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No More NAFLD

The NAFLD nomenclature is changing.





Siavosh Nasseri-Moghaddam MD, MPH, AGAF
Associate Professor of Medicine, TUMS
IAGH monthly Meeting, Tehran, Iran
Aban 25, 1402 (Nov 16, 2023)

In the Beginning……from Bacchus to NASH

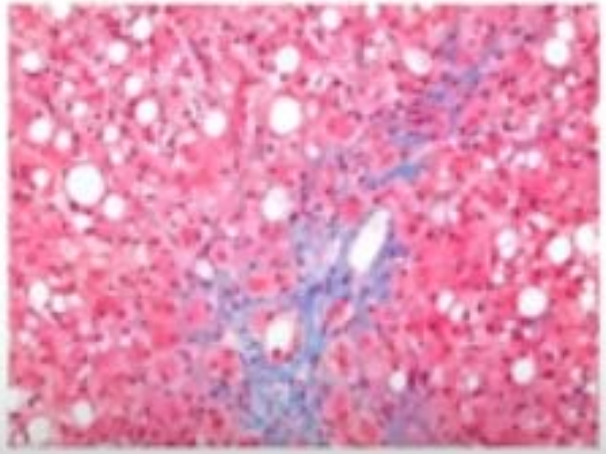
Mayo Clinic Proceedings

Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease.

Ludwig J, Viggiano TR, McGill DB and Oh BJ.

Mayo Clinic Proceedings. 1980 Jul;55(7):434-8





HEPATOLOGY

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PRACTICE GUIDANCE | HEPATOLOGY, VOL. 67, NO. 1, 2018

The Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance From the American Association for the Study of Liver Diseases

Naga Chalasani,[1] Zobair Younossi,[2] Joel E. Lavine,[3] Michael Charlton,[4] Kenneth Cusi,[5] Mary Rinella,[6] Stephen A. Harrison,[7] Elizabeth M. Brunt,[8] and Arun J. Sanyal[9]

The evolution of NAFLD nomenclature



2020

Metabolic dysfunction associated fatty liver disease (MAFLD) proposed

- Calling 'what it is v. what its not'
- Stigma from alcohol in name
- Positive diagnosis
- Recognize close relationship with metabolic disorders

2020

MAFLD defined and promoted as the new nomenclature

- **Elimination of 'steatohepatitis'**
- **Allowance of more liberal alcohol use**

Concern raised over validity of process and impact of MAFLD name and definition change

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SPECIAL ARTICLE | HEPATOLOGY, VOL. 73, NO. 1, 2021

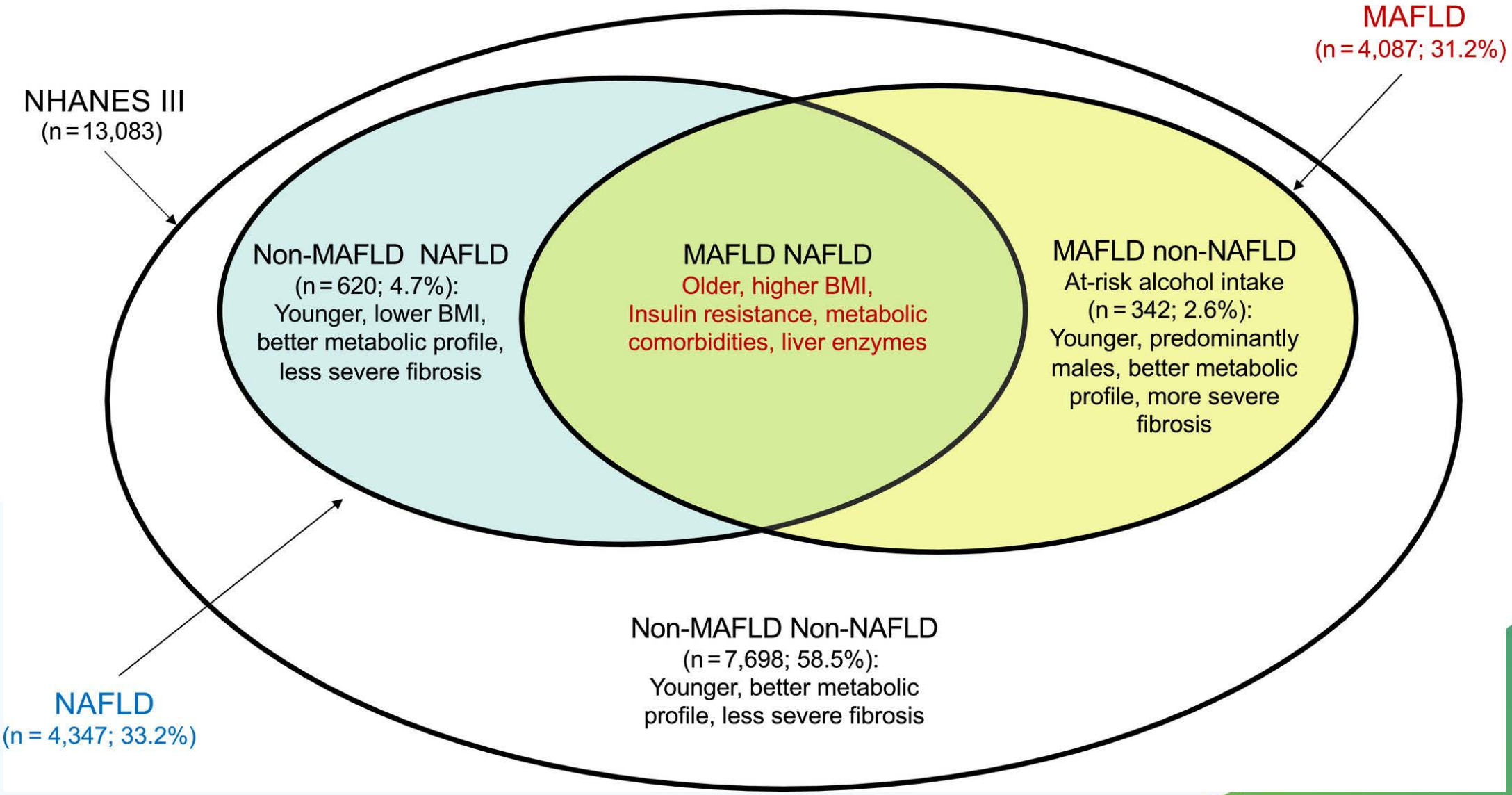
From NAFLD to MAFLD: Implications of a Premature Change in Terminology

- Concern over validity of process
- Impact on disease awareness and stigma
- Drug/biomarker development
- Impact of alcohol
- Lack of clarity on metabolic dysfunction
- Adaptability to emergence of disease phenotypes

