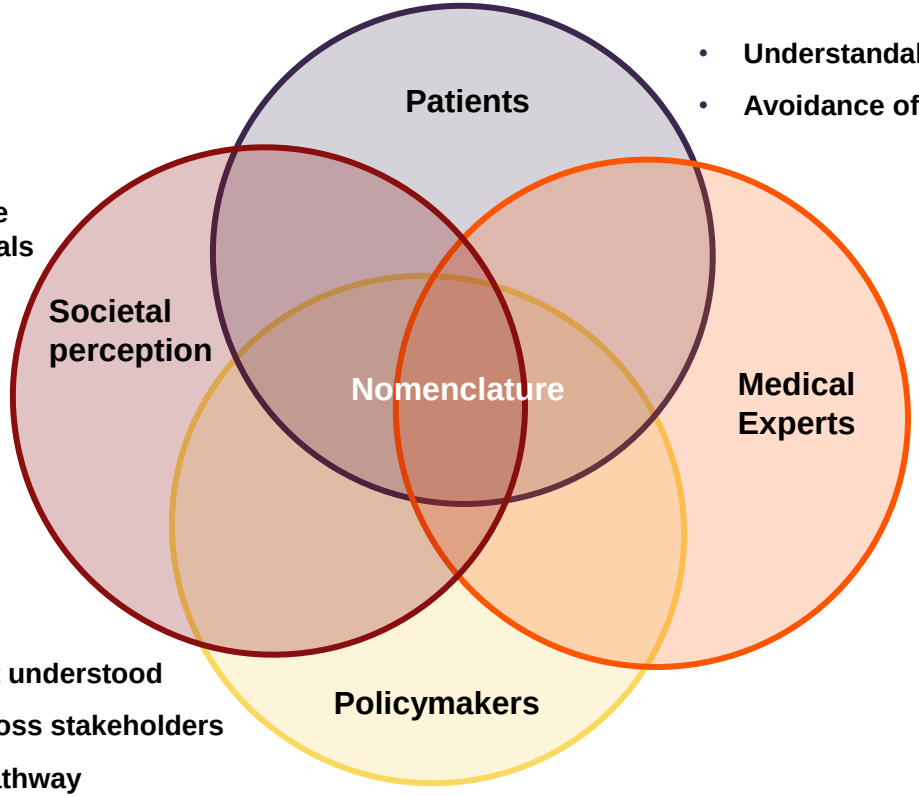
Nomenclature Process: From NAFLD to MAFLD to Steatotic Liver Disease & the Delphi Process

Mary E. Rinella, MD
Professor of Medicine
University of Chicago Pritzker School of Medicine



- Understandable
- Avoidance of stigma

- Cannot marginalize groups or individuals

- Accuracy and precision
- Clear defining characteristics

- Disease impact understood
- Awareness across stakeholders
- Clinical care pathway

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

The Evolution of NAFLD Nomenclature

1980

Term "NASH" coined by Ludwig et al.

2002

First AASLD STC on NAFLD: Alternatives to name discussed

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

Gastroenterology 2020;158:1999–2014

MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease



Mohammed Eslam[1] *Arun J. Sanyal*[2] *Jacob George*[1], *on behalf of the International Consensus Panel*

26/31 (84%) invited to participate in current pan-society nomenclature
24/31 (77%) currently participating (2 recently withdrew from SC)

