

# A multi-society Delphi consensus statement on new fatty liver disease nomenclature

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## ABSTRACT

The principal limitations of the terms nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are the reliance on exclusionary confounder terms and the use of potentially stigmatising language. This study set out to determine if content experts and patient advocates were in favour of a change in nomenclature and/or definition. **Methods:** A modified Delphi process was led by three large pan-national liver associations. Consensus was defined a priori as a supermajority (67%) vote. An independent committee of experts external to the nomenclature process made the final recommendation on the acronym and its diagnostic criteria. **Results:** A total of 236 panellists from 56 countries participated in four online surveys and two hybrid meetings. Response rates across the 4 survey rounds were 87%, 83%, 83% and 78%, respectively. 74% of respondents felt that the current nomenclature was sufficiently flawed to consider a name change. The terms 'non-alcoholic' and 'fatty' were felt to be stigmatising by 61% and 66% of respondents, respectively. Steatotic liver disease (SLD) was chosen as an overarching term to encompass the various aetiologies of steatosis. The term steatohepatitis was felt to be an important pathophysiological concept that should be retained. The name chosen to replace NAFLD was metabolic dysfunction-associated steatotic liver disease (MASLD). There was consensus to change the definition to include the presence of at least one of five cardiometabolic risk factors. Those with no metabolic parameters and no known cause were deemed to have cryptogenic SLD. A new category, outside pure MASLD, termed MetALD was selected to describe those with MASLD who consume greater amounts of alcohol per week (140 to 350 g/week and 210 to 420 g/week for females and males respectively). **Conclusions:** The new nomenclature and diagnostic criteria are widely supported, non-stigmatising and can improve awareness and patient identification.

**Keywords:** Fatty liver disease, NAFLD, NASH, nomenclature, Delphi, MASLD, MetALD, steatohepatitis, steatotic liver disease, alcohol, type 2 diabetes, cardiometabolic, nonalcoholic.

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## INTRODUCCIÓN

Unified global approaches to nomenclature and disease definition are critical for increasing disease awareness, driving policy change, identifying those at risk, facilitating diagnosis and access to care. Language can create or exacerbate stigma, marginalise segments of the affected population and, ultimately, contribute to health inequalities. It has been known for many years that being overweight or obese is associated with hepatic steatosis, hepatocyte injury and liver inflammation and fibrosis. This was formally recognized by the term “nonalcoholic steatohepatitis” in 1980 by Jurgen Ludwig. [1] Subsequently, the term nonalcoholic fatty liver disease (NAFLD) was used to describe the histological spectrum of steatosis to steatohepatitis with its subtypes nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). The histological classification was further expanded upon by various scoring systems categorising steatosis, disease activity and fibrosis.[2-4] This framework has served as the anchor for our current understanding of the disease, data on the burden of disease, and efforts to develop treatment for the condition.

While the nomenclature is widely used, it has always been appreciated that the term “nonalcoholic” did not accurately capture what the aetiology of the disease was, and notably, the term ‘fatty’ has been considered to be stigmatising by some. Furthermore, there are individuals with risk factors for NAFLD, such as type 2 diabetes, who consume more alcohol than the relatively strict thresholds used to define the nonalcoholic nature of the disease that are not adequately recognised by existing nomenclature, are excluded from trials and consideration for treatments.[5] Indeed, there is a recognition now that there are overlapping biological processes which may contribute to both NAFLD and alcohol-related liver disease (ALD). All of these factors have led to growing dissatisfaction with the current nomenclature. This was summarised in a paper by Eslam et al in 2020 and led to the proposal to use the term metabolic dysfunction associated fatty liver disease (MAFLD), which includes patients with a fatty liver regardless of the amount and pattern of alcohol intake under this terminology.[6, 7] While MAFLD was accepted by some, concerns were raised about the mixing of aetiologies, continued use of the term ‘fatty’ considered stigmatising by many, restricting the population to those with 2 metabolic risk factors and allowance of more liberal alcohol use, thus impacting our understanding of natural history.[8-10] One area of particular concern was the potential negative impact of changes in diagnostic criteria for the disease in terms of biomarker and therapeutic development.[7, 9, 10]

These concerns led to a multi-stakeholder effort under the auspices of the American Association for Study of Liver Disease (AASLD) and the European Association for Study of the Liver (EASL) in collaboration with the Asociación Latinoamericana para el Estudio del Hígado (ALEH) with engagement of academic professionals from around the world including hepatologists, gastroenterologists, paediatricians, endocrinologists, hepatopathologists and public health and obesity experts along with colleagues from industry, regulatory agencies and patient advocacy organisations to resolve these concerns and develop a consensus on a change in nomenclature and the diagnostic criteria for the condition. This manuscript summarises the methodology, including a multi-step Delphi process, the results of the process and provides the consensus recommendations endorsed by societies, patient advocacy groups, journals and industry for adoption by all stakeholders.

## METHODS

### Panel Generation and Statement Development

The panel for this Delphi study was generated through an iterative, inclusive process involving diverse liver organisations around the world (Table 1). The Steering Committee (n=36) was composed of two co-chairs (MER, PNN), representing AASLD and EASL, respectively and 34 other members nominated by their respective associations with a view to ensuring broad geographic representation.

The consensus process used a modified Delphi method [11-13] to incorporate input from the literature and a diverse group of content experts, practitioners, and patient advocates.

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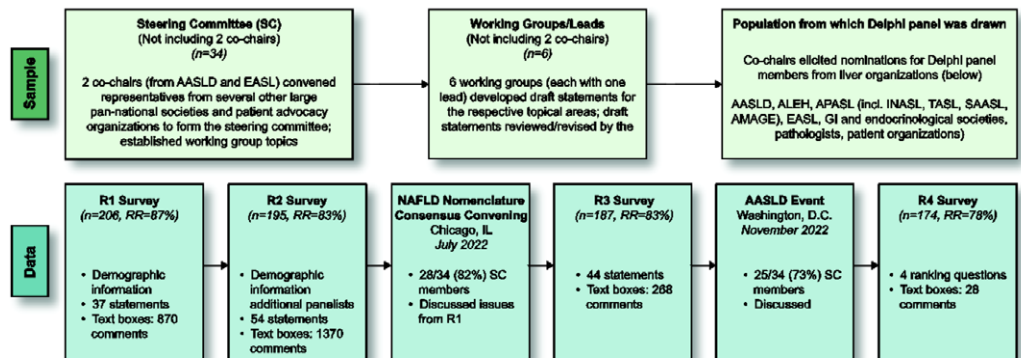
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The steering committee identified 5 areas deemed fundamental to the consideration of a revised nomenclature, namely: 1. What are issues with current nomenclature, and can they be addressed? 2. What is the importance of steatohepatitis in disease definition and endpoints? 3. How should the role of alcohol be accounted for? 4. How might name change impact disease awareness, clinical trials and regulatory approval pathways? and 5. Can an alternative name reduce heterogeneity and allow for future advances? Between late 2021 and early 2022, the steering committee was divided into six working groups, each with a designated lead (SMF, MER, PNN, AJS, VR, FK), responsible for reviews of the literature to inform development of draft statements for their assigned topic area: patient-centred perspective (SMF); pros and cons of the current nomenclature (MER); defining fatty liver disease in the setting of metabolic dysfunction (PNN); disease heterogeneity (AJS); histopathology (VR); and how to manage the role of alcohol in dual aetiology (FK). The preliminary draft statements were compiled and shared with the larger steering committee for review, and the feedback was incorporated into a revised set of draft consensus statements (Supplementary Table 1, <http://links.lww.com/HEP/H885>). Pan-national societies were asked to nominate additional experts and other stakeholders including patient advocacy organisations to be invited (n=267) to participate in the Delphi panel (Figure 1). Nominating societies were instructed to select individuals actively engaged in NAFLD research or clinical practice of patients with NAFLD. Consensus was defined a priori as a supermajority (67%) vote. To increase geographic diversity in the Delphi panel, an additional 30 experts were invited to participate in R2. The characteristics, including demographics, professional expertise, and geographic representation, of Delphi panel participants (n=224) are summarised in Table 1 and Supplementary Table 2, <http://links.lww.com/HEP/H885>.