JOURNAL OF HEPATOLOGY

A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement

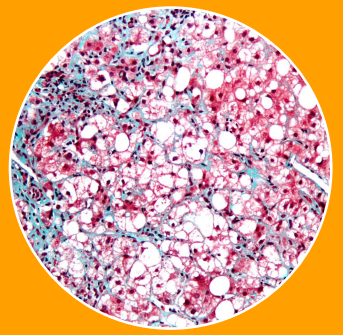
The times they are a-changin' (for NAFLD as well)


MAFLD
(n = 4,087; 31.2%)
NHANES III
(n = 13,083)
Non-MAFLD NAFLD
(n = 620; 4.7%):
Younger, lower BMI,
better metabolic profile,
less severe fibrosis
MAFLD NAFLD
Older, higher BMI,
Insulin resistance, metabolic
comorbidities, liver enzymes
MAFLD non-NAFLD
At-risk alcohol intake
(n = 342; 2.6%):
Younger, predominantly
males, better metabolic
profile, more severe
fibrosis
Non-MAFLD Non-NAFLD
(n = 7,698; 58.5%):
Younger, better metabolic
profile, less severe fibrosis
NAFLD
(n = 4,347; 33.2%)

Renaming NAFLD: Key Questions to Address



What are issues with current nomenclature and can they be addressed?



What is the importance of steatohepatitis in disease definition and endpoints?



How should the role alcohol be accounted for (or not)?



How might name change impact disease awareness, clinical trials and regulatory approval pathways?



Can an alternate name reduce heterogeneity and allow for future advances ?

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Multi-Society Effort – AASLD, EASL and ALEH

Key attributes of a Delphi consensus process:

- Informed by subject matter experts
- Conducted using rigorous methodology
  - Anonymity of voting and reporting of results
  - Transparency of process
- Survey rounds combined with in-person discussion to facilitate consensus building
  - Acknowledgement of the value of diverse opinions
  - Assures that viewpoints are considered and discussed even if they don’t reach the consensus threshold

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Global NAFLD Nomenclature Involvement



- 264 nominees from EASL, AASLD, ALEH, APASL, AMAGE, proportionate to association member size
- 56 countries represented

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Global NAFLD Nomenclature Steering Committee



Publications: 8210
NAFLD publications: >4000
Median NAFLD: 89
Citations: >1,000,000
Average *h*-index: >74

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Overview of process

A priori threshold of consensus: Super majority (≥67%)

- **Round 1:**
  - 35 Questions/statements
  - ≈1000 comments
- **Round 2:**
  - 52 Questions/statements
  - 1366 comments
- **Round 3:**
  - 42 Questions/statements
  - 800 comments
- **Round 4:**
  - 4 Questions/statements

+

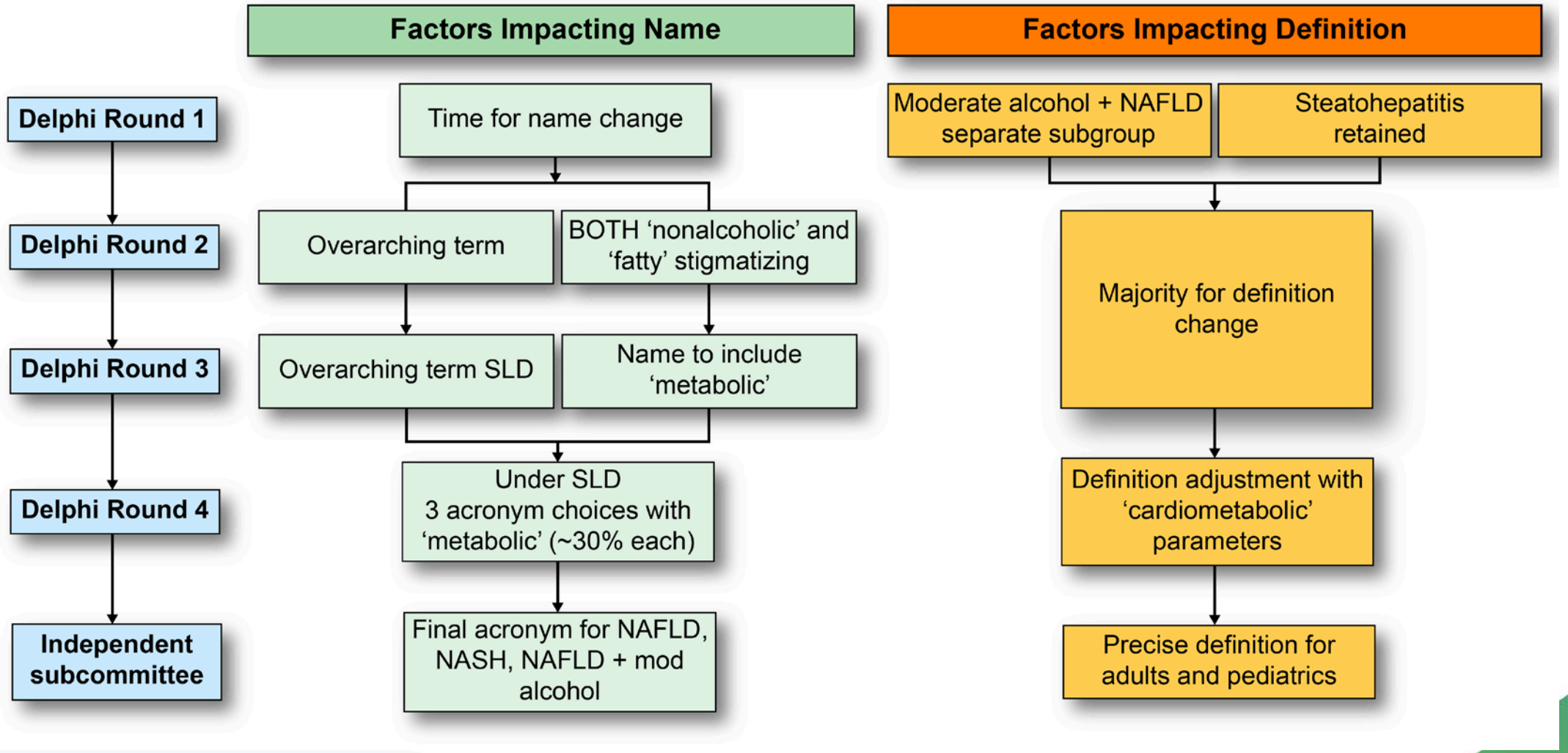


Chicago Nomenclature
Consensus conference
July 8-9, 2022
(61 in person, 69 virtual)