Acknowledgments
Members of the International Consensus Panel:
Arun Sanyal, Virginia Commonwealth University School of Medicine, Richmond, Virginia.
Brent Neuschwander-Tetri, Division of Gastroenterology and Hepatology, Saint Louis University, St. Louis, Missouri.
Claudio Tiribelli, Liver Center, Italian Liver Foundation, Trieste, Italy.
David E. Kleiner, Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland.
Elizabeth Brunt, Department of Pathology and Immunology Washington University School of Medicine, St, Louis, Missouri.
Elisabetta Bugianesi, Division of Gastroenterology and Hepatology, University Hospital, Aarhus, Denmark.
Helena Cortez-Pinto, Clínica Universitária de Gastrenterologia, Laboratório de Nutrição, Faculdade de Medicina, Universidade de Lisboa, Portugal.
Jacob George, Storr Liver Centre, Westmead Institute for Medical Research, Westmead Hospital and University of Sydney, NSW, Australia
Jiangao Fan, Center for Fatty Liver, Department of Gastroenterology, Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China.
Luca Valenti, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, and Translational Medicine, Department of Transfusion Medicine and Hematology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy.
Manal Abdelmalek, Department of Medicine, Duke University, Durham, North Carolina.
Manuel Romero-Gomez, Hospital Universitario Virgen del Rocío de Sevilla, Instituto de Biomedicina de Sevilla, Biomedical Research Networking Center in Hepatic and Digestive Diseases, Sevilla, Spain.
Mary Rinella, Department of Gastroenterology, Northwestern University Feinberg School of Medicine, Chicago, Illinois.
Marco Arrese, Departamento de Gastroenterologia, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile.
Mohammed Eslam, Storr Liver Centre, Westmead Institute for Medical Research, Westmead Hospital and University of Sydney, NSW, Australia.
Pierre Bedossa, Department of Pathology, Physiology and Imaging, Beaujon Hospital Paris Diderot University, Paris, France.
Philip N. Newsome, National Institute for Health Research Biomedical Research Centre at University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham, UK; Centre for Liver and Gastrointestinal Research, Institute of Immunology and Immunotherapy, University of Birmingham, UK; Liver Unit, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK.
Quentin M. Anstee, Institute of Cellular Medicine, Faculty of Medical
Rohit Loomba, Division of Epidemiology, Department of Family Medicine and Public Health, University of California at San Diego, La Jolla, California.
Silvia Sookoian, Department of Clinical and Molecular Hepatology, National Scientific and Technical Research Council (CONICET), University of Buenos Aires, Institute of Medical Research (IDIM), Ciudad Autónoma de Buenos Aires, Argentina.
Shiv K. Sarin, Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India.
Stephen Harrison, Radcliffe Department of Medicine, University of Oxford, Oxford, UK.
Takumi Kawaguchi, Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Kurume, Japan.
Vincent Wai-Sun Wong, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong.
Vlad Ratziu, Sorbonne Université, Assistance Publique-Hôpitaux de Paris, Hôpital Pitié Salpêtrière, Institute of Cardiometabolism and Nutrition (ICAN), Paris, France.
Yusuf Yilmaz, Department of Gastroenterology, School of Medicine, Marmara University, Istanbul, Turkey; Institute of Gastroenterology, Marmara University, Istanbul, Turkey.
Zobair Younossi, Center for Liver Diseases, Department of Medicine, Inova Fairfax Hospital, Falls Church, Virginia.

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


Editorial

HEPATOLOGY

JOURNAL OF HEPATOLOGY

AASLD

SPECIAL ARTICLE | HEPATOLOGY, VOL. 73, NO. 3, 2021

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

Zobair M. Younossi [1,2], Mary E. Rinella [3], Arun J. Sanyal,[4] Stephen A. Harrison,[5] Elizabeth M. Brunt,[6] Zachary Goodman,[1,2] David E. Cohen,[7] and Rohit Loomba[8]

- 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

Eslam et al. *Gastroenterology*. 2020; Eslam et al. *J Hepatol.* 2020; Younossi et al. *Hepatology*. 2021; Ratziu et al. *J Hepatology.* 2021.

Initial Statement Development: Society & Stakeholder Steering Committee Representatives

Orgs/Regions	
AASLD (incl AGA, ACG)	Rinella, Abdelmalek, Guy, Harrison, Kanwal, Loomba, Sanyal, Vos, Younossi
EASL (incl UEG)	Newsome, Anstee, Beuers, Bugianesi, Cortez-Pinto, Francque, Koot, Ratziu, Valenti
ALEH (and other L.A. countries)	Arrese, Castro, Sookian (Argentina)
Asia-Pacific and MENA	El-Kassas, Fan, Sarin, Singh, Yilmaz, Wong
Endo/ Diabetes	Cusi (US), Roden (Europe)

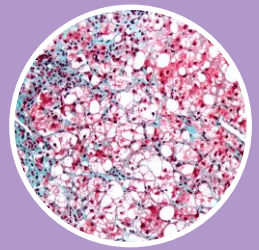
Patient advocacy

- GLI
- Fatty Liver Foundation
- ELPA
- LPI
- ALF

Methodology and consensus development:
Jeff Lazarus & Diana Romero

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?