**FIGURE 1-Summary of the Delphi Process.** The top section depicts the iterative sampling approach employed to generate a large, diverse Delphi panel (267 experts invited and 225 participated across the four rounds). The two co-chairs, from AASLD and EASL, respectively, convened representatives from several other large pan-national societies and patient advocacy organizations to form the Steering Committee. This group identified six topics/working groups that led the development of a preliminary set of consensus statements, which were reviewed by the larger steering committee and subsequently revised. The co-chairs elicited nominations for Delphi panel members from a diverse group of liver organizations. The bottom section depicts the four survey rounds (R1-R4) of data collection from the full Delphi panel, which involved panelists' indicating their level of agreement/disagreement (i.e., consensus) with statements in each survey round, as well as the ability to provide comments in open-ended text boxes. Draft consensus statements were revised based on panelists' comments for subsequent rounds. Two large expert convenings were held following R2 and R3 to permit group discussion of issues raised from the survey data collection components of the Delphi methodology. RR = response rate.

**TABLE 1. Delphi Panel Characteristics (N=225)**

	N	%
<b>Professional characteristics</b>		
<b>Primary sector of employment</b>		
Civil society	7	3
Private	21	9
Public	34	15
Academic	158	70
Other	4	2

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	N	%
<b>Primary field/area of work</b>		
Clinical research	118	54
Healthcare provider	61	28
Non-clinical research	13	6
Patient/policy advocacy	18	9
Other	7	4
<b>Primary area of specialty/expertise* (among healthcare providers, clinical and non-clinical researchers)</b>		
Gastroenterology	7	4
Endocrinology	13	7
Hepatology	151	82
Other	13	8
<b>Years working in the field post-training</b>		
0-12	53	29
13-24	69	37
25-36	51	27
37-48	13	7
<b>% of work in NAFLD-related clinical care, research or both</b>		
0-25	26	12
26-50	61	27
51-75	68	30
76-100	44	19
<b>Number of articles (co)authored on topic of NAFLD</b>		
<6	32	17
6-20	42	22
21-50	39	21
>50	74	40
<b>Liver organization associated with (N invited)</b>		
AASLD (72)	60	27
ALEH (30)	27	12
APASL, AMAGE, INASL, SAASL, TASL (41)	29	13
EASL (70)	66	29
GI and endocrinological societies (21)	15	7
Pathology societies (4)	3	1
Patient organization (29)	24	11
<b>Personal Characteristics</b>		
<b>Gender</b>		
Woman	88	40
Man	135	60
Non-binary or gender diverse	0	0
Prefer not to say	0	0
<b>Country where born (N=59)*</b>		
High income	163	73
Low and middle income	61	27
<b>Country where currently working (N=54)*</b>		
High income	183	82
Low and middle income	41	18
<p>Notes: Ns for different characteristics vary due to missing data; percentages may not sum to 100 due to rounding. With respect to respondent area of expertise 184 of 192 participating healthcare providers and researchers responded to the request to provide their area of expertise. *24 panelists indicated that in their clinical practice or liver-focused research, they routinely care for or focus on liver disease patients who are under 18 years old. Note that numbers represent those that engaged in the process, rather than those who were invited to join the process, but did not respond. +N of total countries represented.</p> <p>Abbreviations: AASLD, American Association for the Study of Liver Disease; ALEH, Asociación Latinoamericana para el Estudio del Hígado (Latin American Association for the Study of the Liver); AMAGE, African Middle East Association of Gastroenterology; APASL, Asian Pacific Association for the Study of the Liver; EASL, European Association for the Study of the Liver; GI, gastrointestinal; INASL, Indian National Association for the Study of the Liver; NAFLD, non-alcoholic fatty liver disease; SAASL, South Asian Association for Study of the Liver; TASL, Taiwan Association for the Study of the Liver.</p>		

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TABLE 2. NAFLD Nomenclature Consensus Group

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Naim	Alkhouri	United States
Alina	Allen	United States
Michael	Allison	United Kingdom
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Marco	Arrese	Chile
Diego	Arufe	Argentina
Pablo	Aschner	Colombia
Amon	Asgharpour	United States
Gyorgy	Baffy	United States
Maya	Balakrishnan	United States
Meena	Bansal	United States
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Renata	Belfort	United States
Carlos	Benitez	Chile
Thomas	Berg	Germany
Annalisa	Berzigotti	Germany
Michael	Betel	United States
Ulrich	Beuers	Netherlands
Cristiana	Bianco	Italy
Jerome	Boursier	France
Clifford	Brass	United States
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Elizabeth Matthews	Brunt	United States
Elisabetta	Bugianesi	Italy
Maria	Buti	Spain
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Graciela	Castro-Narro	México
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Wah Kheong	Chan	Malaysia
Phunchai	Charatcharoenwitthaya	Thailand
Michael	Charlton	United States
Amanda	Cheung	United States
Daniela	Chiodi	Argentina
Ray	Chung	United States
David	Cohen	United States
Kathleen	Corey	United States
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Helma P.	Cotrim	Brazil
Javier	Crespo	Spain
Deborah	Crosby	United States
Donna	Cryer	United States
Kenneth	Cusi	United States
Yock Young	Dan	Singapore
Anuradha	Dassanayake	Sri Lanka
Nicholas	Davidson	United States
Robert	De Knegt	Netherlands
Victor	De Ledinghen	France
Münevver	Demir	Germany
Moutaz	Derbala	Qatar
Sebastian	Diaz	Colombia
Anna Mae	Diehl	United States
Bruce	Dimmig	United States