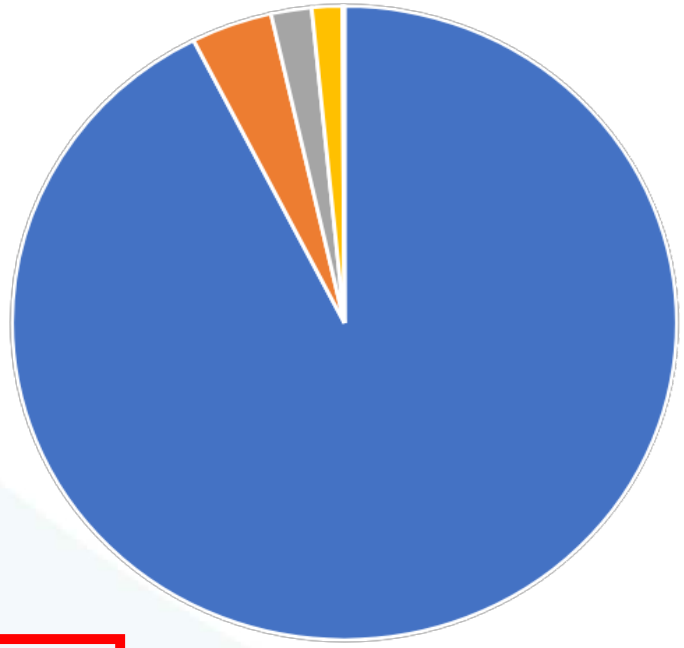


Pan-society nomenclature meeting,
Washington DC, TLM 2022

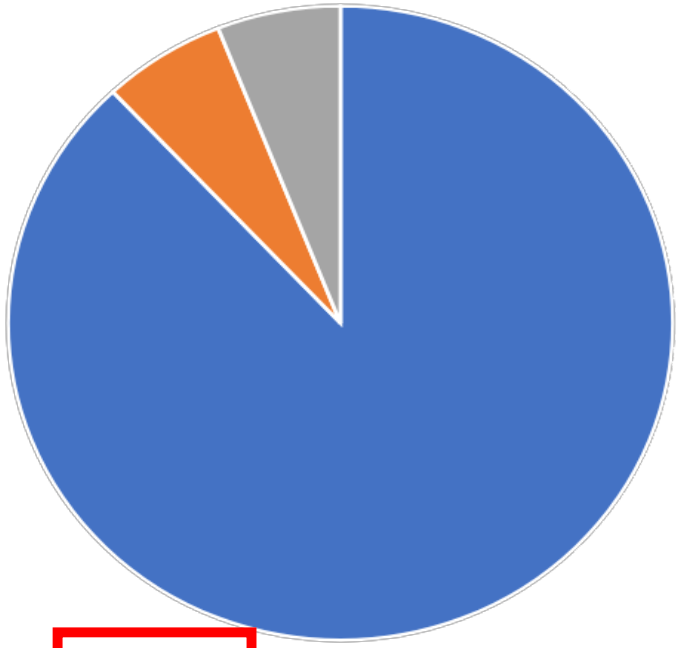
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Delphi Round 1
Delphi Round 2
Delphi Round 3
Delphi Round 4
Independent subcommittee
Factors Impacting Name
Time for name change
Overarching term
BOTH 'nonalcoholic' and 'fatty' stigmatizing
Overarching term SLD
Name to include 'metabolic'
Under SLD
3 acronym choices with 'metabolic' (~30% each)
Final acronym for NAFLD, NASH, NAFLD + mod alcohol
Factors Impacting Definition
Moderate alcohol + NAFLD separate subgroup
Steatohepatitis retained
Majority for definition change
Definition adjustment with 'cardiometabolic' parameters
Precise definition for adults and pediatrics

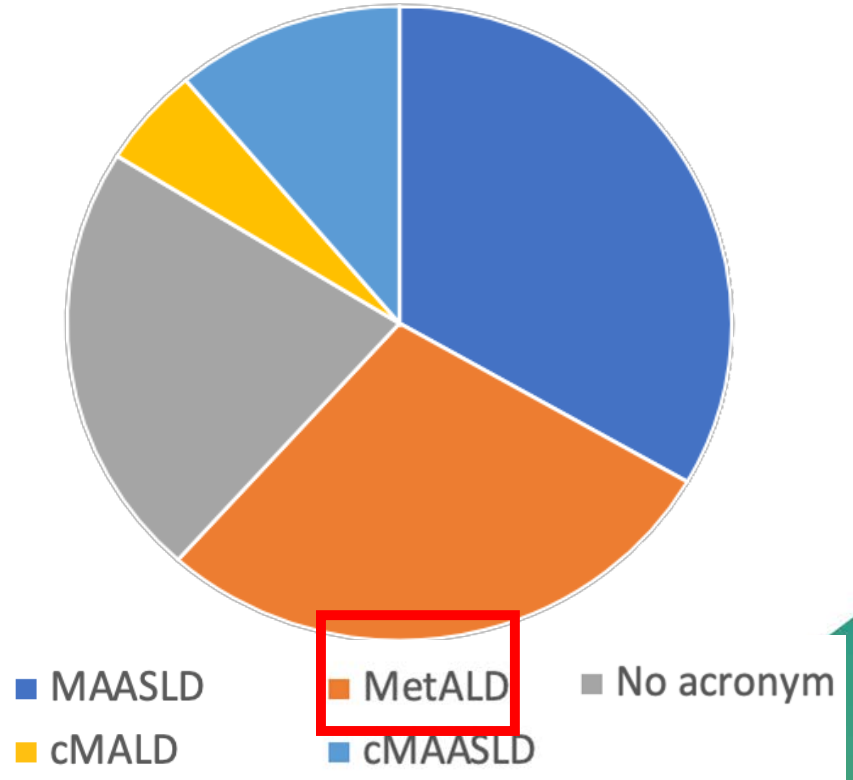
Acronym to replace NAFLD, NASH and overlap with alcohol



Metabolic dysfunction associated steatotic liver disease



Metabolic dysfunction associated steatohepatitis



Metabolic dysfunction and alcohol associated liver disease

Definition

- Affirmative set of diagnostic criteria for MASLD
- Near universal agreement to err on side of being inclusive
- Minimize patient heterogeneity and be adaptable to future insights
- Simple, readily available and easily measurable parameters
- The diagnostic criteria were also selected to align with cardiometabolic risk factors already well established and validated in other metabolic health disorders
- The set of criteria for adults was then submitted to a subcommittee of five pediatric hepatologists who adapted them for the pediatric population