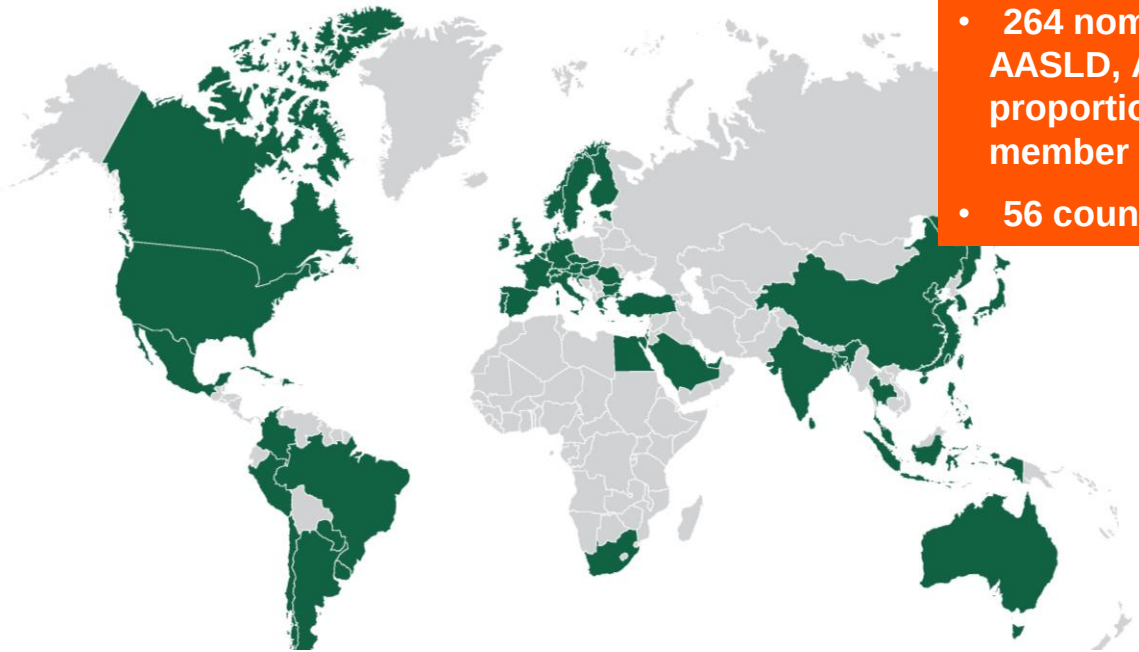
How should the role alcohol be accounted for (or not)?