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Mohammed	El-Kassas	Egypt
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Jiangao	Fan	China
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Yasser	Fouad	Egypt
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Dave	Frank	United States
Scott	Friedman	United States
Angie	Fry Carpenter	United States
Michael	Fuchs	United States
Rino	Gani	Indonesia
Amalia	Gastaldelli	Italy
Anja	Geerts	Belgium
Andreas	Geier	Germany
Marcos	Giral	Paraguay
George	Goh	Singapore
Nicolas	Goossens	Switzerland
Cheryl	Grainger	United States
Isabel	Graupera	Catalonia
Cynthia	Guy	United States
Hannes	Hagström	Sweden
Stephen	Harrison	United States
Zachary	Henry	United States
Bela	Hunyady	Hungary
Alan	Hutchison	United States
Scott	Isaacs	United States
Jidong	Jia	China
François	Jornayvaz	Switzerland
Fasiha	Kanwal	United States
Cynthia	Kemp	United States
Denise	Kile	United States
Won	Kim	South Korea
Seung Up	Kim	South Korea
George	KK Lau	Hong Kong
Samuel	Klein	United States
David	Kleiner	United States
Rohit	Kohli	United States
Bart	Koot	Netherlands
Yannoula	Koulla	Cyprus
Marcelo	Kugelmas	United States
Joel	Lavine	United States
Jeffrey	Lazarus	Spain
Mariana	Lazo	United States
Hye Won	Lee	South Korea
Nathalie	Leite	Rio de Janeiro
Han-Chieh	Lin	Taiwan
Michelle	Long	United States
Rohit	Loomba	United States
Susan	Love Hawfield	United States
Adelina	Lozano	Peru
Panu	Luukkonen	Finland
Paula	Macedo	Portugal
Dina	Mansour	United Kingdom
Christos	Mantzoros	United States
Giulio	Marchesini	Italy
Sebastián	Marciano	Buenos Aires
Claudia P.	Marques Souza de Oliveira	Brazil
Kim	Martinez	United States
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Claudia P.	Oliveira	Brazil
Massao	Omata	Japan
Arlin	Ong	Philippines
Martín	Padilla	Perú
Raluca	Pais	France
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Diana	Payawal	Philippines
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Gianluca	Perseghin	Italy
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Massimo	Pinzani	United Kingdom
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Diane	Tovar	United States
Michael	Trauner	Austria
Emmanuel	Tsochatzis	United Kingdom
Luca	Valenti	Italy
Laurens	Van Kleef	Netherlands
Saskia	Van Mil	Netherlands
Lisa	VanWagner	United States
Adriana	Varon Puerta	Colombia
Jose Antonio	Velarde Ruiz Velasco	Mexico
Mette	Vesterhus	Norway
Eduardo	Vilar-Gomez	United States
Anthony	Villotti	United States
Miriam	Vos	United States
Kymberly	Watt	United States
Julia	Wattacheril	United States
Fonda	Wilkins	United States
José	Willemse	Netherlands
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Stavra	Xanthakos	United States
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## Data Collection

The Delphi process comprised six components of online data collection (via the Qualtrics platform) and in-person discussions, including a first round (R1) survey (7 Apr-9 May 2022); a second round (R2) survey (15-27 June 2022 plus additional panellists 8 Sept-16 Oct); a large-group nomenclature consensus meeting (Chicago, IL, USA, July 2022); a third round (R3) survey (17-27 Oct 2022); a second convening (AASLD annual meeting, Washington, DC, USA, Nov 2022) involving both steering committee and larger panel discussions; and, a fourth round (R4) survey (2 Dec 2022-22 Jan 2023) (Figure 1). Draft consensus statements contained predominantly 4-point Likert-type response categories related to agreement/disagreement (e.g. agree/somewhat agree/somewhat disagree/disagree), support/opposition, etc., and 3-point responses (e.g., increase, no change, decrease). All statements included a 'not qualified to respond' option to accommodate the diverse expertise represented in the panel. In addition, in line with established Delphi processes, [11-13] text boxes appeared after panellists entered responses to each statement so they could provide comments and suggest edits, if desired. These were reviewed and used to modify statements in subsequent survey rounds.

## Analysis Plan

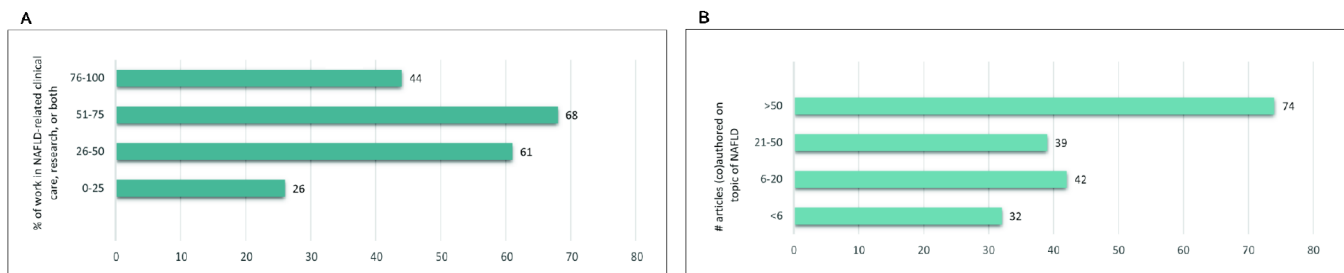
The survey question and textbox data in the Delphi study required quantitative and qualitative analysis. For the survey question, responses were generated and frequencies for all response categories were recoded to the 4-point response statements to dichotomous construction (e.g., agree + somewhat agree vs. somewhat disagree + disagree) to determine if the level of consensus with individual statements reached the minimum super-majority (i.e. >67%) cut-off, which was agreed upon a priori. For each statement, those selecting 'not qualified to respond' were removed from the denominator to calculate statement frequencies from the relevant sample. The qualitative data collected from the text boxes were reviewed individually by the co-chairs and working group leaders and then discussed in a series of meetings following each survey round to inform decisions regarding statement modification, deletion and/or addition.

For the final decision on both acronym and definition, an external expert committee, comprising content experts from hepatology, endocrinology, paediatrics and patient advocacy representatives, was created and led by two members of the Steering Committee (VR, AJS). The committee was established to represent diversity in terms of expertise and geography, with members chosen based on a prior substantial high-impact publication record in the field. It was composed of 21 members (including 15 who were not part of the Steering Committee) and included 4 endocrinologists and 5 paediatric hepatologists. The external committee discussed and recommended the final name and acronym from the top three choices that emerged from the final Delphi round. Additionally, based on the output from the Delphi process up to this point, the external committee refined the definition, including metabolic parameters for both adult and paediatric disease. The proposal from this external committee was discussed and approved by the broader NAFLD Nomenclature Steering Committee, and then presented to societies' leadership (AASLD, EASL and ALEH) for additional commentary and approval.