*Cardiometabolic criteria

Adult Criteria

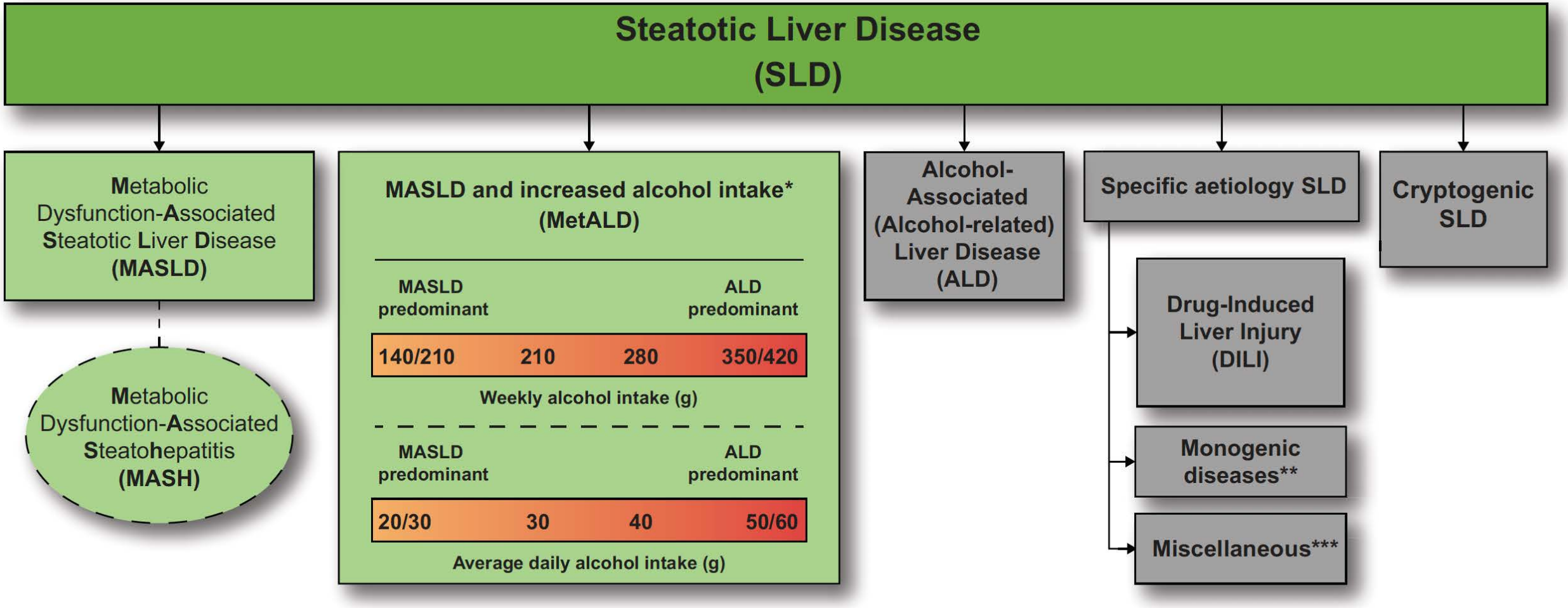
At least 1 out of 5:

- ☐ BMI ≥ 25 kg/m² [23 Asia] **OR** WC > 94 cm (M) 80 cm (F) **OR** ethnicity adjusted equivalent
- ☐ Fasting serum glucose ≥ 5.6 mmol/L [100 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol/L [≥140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** type 2 diabetes **OR** treatment for type 2 diabetes
- ☐ Blood pressure ≥ 130/85 mmHg **OR** specific antihypertensive drug treatment
- ☐ Plasma triglycerides ≥ 1.70 mmol/L [150 mg/dL] **OR** lipid lowering treatment
- ☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [40 mg/dL] (M) and ≤ 1.3 mmol/L [50 mg/dL] (F) **OR** lipid lowering treatment

Pediatric Criteria

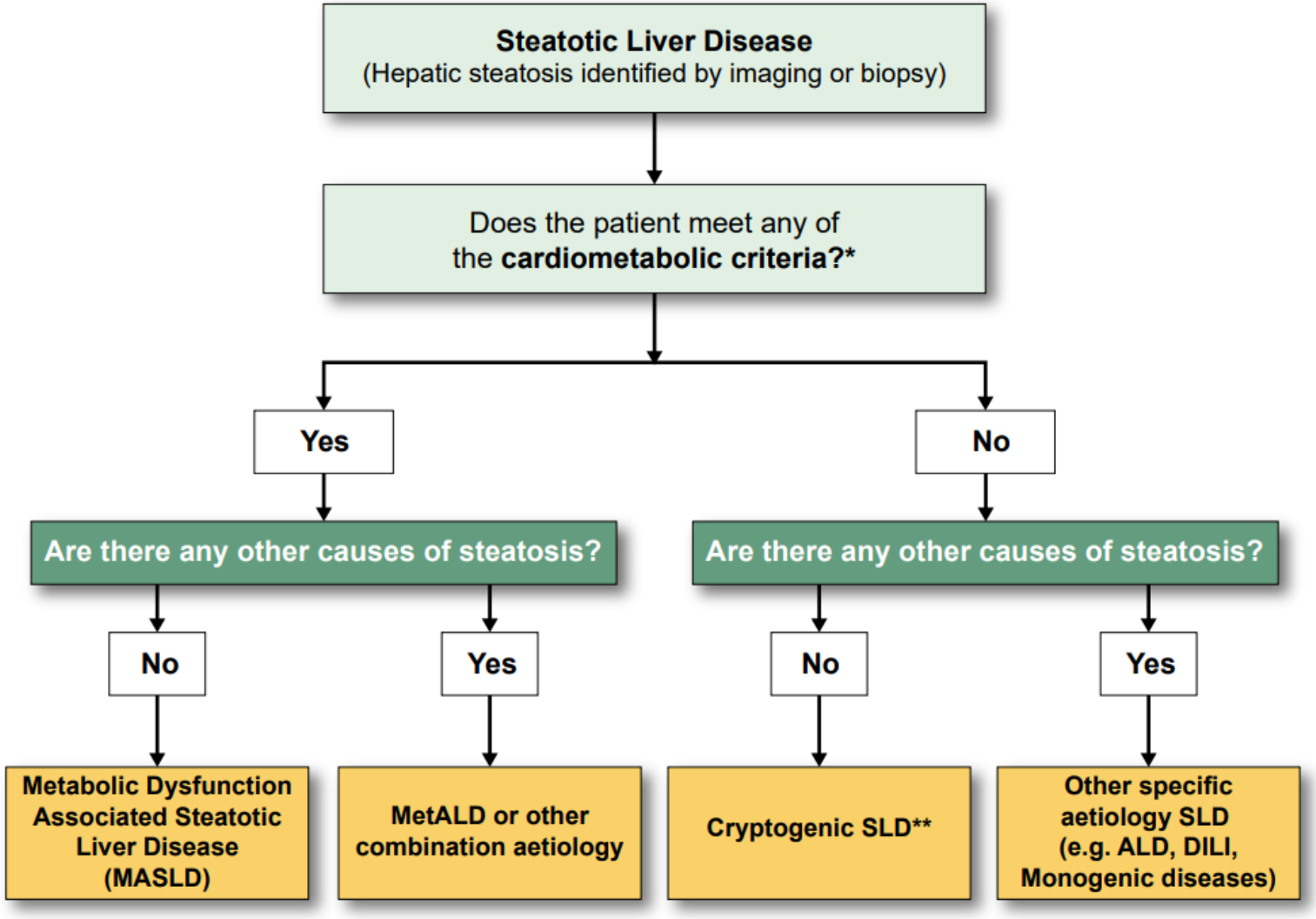
At least 1 out of 5:

