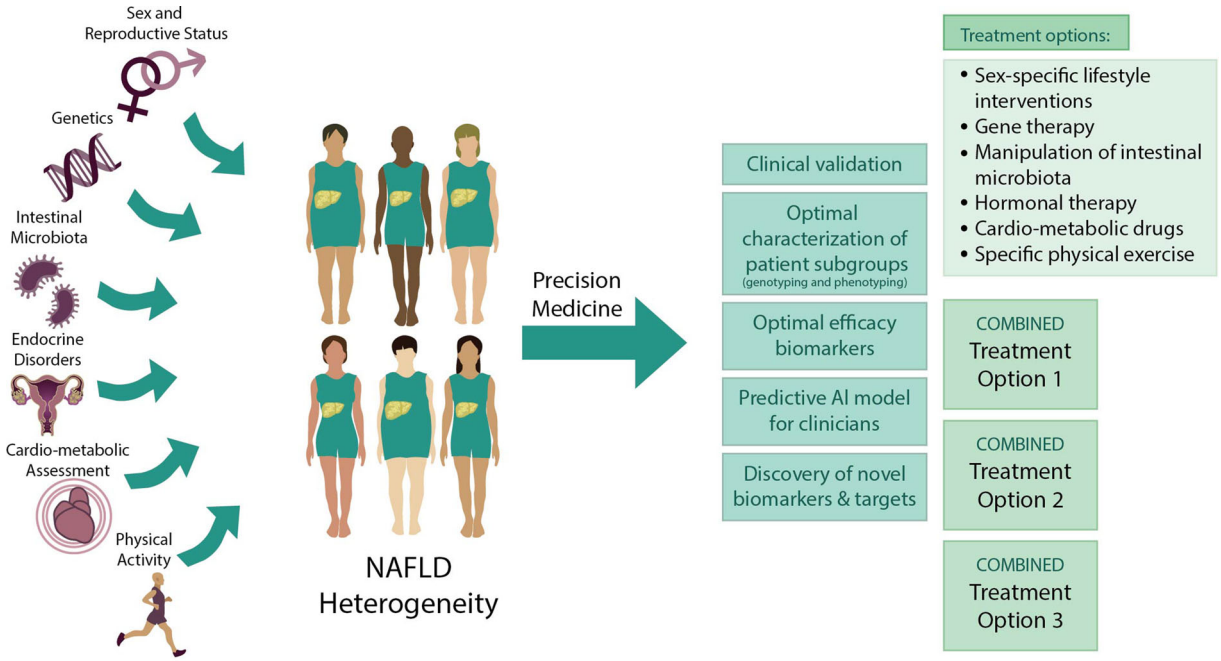

Fig. 1 Precision medicine in NAFLD. Schematic illustration depicting our proposal for a precision medicine approach in NAFLD. Careful consideration of some of the determinants of NAFLD heterogeneity such as sex and reproductive status, genetics, intestinal microbiota diversity, endocrine disorders (such as polycystic ovarian syndrome), cardio-metabolic assessment, and physical activity is suggested in order to develop a more targeted approach based on these factors. An optimal characterization of patient subgroups would allow tailored evaluation and management of patients with NAFLD. To that end, more studies are needed to validate and refine tools such as microbiota signatures and polygenic risk scores that might be useful for risk stratification and therapeutic decisions. In addition, the use of predictive artificial intelligence (AI) models, discovery and clinical validation of novel biomarkers and targets, and clinical studies that clarify the optimal use of these tools to match specific patient populations with the best treatment options is needed. A multicomponent therapeutic approach might have a better chance of achieving NASH resolution and/or reversal of severe histological outcomes, and of reducing not only liver-related but also metabolic syndrome-associated morbidity and mortality

through machine learning strategies [187–189] may be of help to better stratifying patients and defining tailored treatment strategies. A more accurate phenotyping of patients may also allow for grouping into more homogenous categories in clinical trials leading to more granular data on the efficacy of drugs in well-defined patient subgroups [26, 190]. Finally, artificial intelligence tools and high-performance computing could be useful to link biological information to health data in electronic medical records, thus advancing the discovery of novel associations using data-mining analysis.

Although significant advances in the path to precision medicine in NAFLD have been made, translation into the clinical arena, bringing recent discoveries to patient management, needs more data and studies to overcome multiple knowledge-based, value-based, and logistic barriers [191]. In the meantime, as practicing clinicians, our efforts should be put into managing NAFLD with an individualized approach. In this regard, adopting the newly proposed nomenclature MAFLD, which uses an inductive approach in contrast to the deductive-negative diagnosis of NAFLD [15, 16], seems logical and has met large consensus [192]. However, additional NAFLD-MAFLD comparative studies are awaited. The positive criteria proposed by an international expert panel separates three subgroups (i.e., obese, lean, and diabetic NAFLD) that may actually prove to

follow different natural histories [16]. Indeed, a sharper discrimination among subgroups could be possible in the future by applying some of the concepts delineated in the present article (Fig. 1). Identifying more homogenous cohorts of patients with either NAFLD or MAFLD to address natural history and evaluate novel treatment strategies would enlighten our knowledge of the disease and contribute to implementing the practice of precision medicine in NAFLD diagnosis and management.

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