## RESULTS

### Delphi Panel Characteristics

Invitation to participate on the Delphi panel included seven societies or organisation types, with 29% from EASL, 27% from AASLD, 13% from APASL, 12% from ALEH, 7% from other societies, and 11% from patient advocacy organisations. We collected descriptive information from all Delphi panel participants including demographic and professional data (Table 1). The panel was geographically and demographically diverse; panellists from over 50 countries participated with regard to both country of birth (n=59 countries) and country where currently working (n=54 countries). Among the panellists, 40% identified themselves as female and 60% as male. Seventy of the panellists were from the academic sector, with smaller proportions from the public (15%), private (9%), and civil society (3%) sectors. The two largest fields/areas of work were clinical research (54%) and clinical care (28%), with hepatology (82%) accounting for an overwhelming majority of the areas of specialisation. There was substantial NAFLD-related expertise among panellists with 76% indicating they spend 26-100% of their work time in NAFLD-related clinical care, research, or both, and 61% reporting having authored >21 and 40% had >50 publications on the topic of NAFLD (Figure 2).



**FIGURE 2** NAFLD-Related Professional Characteristics of Delphi Panelists. NAFLD = nonalcoholic fatty liver disease. Data in panel A represent the number of respondents (x axis) and percentage (y axis) of time spent in NAFLD-related clinical care, research or both. Similarly, panel B depicts the number of respondents (x axis) and percentage (y axis) that have (co)authored articles on the topic of NAFLD.

## Response rates and panel participation

The R1 survey consisted of 37 statements within three domains: (1) Nomenclature and distinctions among disease elements (e.g., diagnostic criteria, prognosis, treatment); (2) Other factors possibly influencing consideration of additional or alternative terms; (3) Name/term preferences (Supplementary Table 1, <http://links.lww.com/HEP/H885>). Of 236 invited experts in R1, 206 participated and rated these statements (Response rate [RR] = 87%). They also provided 870 comments, which were reviewed and incorporated as additional statements and a new paediatric focused domain into the second round of consensus statements, with a total of 54 statements. Of the 236 panellists invited for R2, 195 participated in R2 (overall participation, 195+30, RR=83%), providing 1,370 comments. Comments were organised thematically by their content and reviewed by the leads who then proposed modifications to statements if appropriate, eliminated statements if redundant or as suggested by comments, or carried the statements forward to the next round. To minimise survey fatigue, statements thought to be repetitive or ambiguous were removed from the following round. Additionally, statements covering areas of high consensus were not carried forward to R3. Revised statements were shared with the full Steering Committee before proceeding with the next round. For example, in R3, statement revision resulted in 44 statements; there were 187 participants (of 226 invited, RR=83%) who provided an additional 268 comments.

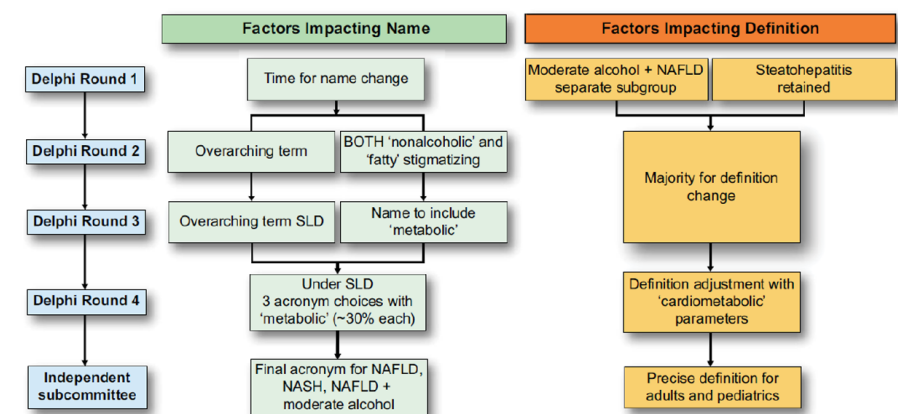
After R2, all Delphi panellists were invited to an in-person (hybrid, i.e. with remote access) 1.5-day nomenclature consensus conference co-hosted by AASLD and EASL in Chicago, IL, USA July 8-9, 2022 for in-depth discussion of the extensive feedback generated from the first two rounds of data collection. This convening provided valuable guidance from a broader group that included the steering committee as well as the broader group of survey panellists to inform statement revision for the third round. The second in-person convening occurred at the annual AASLD conference on 6th November 2022 in Washington DC, USA with two fora for consideration and discussion of the third Delphi round - a closed meeting of the steering committee (n=34 in attendance) followed by a large-group session open to all 2022 AASLD participants including all Delphi panellists. These discussions provided further clarity on the key elements to include in the final round of the nomenclature consensus process.

Based on this feedback, the R4 survey took panellists through a series of four questions that allowed them to select their first and second choices pertaining to terminology preference, whether the term metabolic should be included in the name, the preferred nomenclature (based on their prior choices), and whether or not diagnostic criteria should be revised. Of 224 invited panellists, 174 participated (RR=78%) and provided 28 comments in a final open-ended textbox. (Supplementary Figure 1, <http://links.lww.com/HEP/H886>)

## Data informing nomenclature considerations (R1-R4+)

Supplementary Table 1, <http://links.lww.com/HEP/H885> shows the evolution of survey statements across survey rounds 1-3 and the degree of agreement in each round. Statements were modified for clarity, changed or removed based on review of open text comments, and output from face-to-face meetings. The main conclusions emerging by survey rounds

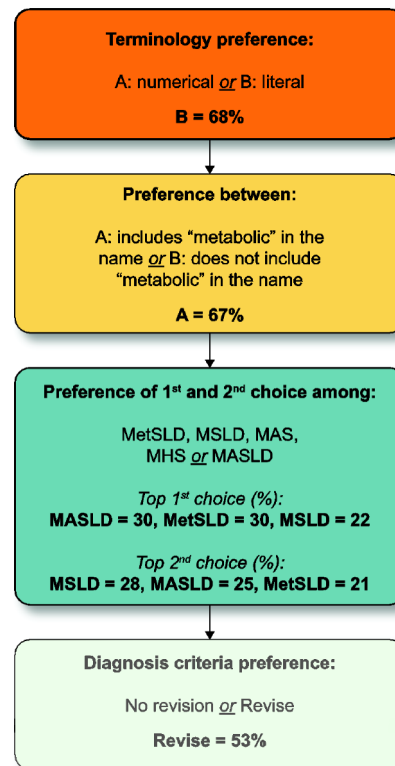
**FIGURE 3 Overview of main findings by Delphi round.** The conclusions reached at the end of each Delphi round are depicted here. Results are shown at each corresponding Delphi round with respect to name change and definition, depicted in light green and orange, respectively. An independent subcommittee comprised of expert endocrinologists, hepatologists, pediatricians and patients chose between the top 3 acronyms emerging from the 4<sup>th</sup> Delphi round and outlined the specifics of the definition to include cardiometabolic parameters, as dictated by the 4<sup>th</sup> Delphi round.