- ☐ BMI ≥ 85th percentile for age/sex [BMI z score ≥ +1] **OR** WC > 95th percentile **OR** ethnicity adjusted equivalent
- ☐ Fasting serum glucose ≥ 5.6 mmol/L [≥ 100 mg/dL] **OR** serum glucose ≥ 11.1 mmol/L [≥ 200 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol [140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** already diagnosed/treated type 2 diabetes **OR** treatment for type 2 diabetes
- ☐ Blood pressure age < 13y, BP ≥ 95th percentile **OR** ≥ 130/80 mmHg (whichever is lower); age ≥ 13y, 130/85 mmHg **OR** specific antihypertensive drug treatment
- ☐ Plasma triglycerides < 10y, ≥ 1.15 mmol/L [≥ 100 mg/dL]; age ≥ 10y, ≥ 1.70 mmol/L [≥ 150 mg/dL] **OR** lipid lowering treatment
- ☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [≤ 40 mg/dL] **OR** lipid lowering treatment



*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease, human immunodeficiency virus (HIV)

Decision Support Tool

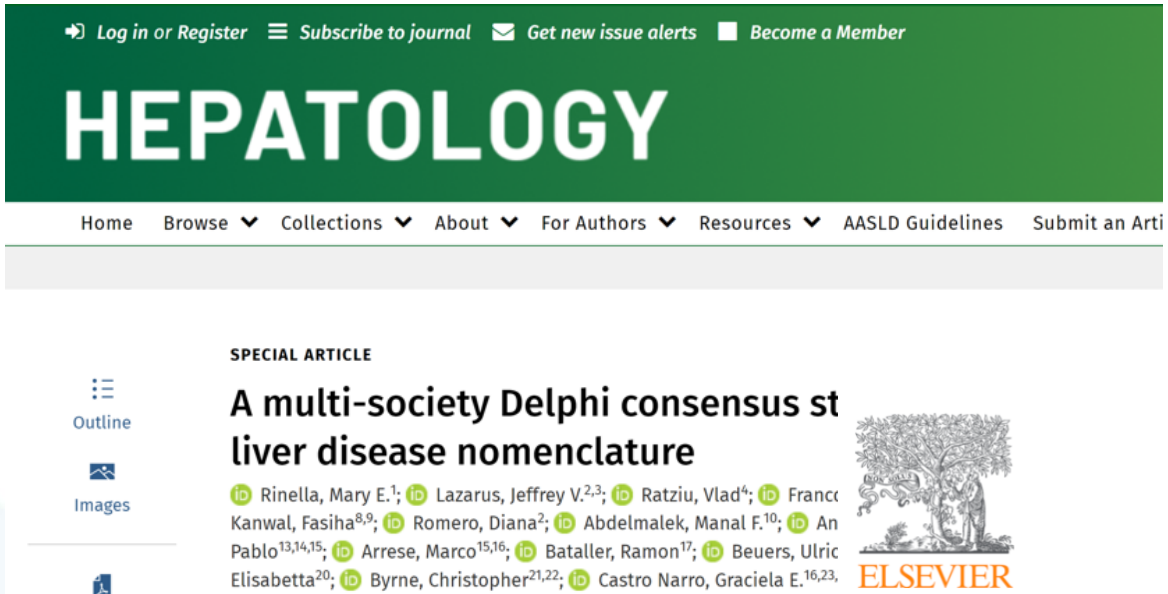


Journal Pre-proof



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

Mary E. Rinella, Jeffrey V. Lazarus, Vlad Ratziu, Sven M. Francque, Arun J. Sanyal, Fasiha Kanwal, Diana Romero, Manal F. Abdelmalek, Quentin M. Anstee, Juan Pablo Arab, Marco Arrese, Ramon Bataller, Ulrich Beuers, Jerome Boursier, Elisabetta Bugianesi, Christopher D. Byrne, Graciela E. Castro Narro, Abhijit Chowdhury, Helena Cortez-Pinto, Donna Cryer, Kenneth Cusi, Mohamed El-Kassas, Samuel Klein, Wayne Eskridge, Jiangao Fan, Samer Gawrieh, Cynthia D. Guy, Stephen A. Harrison, Seung Up Kim, Bart Koot, Marko Korenjak, Kris Kowdley, Florence Lacaille, Rohit Loomba, Robert Mitchell-Thain, Timothy R. Morgan, Elisabeth Powell, Michael Roden, Manuel Romero-Gómez, Marcelo Silva, Shivaram Prasad Singh, ...i, Miriam B. Vos, ...unossi, Ansley ...of the NAFLD



Annals of Hepatology
Available online 24 June 2023, 101133
In Press, Journal Pre-proof What's this?



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

Mary E. Rinella [1], Jeffrey V. Lazarus [2 3], Vlad Ratziu [4], Sven M. Francque [5 6], Arun J. Sanyal [7], Fasiha Kanwal [8 9], Diana Romero [2], Manal F. Abdelmalek [10], Quentin M. Anstee [11 12], Juan Pablo Arab [13 14 15], Marco Arrese [15 16], Ramon Bataller [17], Ulrich Beuers [18], Jerome Boursier [19], Elisabetta Bugianesi [20], Christopher D. Byrne [21 22], Graciela E. Castro Narro [16 23 24], Abhijit Chowdhury [25], Helena Cortez-Pinto [26], Donna Cryer [27]...Philip N. Newsome (senior) [66 67]