Legend: the flow chart on the left illustrates the evolution in decision-making as regards naming, whereas the one on the right illustrates decision-making as regards definition.



**FIGURE 4 NAFLD Nomenclature Result: Round 4 (Summary).** Delphi round 4 consisted of 4 questions. All respondents responded to all questions irrespective of their response to the preceding question. These are the aggregate results for respondents on each question. The first question addressed whether a literal term to replace NAFLD was preferred over a numerical subtype (e.g. Type 1,2,3 etc.) and 68% preferred the literal term. The second was whether or not the term 'metabolic' should be included in the name and 67% felt it should. The third presented a choice of acronyms that had emerged as the top 4 in Delphi R3 and the top 3 (nearly equal in preference) were advanced to the expert panel for a final decision as there was no clear majority. The last question was binary and simply asked if the definition of the NAFLD replacement term should be retained or refined to include a cardiometabolic qualifier.



are summarised in Figure 3. In the 4th Delphi round only 4 questions were asked to clarify remaining points of disagreement. (Figure 4, Supplementary Figure 1, <http://links.lww.com/HEP/H886>)

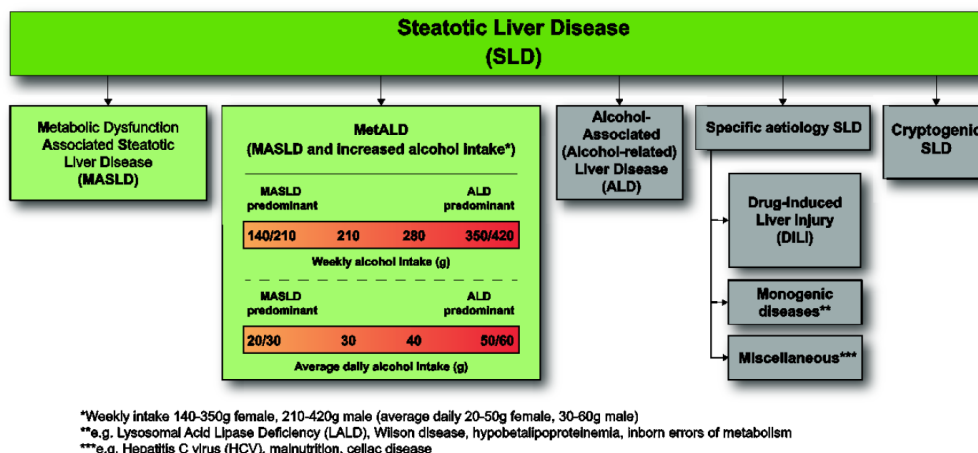
### *Desire for a name change and the role of stigma*

During round 1, a supermajority of respondents (74%) felt that the current names NAFLD and NASH were sufficiently flawed to consider a name change. (Supplementary Table 1, <http://links.lww.com/HEP/H885>) The terms 'nonalcoholic' and 'fatty' were deemed to be stigmatising by 61% and 66% of respondents, respectively. A nomenclature that describes the underlying cause of the disease was preferred by 89% of respondents. While there were concerns over the precise meaning of 'metabolic' and to what extent this term was understood by clinicians, a super-majority felt that having 'metabolic disease or dysfunction' in the name would help patients better understand their disease (72%) and help healthcare professionals better explain or understand the disease (80%). Only a simple majority (56%) felt the terminology of 'metabolic dysregulation' to be a clearly defined clinical entity, although a supermajority (86%) felt that it highlighted a central aspect of disease pathophysiology.

### *Considerations regarding structure and composition of a new name*

When given the choice of whether to select an 'umbrella' term encompassing different disease subcategories, 78% of respondents preferred the idea of an overarching term to encompass the replacement term for NAFLD, ALD and other conditions resulting in hepatic steatosis. Potential overarching terms were informed by survey rounds 2 and 3 and included fatty liver disease, steatotic liver disease, and lipogenic liver disease. Panellists were instructed to rank order their preference, as first, second and third choice. Fatty liver disease, steatotic liver disease, and lipogenic liver disease garnered 46%, 48% and 7% of first choice selections, respectively. When considering the combination of 1st and 2nd choice votes, steatotic liver disease was chosen by 95% of respondents. Sixty-eight % of the panellists preferred the use of a literal name (such as steatotic liver disease) as opposed to using a numerical subtype (such as type 1, type 2, etc.) as part of the new nomenclature. In round 4, 67% of respondents felt that the term 'metabolic' should be included in the revised nomenclature for the alternative name for NAFLD, as a subtype under the overarching term of steatotic liver disease chosen in R3

(Figure 5). Respondents were also asked whether a cardiometabolic risk factor should be added to the current definition and a simple majority were in favour of adding a metabolic qualifier to the definition.



**FIGURE 5 Steatotic Liver Disease sub-classification.** This depicts the schema for Steatotic Liver Disease (SLD) and its sub-categories. SLD, diagnosed histologically or by imaging, has many potential etiologies. MASLD, defined as the presence of hepatic steatosis in conjunction with one CMRF and no other discernible cause, ALD, and an overlap of the 2 (MetALD), comprise the most common causes of SLD. Within the MetALD group there exists a continuum across which the contribution of MASLD and ALD will vary. To align with current literature, limits have been set accordingly for weekly and daily consumption, understanding that the impact of varying levels of alcohol intake are evolving. Other causes of SLD need to be considered separately, as is already done in clinical practice, given their distinct pathophysiology. Multiple etiologies of steatosis can coexist. If there is uncertainty and the clinician strongly suspects metabolic dysfunction despite the absence of CMRF then the term possible MASLD can be considered pending additional testing (e.g., HOMA-IR, OGTT). Those with no identifiable cause (cryptogenic SLD) may be recategorised in the future pending developments in our understanding of disease pathophysiology. Lastly, the ability to provide an affirmative diagnosis allows for the coexistence of other forms of liver disease with MASLD, e.g. MASLD + autoimmune hepatitis or viral hepatitis.

### Considerations for disease definition

Respondents were asked their opinion regarding the concept of steatohepatitis as an important entity, and 95% of respondents felt the presence of steatohepatitis had prognostic implications and should remain an important distinction. Additionally, given the role of 'resolution of steatohepatitis' as one of the two European Medicines Agency (EMA) and US Food and Drug Administration (FDA) approvable endpoints, 93% felt it should remain for both clinical practice and trial endpoints.[14, 15] The current definition of NAFLD excludes consumption of >20g/30g of alcohol per day in females and males, respectively, with a more liberal approach to concomitant alcohol use proposed in the original MAFLD definition. [5, 7] To establish the permissibility of greater alcohol consumption, several questions were asked to better understand the impact of alcohol on the natural history of the disease and also how to characterise various levels of alcohol use in the definition. A supermajority felt that consumption of 30g-60g of alcohol daily in the setting of NAFLD alters the natural history of disease (95%) and may alter response to therapeutic interventions (90%). Furthermore, 90% felt that individuals with steatosis related to metabolic risk factors who consume more than minimal alcohol (30g-60g daily) represented an important group that should be considered in a different disease category and studied independently.