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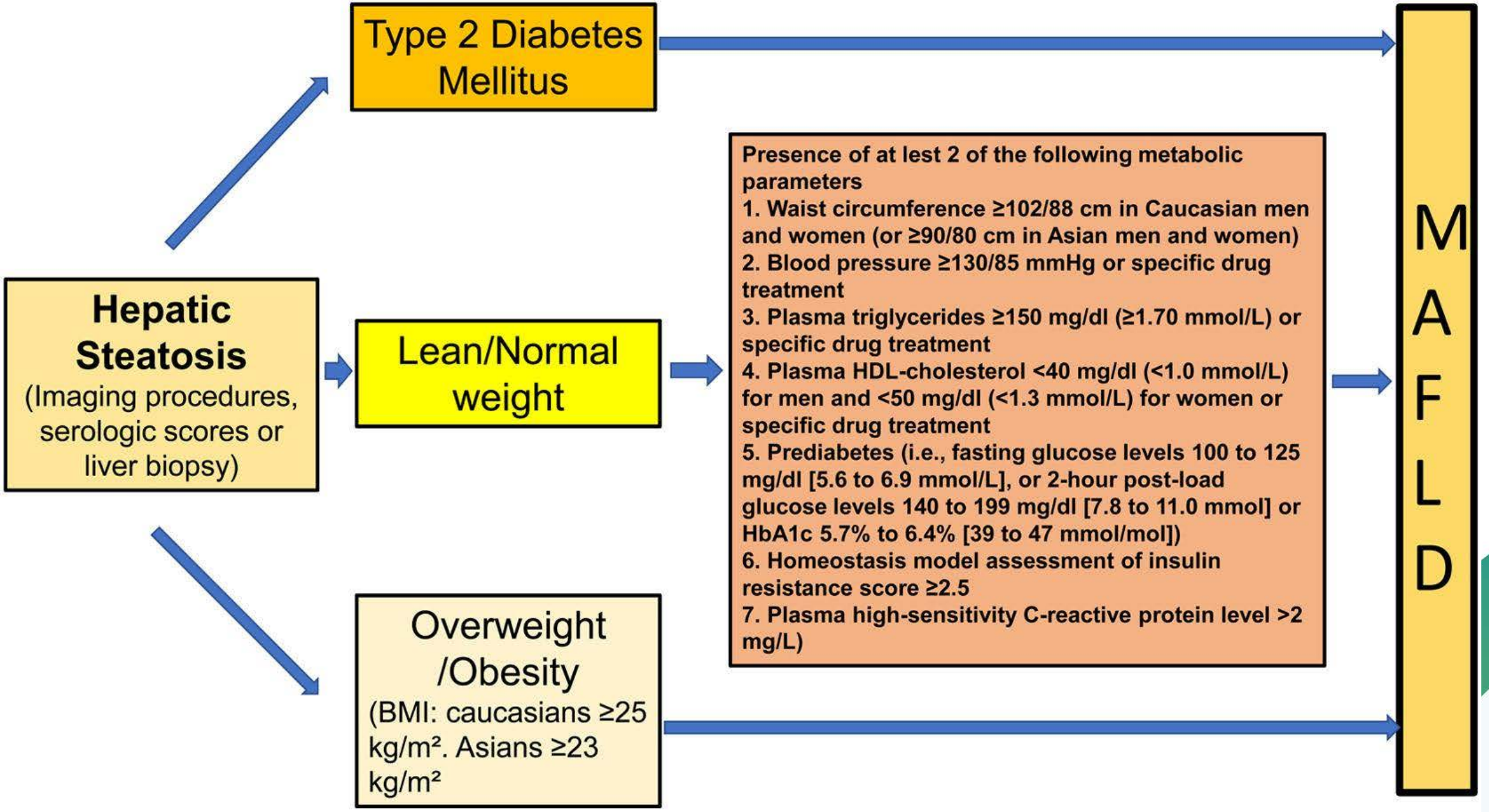
Endorsements – more than 70 societies



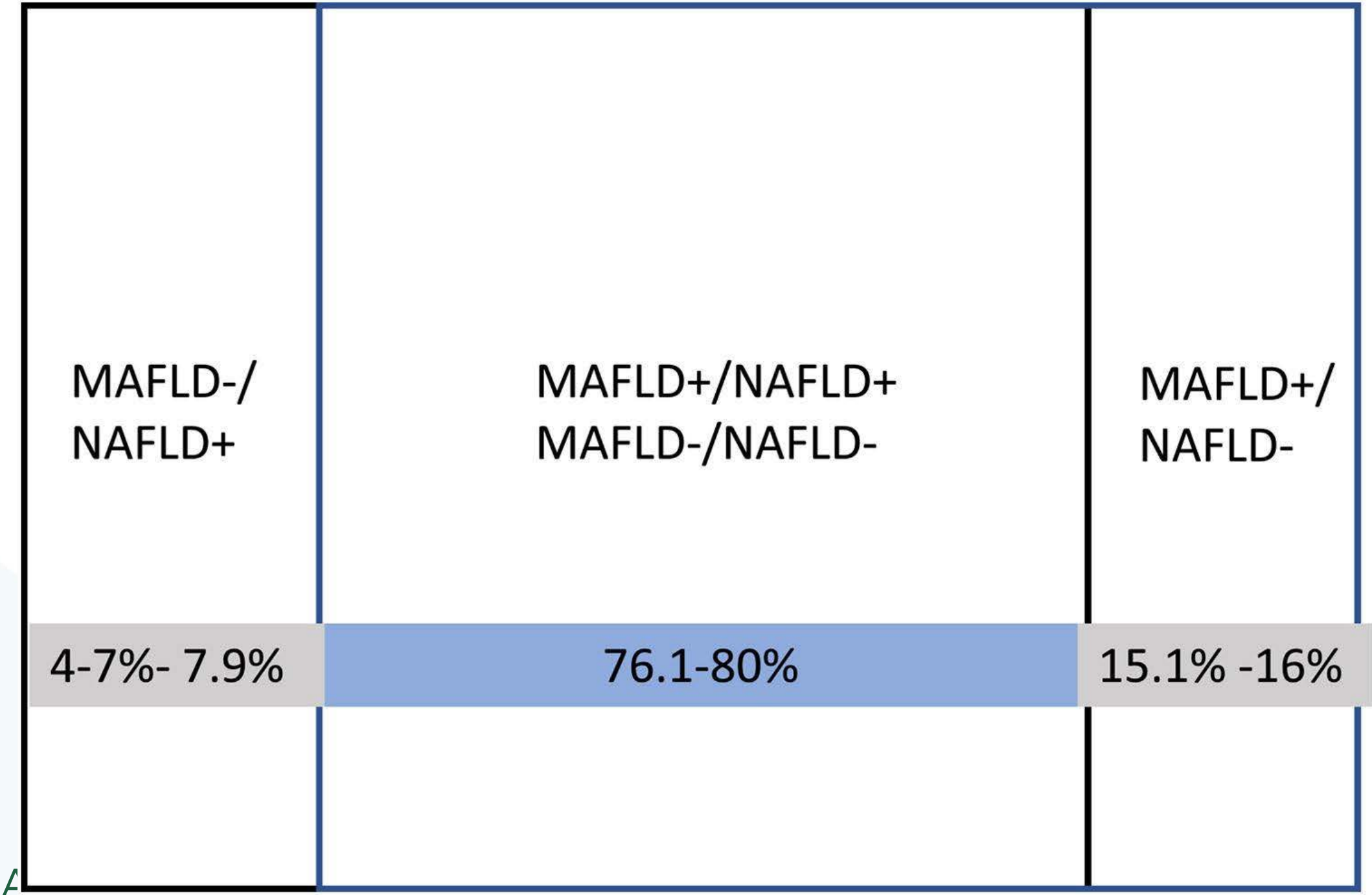
Overlap between NAFLD and MASLD

- Impact interpretation of previously published data?
- Impact on clinical trials?
- Impact on qualification of biomarkers?