### Perceived impact of name and/or definition change on disease awareness, development of biomarkers or clinical trials

When considering the potential impact of a change in name, definition or both, fifty-six percent felt that a change in nomenclature would positively impact disease awareness. In assessing the impact of a change in name only on the interpretation of existing and emerging clinical trial results, 18%, 72% and 11% (Supplementary Table 1, <http://links.lww.com/HEP/H885; R3, Statement 27>) felt it would hinder, have no impact and enhance, respectively.

When a similar question was asked about the impact on regulatory approval of biomarkers if the name but not the definition changes, 12%, 63% and 25% felt it would accelerate, have no impact or delay approval respectively. In the event of both a name and definition change, 60% of respondents were concerned this could hinder the interpretation of existing and emerging clinical trial results that used the currently accepted definition of NAFLD, whereas 20% felt it would enhance and 20% thought there would be no impact. A simple majority (59%) felt that a change in disease definition would likely delay regulatory approval of biomarkers (R3 – S24) whereas 63% felt a change in name only would have no effect. Of note these questions did not discuss the proposed change to the definition.

### *Paediatric perspective*

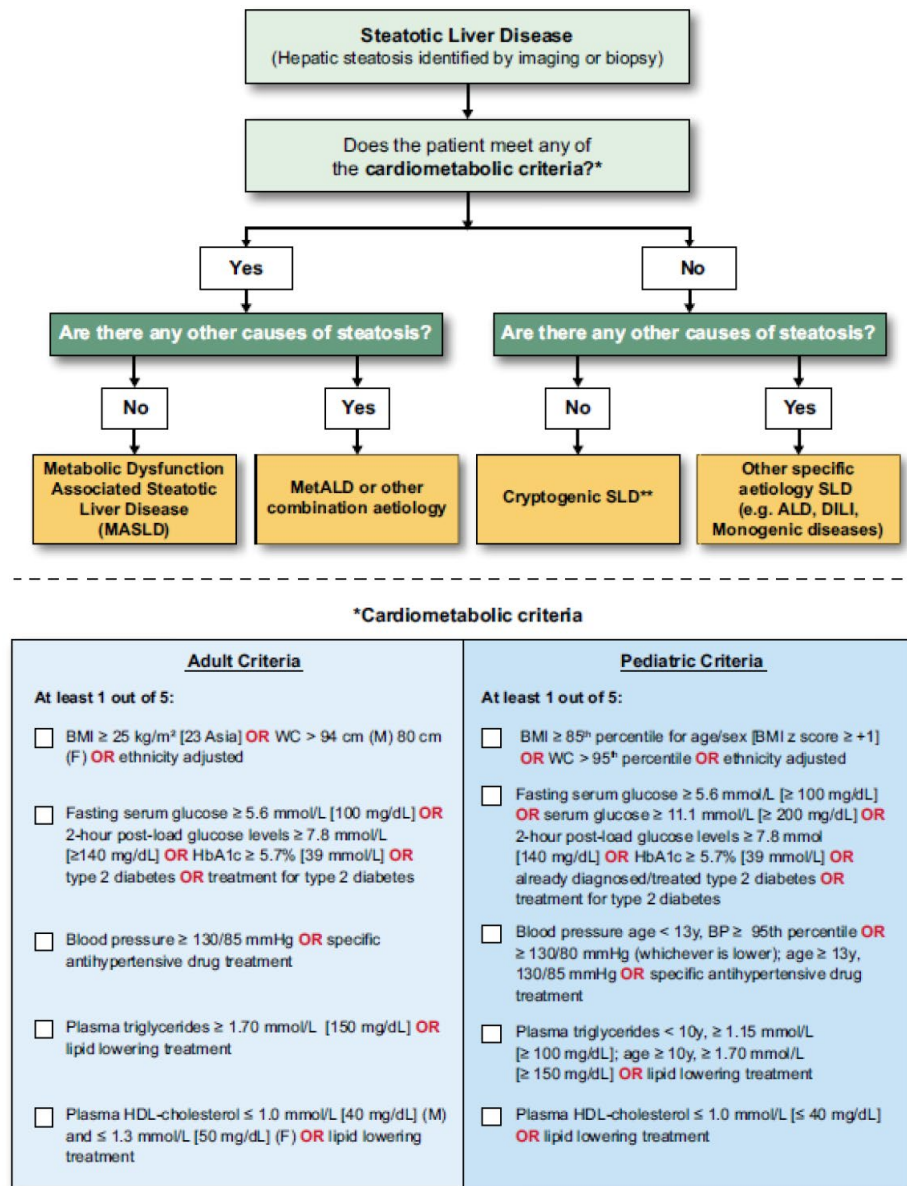
There was a high degree of consensus among the paediatric panellists when considering statements/questions pertaining to the paediatric population. Only paediatricians answered the paediatrics specific questions, and the main themes addressed the role of stigma, use of the term ‘metabolic’ and the histological definition of the disease. In children and adolescents, 60% felt that use of the term ‘nonalcoholic’ was stigmatising for parents and/or paediatric patients, with 55% finding this to be the case with the term ‘fatty’. When asked if the current definition of NASH is less useful in children and adolescents due to a lower frequency of hepatocyte ballooning, 95% agreed that a reassessment of the definitions of steatohepatitis in the paediatric setting would be beneficial. In considering incorporation of the term ‘metabolic’ into the nomenclature, 90% estimated that this term may be confusing in the paediatric context since inborn errors of metabolism are referred to as ‘metabolic liver disease’.

### *Proposed new nomenclature for NAFLD, NASH and NAFLD with increased alcohol consumption*

When considering different subcategories under the overarching term of SLD, 67% of respondents preferred the NAFLD replacement term to include the word ‘metabolic’. The top 3 acronyms, metabolic dysfunction-associated steatotic liver disease (MASLD), MetSLD, or metabolic steatotic liver disease (MSLD) were 30%, 30% and 22%, respectively (Figure 4). In total, 75% of respondents of the external expert committee chose metabolic dysfunction-associated steatotic liver disease (MASLD) as the replacement term for NAFLD and 88% metabolic dysfunction-associated steatohepatitis (MASH) as the replacement term for NASH. The acronym MetALD was chosen by 28% and MAASLD by 33% to represent a separate group of patients with MASLD that consume 140-350 g/week for females and 210-420 g/week for males. MetALD was chosen to avoid the possible confusion or perception associated with the acronym AASLD within MAASLD that may link the acronym to a specific professional association. Within MetALD there is a continuum where conceptually the condition can be seen to be MASLD or ALD predominant. This may vary over time within a given individual.

### *Proposed modifications to current definition*

The strong epidemiological and pathogenic link between NAFLD, metabolic dysfunction and insulin resistance, informed a view in the external expert committee that the diagnosis be based on affirmative rather than exclusionary criteria such as nonalcoholic. There was near universal agreement that the criteria be defined sufficiently broadly to identify both individuals with obesity and cardiometabolic risk factors in the context of regional/ethnic differences. Simple, readily available and easily measurable parameters were also deemed necessary for this set of criteria to be broadly applied in clinical practice and in various clinical settings. Finally, the diagnostic criteria were selected to align with cardiometabolic risk factors believed to be associated with insulin resistance and already well-established and validated in the context of cardiovascular disease. [16] It was agreed that patients with steatosis and any one of the cardiometabolic criteria outlined in Figure 6 would be considered to have MASLD. Of note, making a diagnosis of MASLD does not imply that other causes of SLD do not need to be considered, which is particularly relevant in children where it is imperative to exclude other causes of hepatic steatosis prior to applying the MASLD diagnostic criteria to ensure that dual pathology is not missed.[17]



**FIGURE 6 MASLD diagnostic criteria.** In the presence of hepatic steatosis, the finding of any of a cardiometabolic risk factor, would confer a diagnosis of MASLD if there are no other causes of hepatic steatosis. If additional drivers of steatosis are identified, then this is consistent with a combination etiology. In the case of alcohol this is termed MetALD. In the absence of overt cardiometabolic criteria, other etiologies must be excluded and if none is identified, this is termed cryptogenic SLD, although depending on clinical judgment could also be deemed to be possible MASLD and thus would benefit from periodic reassessment on a case-by-case basis.

Switching from a definition based on the exclusion of any other liver disease (i. e. NAFLD) to a definition based on specific, primarily cardiometabolic risk factors (i. e. MASLD) has potential limitations. Firstly, the key metabolic dysfunction underlying MASLD is insulin resistance, and the selected metabolic risk factors do not equally predict insulin resistance, as for example diastolic blood pressure and HDL-C are only weakly associated with insulin resistance.[18] Secondly, insulin resistance and steatosis may be present in the absence of any cardiometabolic risk factors, especially in younger adults in the primary care setting. Thus, patients with steatosis without overt cardiometabolic risk factors or other discernible cause are labelled as cryptogenic. If there is uncertainty and the clinician strongly suspects metabolic dysfunction despite the absence of CMRF then the term possible MASLD can be considered pending additional testing (e.g., HOMA-IR, OGTT) although this should be left to the discretion of the clinical team. Such cases and also cryptogenic cases that subsequently manifest CMRF can be rebagged as MASLD.

### *Role of alcohol in disease definitions*

With respect to alcohol intake, the overwhelming consensus was to continue to limit alcohol intake (as previously limited for NAFLD) in the context of steatosis. The purpose of this process was to focus on NAFLD, not alcohol-related liver disease, but it was seen as relevant to comment on situations where these was overlap. We therefore created a separate category outside of pure MASLD, namely MetALD, with alcohol intake greater than that allowed for NAFLD/MASLD. Within the group of patients with MetALD, there may be individuals where MASLD is the perceived dominant driver and others where ALD is the perceived dominant driver, and indeed this may change over time. (Figure 5).

## DISCUSSION

Identification of a new name and definition for the condition formerly known as nonalcoholic fatty liver disease has been a challenging process given the broad range of global stakeholders. It is imperative that any new proposal be sufficiently better than the existing nomenclature and that it enhances awareness, understanding of the disease and drug/biomarker development. This robust, representative, patient-centric Delphi process systematically addressed all the issues and views over the past years and through consensus has arrived at both a new name and a refined definition. By inclusion of patient advocacy groups throughout the entire process, the new nomenclature strives to accelerate disease awareness whilst minimising stigma associated with use of terms perceived as stigmatising by some patients and their caregivers.

Several important findings emerged from the nomenclature consensus process; there was clear support for a name change, use of an overarching term which could accommodate the evolution of disease understanding, and use of a metabolic descriptor in the new nomenclature. Both the overarching term of steatotic liver disease (SLD) and the more specific metabolic dysfunction-associated steatotic liver disease (MASLD) provide an affirmative non-stigmatising description of the condition rather than a diagnosis of exclusion. This is also seen in the definition, which requires the presence of at least one cardiometabolic risk factor in addition to hepatic steatosis. The proposed nomenclature is not intended to be static, but rather allows the flexibility for refinement as new evidence emerges about underlying pathophysiology and risk factors.

A key consideration is the preservation of existing data on natural history, biomarkers and clinical trials as part of these changes. To address the impact of the refined definition, an analysis of the LITMUS consortium European was performed, which demonstrated that 98% of the existing Registry cohort of patients with NAFLD would fulfill the new criteria for MASLD.[19] Conceptually patients with the previous definition (NAFLD) can now be seen to be completely covered by the categories of MASLD and possible MASLD. The introduction of a separate MetALD subcategory where metabolic and alcohol-related risk factors coexist sits outside MASLD/NAFLD and is an opportunity to generate new knowledge for this common group of patients. In addition, maintenance of the term, and clinical definition, of steatohepatitis ensures retention and validity of prior data from clinical trials and biomarker discovery studies of patients with NASH to be generalizable to individuals classified as MASLD or MASH under the new nomenclature, without impeding the efficiency of research.

The Delphi process utilised a super-majority threshold of  $\geq 67\%$  with two exceptions, the consideration of stigma and a binary question to retain or revise the current definition. Whilst recognizing that perceptions of stigma differ widely,[20, 21] especially across different languages and cultures, in this study it became clear that substantial proportions of the respondents deemed terms such as ‘fatty’ stigmatising, hence its exclusion as part of any new name. Although health care professionals may contend that patients have not reported this previously, this likely reflects in part a failure to ask the question in the first place and the power imbalance in the doctor-patient relationship. Moreover, a recent large study indicated that some health care professionals and patients considered the terms fatty and nonalcoholic to be pejorative and stigmatising.[21] The use of medical terminology such as steatosis may at one level be seen as over-medicalising the lexicon yet it affords patients the opportunity to disclose their condition to friends and colleagues without having to face prejudice and stigma that can

be inherent to the word ‘fatty’.[21, 22] Efforts to increase disease awareness have had modest success, possibly impacted by the perception that care providers deem the term ‘fatty liver’ as describing an indolent condition. With therapeutics on the horizon, there is renewed energy to identify ‘at-risk’ patients, which in conjunction with new terminology may bolster awareness and sense of importance.