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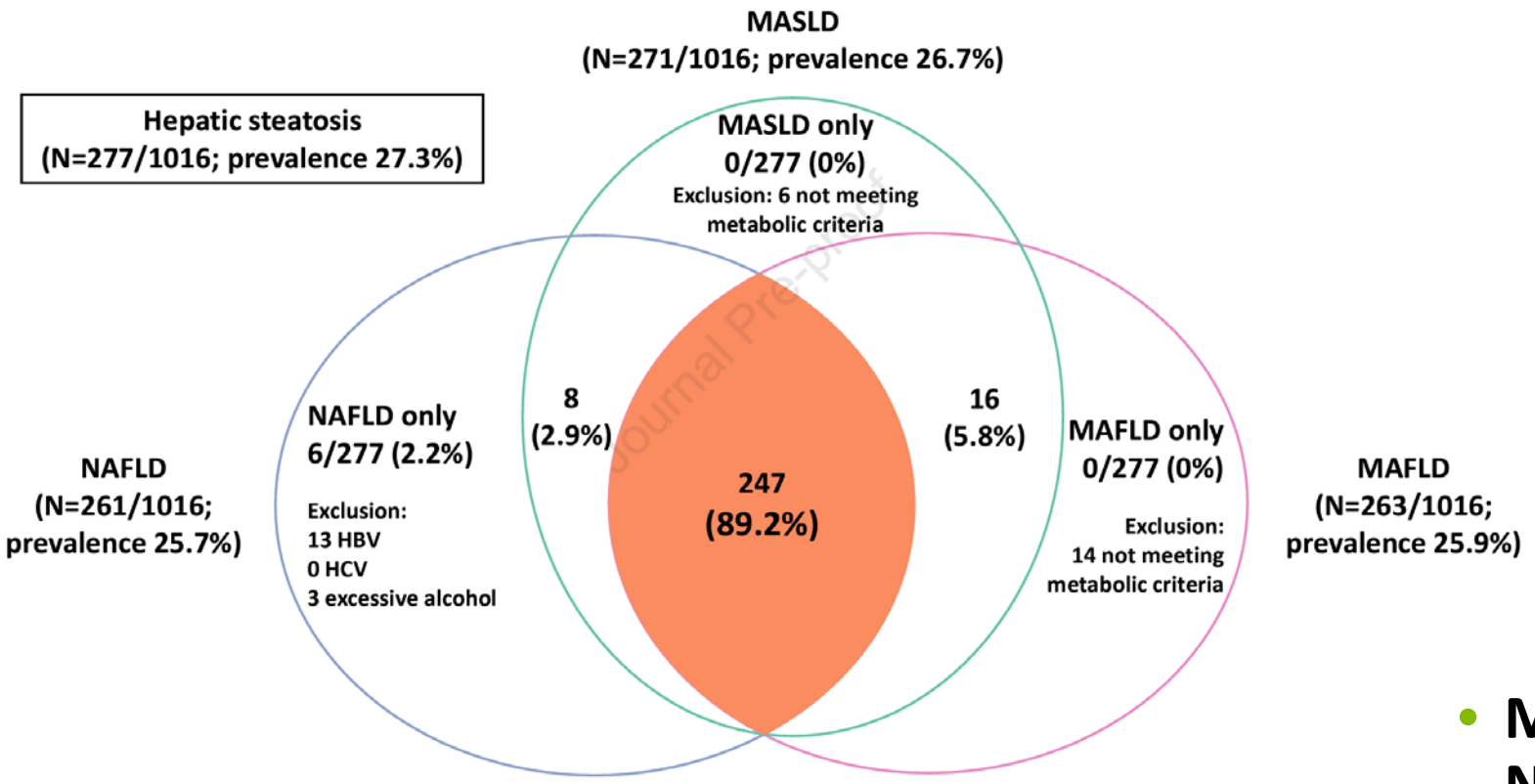


Ann Hepatol. 2022;27:



Ann Hepatol. 2022;27:

MASLD near complete overlap with NAFLD population



	% not fulfilling MASLD	% not fulfilling MAFLD
Community sample (HK) NAFLD	2.3%	5.4%
Incident NAFLD	10%	24%
Biopsy proven NAFLD	0.2%	2.2%

- **MASLD closer overlap with NAFLD than MAFLD in 3 Asian cohorts**

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Song et al. Can we use old NAFLD data under the new MASLD definition? *J Hep* 2023

Near complete overlap in biomarker population

Metabolic risk factor (MRF)	Entire database (N=2187)		Subcohort with all five MRF available (N=1369)
	Missing data* %, (n)	Criteria fulfilled#, % (n)	Criteria fulfilled#, % (n)
BMI ≥25 kg/m^2 OR waist circumference >94 cm (M) 80 cm (F)	2.2 (49)	96.7 (2 067)	98.4 (1347)
Fasting serum glucose ≥5.6 mmol/l OR HbA1c ≥5.7% OR type 2 diabetes OR treatment for type 2 diabetes	18.9 (413)	87.0 (1 544)	84.8 (1161)
Blood pressure ≥130/85 mm Hg OR specific antihypertensive drug treatment	24.5 (536)	84.7 (1 399)	82.5 (1130)
Plasma triglycerides ≥1.70 mmol/l OR lipid lowering treatment	15.3 (335)	74.8 (1 386)	77.8 (1065)
Plasma HDL-cholesterol ≤1.0 mmol/ (M) and ≤1.3 mmol/l (F) OR lipid lowering treatment	15.5 (340)	81.0 (1 496)	84.8 (1161)
No MRF present		1.6 (35§)	0.1 (1)
At least one MRF present		98.4 (2 152)	99.9 (1 368)
At least two MRFs present		89.8 (1 963)	97.7 (1 338)
At least three MRFs present		77.3 (1 690)	92.1 (1 261)
At least four MRFs present		58.3 (1 275)	79.3 (1 085)
All five MRFs present		37.1 (812)	59.3 (812)

- Data acquired for NAFLD are valid for MASLD
- Nomenclature change will not impact biomarker development

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Ratziu et al. Confirmatory biomarker diagnostic studies are not needed when transitioning from NAFLD to MASLD. J Hep 2023

Capture of ‘lean’ NAFLD – MASLD captures more left out with MAFLD criteria

- Indian real world cohort of 1643 patients with NAFLD, 170 ‘lean’
- 84% fulfilled MASLD definition
- 49.4% fulfilled MAFLD definition

De et al. Metabolic dysfunction-associated steatotic liver disease (MASLD) definition is better than MAFLD criteria for lean patients with non-alcoholic fatty liver disease (NAFLD). J Hep 2023

Stigma

- Stigma varies between individuals, cultures and languages
- When possible, its important to avoid the use of potentially stigmatizing language
- More on stigma is forthcoming



Search results

Save Email Ser

> Hepatology. 2023 May 1;77(5):1712-1721. doi: 10.1097/HEP.0000000000000043. Epub 2023 Jan 3.

Examining the interim proposal for name change to steatotic liver disease in the US population

Cheng Han Ng [1], Kai En Chan [1], Mark Muthiah [1 2 3], Caitlyn Tan [1], Phoebe Tay [1], Wen Hui Lim [1], Darren Jun Hao Tan [1], Clarissa Elysia Fu [1], Jie Ning Yong [1], Zhen Yu Wong [4], Benjamin Koh [1], Nicholas Ws Chew [1 5], Nicholas Syn [1 6], Daniel Q Huang [1 2 3], Yock Young Dan [1 2 3], Mohammad S Siddiqui [7], Arun J Sanyal [7], Mazen Noureddin [8]

Affiliations + expand

PMID: 36645228 DOI: 10.1097/HEP.0000000000000043

Abstract

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New opportunities for research

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SLD subtypes: Comparison of all-cause mortality

Group	HR[a] (95% CI)	*P* value	HR[b] (95% CI)	*P* value
without hepatic steatosis	Reference	-	Reference	-
Non-MASLD steatosis	0.761 (0.337-1.722)	0.513	0.874 (0.391-1.953)	0.874
Pure MASLD	1.234 (1.118-1.362)	<0.0001	1.097 (0.972-1.238)	1.097
MetALD	1.690 (1.213-2.355)	0.002	1.368 (1.019-1.838)	0.037
ALD with metabolic dysfunction	1.995 (1.275-3.121)	0.003	1.774 (1.172-2.685)	0.007

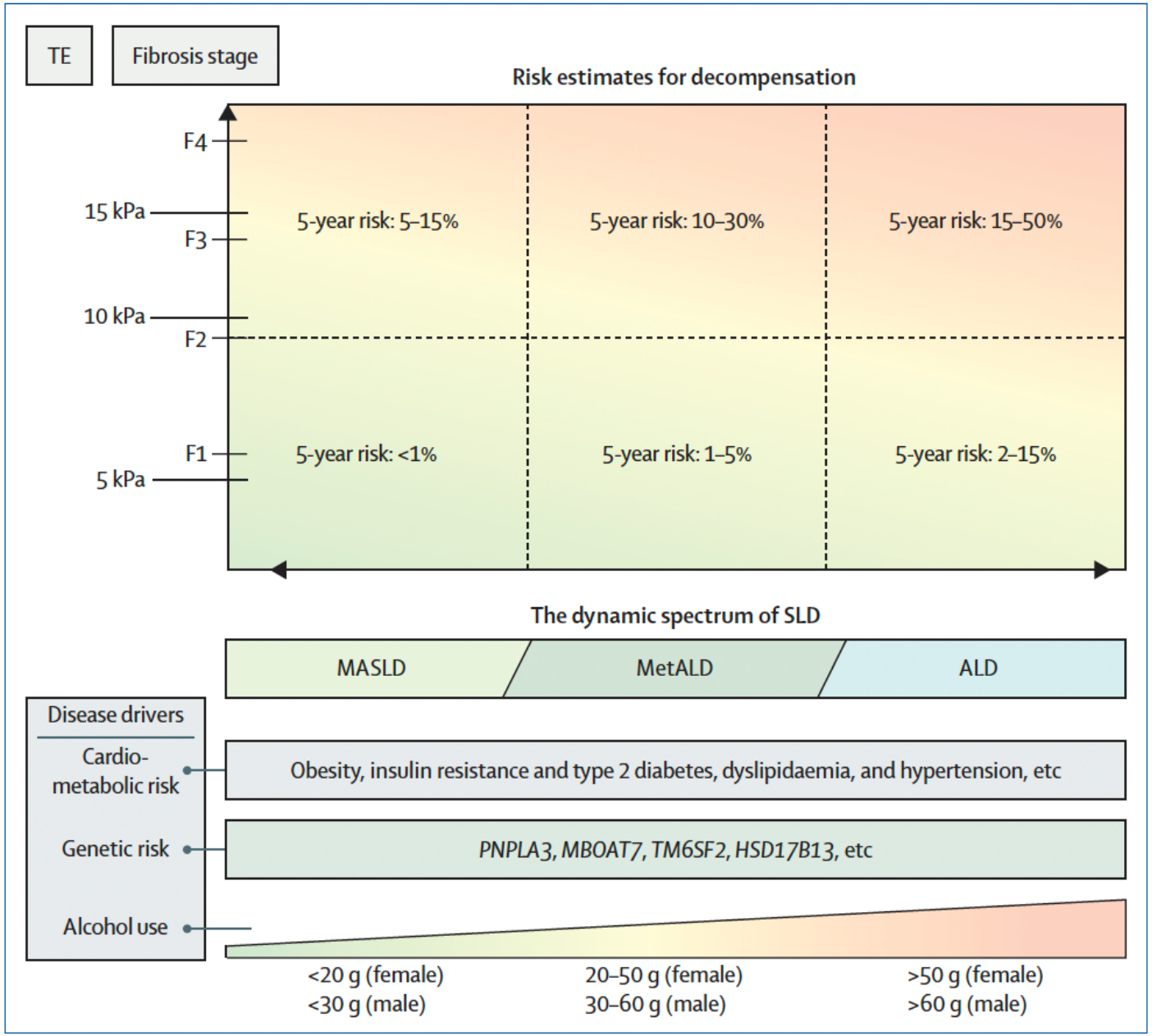
Pre-proof

Li and Xie. Are there all-cause mortality differences between metabolic dysfunction-associated steatotic liver disease subtypes? J Hep 2023

Ciardullo et al. Exploring the landscape of steatotic liver disease in the general US population. Liver International 2023

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Dynamic spectrum of MASLD-MetALD-ALD



- Alcohol use interacts with cardiometabolic risk factors and impacts risk of decompensation

Israelsen et al. MetALD: new opportunities to understand the role of alcohol in steatotic liver disease. Lancet GI Hep 2023

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Official Nomenclature Launch – June 24, 2023 (ILC)

Marketing/Press release

- Leadership Message from Norah Terrault
- Press release – issued Saturday June 24
- Membership Message from Norah Terrault
- SIG Message from NAFLD SIG co-chairs

Website/Social media

- New page built with videos and figures
- Twitter posts - https://twitter.com/AASLDtweets
- Videos - https://www.aasld.org/new-nafld-nomenclature
- Diagnosis tool in development



Effective implementation

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Public

Govt

Awareness and implementation

Discussion at meetings

- ILC
- ALEH meeting
- UEG
- AASLD
- Other national meetings
- Individual symposia and society meetings

Use in publications

- Pan-society leadership editorial
- Delphi paper in 3 journals
- Editorials in society journals and outside

Use in practice

- Consultation with providers
- Patient focus groups
- FAQs

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Dissemination





- Endorsement process ongoing
- Engagement ongoing

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Next Steps

- Stakeholder meetings to determine implementation challenges and needs
- Development of:
  - MASLD living guidelines on aasld.org
  - Decision tree and infographics
  - PowerPoint presentations on the new nomenclature available for use
- Campaign to increase awareness and adoption
  - Society driven
  - Collaboration with industry

Thank you for your attention



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