The overarching term of steatotic liver disease encompasses the spectrum of causes of hepatic steatosis, thus allowing precise classification once a specific aetiology has been identified. The new names also allow for further characterization of fibrotic severity, e.g. MASH with stage 3 fibrosis. Disease staging and severity are not altered by this process, although it is anticipated that in the near to medium term, disease staging will be achieved using non-invasive tests, which can be incorporated into further clarifications of disease stage. Thus, the current consensus process does not deviate from prior case definitions for steatohepatitis and disease stages.[23] The diagnosis of MASLD/MASH with advanced fibrosis cirrhosis, when steatosis may not be present, will be based upon existing agreed criteria for NASH cirrhosis.[23] This also applies to patients with MetALD and ALD with significant fibrosis who may not have steatosis, yet have SLD as part of the over-arching nomenclature, reflecting the mechanism of injury.

The proposed nomenclature also improves upon the prior “nonalcoholic” label and appropriately assigns a metabolic basis for this liver disease which was long recognized as “the hepatic manifestation of the metabolic syndrome”. [5] This important conceptual change has several practical consequences. First, when addressing patients, it allows for a coherent and straightforward explanation of the disease as it is intuitively easier to understand in the context of its underlying cardiometabolic abnormalities linked to insulin resistance and its association with the patient’s other conditions, rather than in the framework of a diagnosis of exclusion. This also helps to communicate to the patient the main therapeutic actions to be taken both from a liver and a holistic perspective. Secondly, we believe that using this classification will enhance disease awareness, since the alignment of the diagnostic criteria for MASLD with widely recognized phenotypic traits in diabetes and cardiovascular medicine will make it easier for the larger community of healthcare providers to identify individuals with this condition. There is a strong convergence between the metabolic set of criteria we propose for diagnosing MASLD and those proposed by Eslam et al. for MAFLD. [24] However, the current consensus approach decided to prioritise robust and easily accessible clinical criteria and biological measurements, and as such these criteria do not include direct measurements of insulin resistance (such as fasting insulin or HOMA-IR) because of their complexity, cost and variability between laboratories. However, in patients with hepatic steatosis in the absence of overt cardiometabolic risk factors, secondary testing for insulin resistance may be useful to identify those with possible MASLD. It is important to understand that the set of diagnostic criteria for MASLD are not intended to diagnose “metabolic syndrome” or predict the occurrence of cardiovascular outcomes. The cardiometabolic risk factors are intended to identify patients likely to have insulin resistance as the main cause of hepatic steatosis. There was consideration of providing differential weighting for the cardiometabolic risk factors such as type 2 diabetes although the literature is conflicting in that regard with some indicating no parameter is better than another at identifying hepatic steatosis.[25]

This process focusses on nomenclature and definition of NAFLD rather than a determination of what constitutes hepatic steatosis or assessment of disease severity. There is an extensive literature on the confirmation of hepatic steatosis [26, 27] which we did not seek to interrogate – often this is a pragmatic determination in clinical practice which is where this guidance starts. Moreover, this nomenclature process, in line with published guidance,[21, 28, 29] is not advocating for the routine use of tests to confirm hepatic steatosis although in reality most, if not all, patients will usually have imaging at some point. Finally, we recognise it is the evaluation of fibrosis either as part of screening strategies or individual clinical decisions, which is relevant for most clinical settings.[30] That remains unchanged after this process, other than the name (e.g. MASLD with advanced fibrosis).

Contrary to the initial proposal by Eslam et al, the Delphi process revealed that most experts consider that MetALD patients should be classified in a category distinct from MASLD, mainly because of the added pathogenic value of alcohol consumption and consequential prognostic

implications. The condition MetALD provides an opportunity to better define the natural history for such patients and the development of biomarkers and therapies which are currently lacking for this group of patients.[31] ALD is a distinct liver disease (of which steatosis is one of the features) and thus categorised under the SLD umbrella. This should raise awareness of alcohol as a driver of steatosis and highlight the impact of excessive alcohol consumption (i.e., higher than 50–60 g daily in females and males, respectively) irrespective of their association with metabolic dysfunction. Studies have shown that even in excessive drinkers, obesity increases the prevalence of cirrhosis and glycaemic dysregulation increases fibrosis severity.[32, 33] Patterns of alcohol use must also be taken into consideration as bingeing (even within the total weekly ‘allowable limit’ for MASLD) can be detrimental. We also recognise that validated objective tools are not currently available to determine the relative contribution of MASLD and ALD in patients with MetALD and hence we rely on self-reported alcohol intake which can be inaccurate. In that regard this is a conceptual construct and might be better seen as a disease spectrum with different weights of different modifiable disease drivers (cardiometabolic factors and alcohol). This is also relevant for the distinction between patients with MetALD and those drinking more heavily that are termed as having ALD. Also the category of ALD without metabolic factors is relatively rare amongst patients with significant fibrosis but it was felt to represent part of the spectrum.

In addition to defining a distinct category for patients with MASLD and greater alcohol consumption (MetALD), the proposed nomenclature allows, by introducing the umbrella term of steatotic liver disease, for diagnostic subgroups of steatotic liver disease to be identified, namely those that are drug-related as well as others. The latter encompasses the many “secondary” causes of NAFLD, most of which are rare diseases, including monogenic diseases.[31] This is particularly relevant in children, in whom rare genetic metabolism defects can cause steatosis and must be considered.[17] Patients with steatosis without overt cardiometabolic risk factors or other discernible cause are labelled as cryptogenic, although depending on clinical judgement could also be deemed to have possible MASLD and would benefit from periodic reassessment on a case-by-case basis. Of note, genetic variants influencing the prevalence and/or severity of MASLD such as PNPLA3, TM6SF2 and HSD17B13, and other genetic risk variants that are common in the general population, were not considered a distinct nosological entity. This was because these variants are disease modifiers for both MASLD and ALD rather than causative factors, in contrast to rare variants responsible for monogenic diseases. The change in nomenclature in favour of a positive diagnosis based on the presence of cardiometabolic risk factors will also allow for a rational reclassification of most cases of the condition formerly known as “lean NASH” into the regular MASLD category, as long as currently defined metabolic risk factors are present. The “cryptogenic” category will, as mentioned, also accommodate the rare specific causes of steatotic liver disease unrelated to metabolic dysfunction, alcohol consumption, drug intake or other causes [34] while waiting for a precise identification of the causal agent by future research.

Despite the many strengths of this rigorous process, we acknowledge limitations. The individual statements changed between R1 and R3 (Supplementary Table 1, <http://links.lww.com/HEP/H885>) and there was variation in levels of agreement for individual statements although this reflects their evolution, as important issues arose that we needed to consider regarding the NAFLD nomenclature. Furthermore, the lack of uniform agreement on many topics reflects the diversity of opinions involved in the process. A priori, we chose a threshold of 67% (supermajority) to define consensus, which meant that some opinions, although held by a simple majority (more than 50% but less than 67%), did not influence the final decisions, with the exception of stigma and the decision to alter the disease definition. Nonetheless, we are confident that statements supported by a super majority were addressed and incorporated.

In conclusion, we believe this process, which has multi-stakeholder endorsement, provides a strong platform from which we can increase disease awareness, reduce stigma and accelerate drug and biomarker development for the benefit of patients with MASLD, MASH and MetALD.

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