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

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

Picture: Steatohepatitis Micrograph

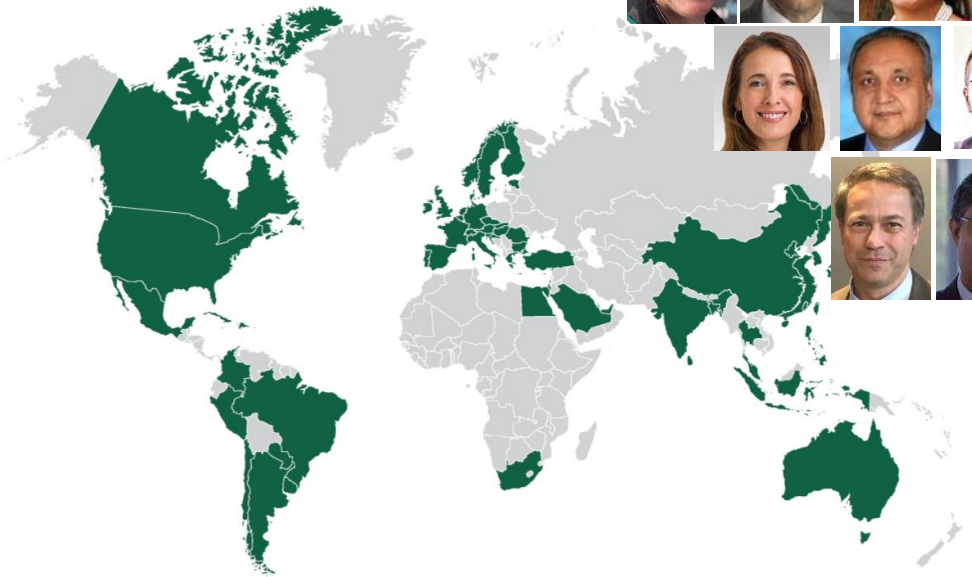
Global NAFLD Nomenclature Involvement



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

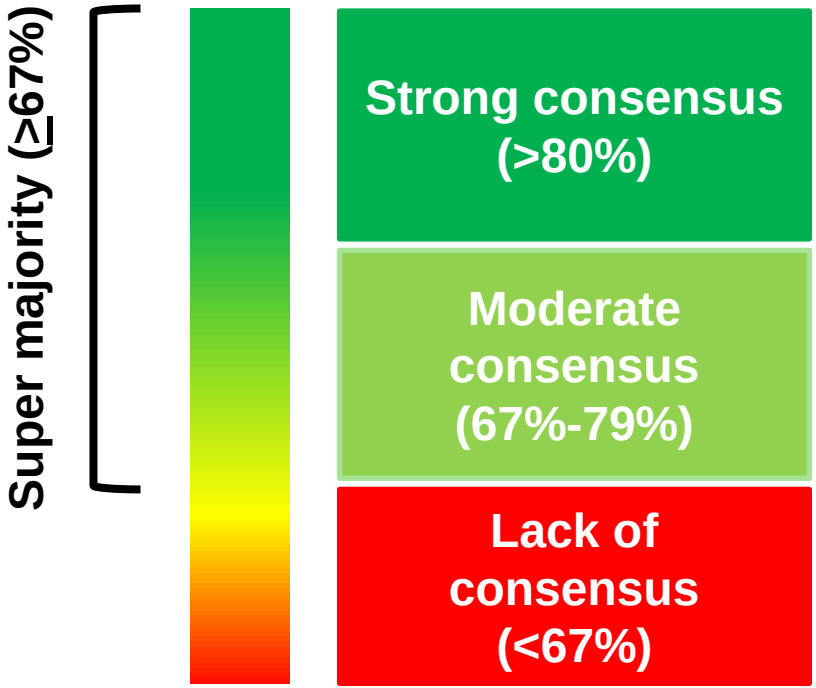
Global NAFLD Nomenclature Steering Committee

N=36



Publications: 8210
NAFLD publications: 3586
Median NAFLD: 88
Citations: 914,918
Average *h*-index: 74

Survey Rounds and Defining Consensus



- ☑ **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

Stigma – R3 Data

- **Perceived to be stigmatizing**
  - Non-alcoholic **(61%)**
  - Fatty **(66%)**

Areas of Strong Consensus (>80%) Up to R4

- **Role of alcohol**
  - 30-60 g/day of EtOH alters natural history of disease (95%), may alter response to therapeutics (90%)
  - 30-60 g/day in combo with Met RF should be an independent category (83%)
  - >60g/d + Met RF = ALD with Met dysfunction (86%)
  - >60g/day (irrespective of Met RF) = ALD (82%)
- Steatohepatitis
  - The distinction between steatosis and **steatohepatitis has prognostic implications** (95%)
  - NASH resolution should remain an important classifier of disease activity (93%)
- **Disease classification**
  - Those with steatosis without Met RF should be characterized separately (81%)
  - The term ‘metabolic dysfunction’ highlights a central aspect of disease pathophysiology (86%)

Pediatrics – R3

Strong consensus (>80% Agree or Somewhat Agree)

The current definition of non-alcoholic steatohepatitis (NASH) is less useful in children and adolescents because hepatocyte ballooning is less frequent, thus, a reassessment of the definitions of steatohepatitis in the pediatric setting would be beneficial.

Agree 95%
Disagree 5%

Strong consensus (>80% Agree or Somewhat Agree)

In children and adolescents, use of the term 'metabolic' is confusing because inborn errors of metabolism are called 'metabolic liver disease.'

Agree 90%
Disagree 10%

Areas of Moderate Consensus (>67%) Up to R4

- **Nomenclature**
  - Current **names** (NAFLD/NASH) are sufficiently flawed to warrant consideration of a name change (74%)
  - Preference for overarching 'umbrella' term (NAFLD/replacement, combo disease with ALD, non-NAFLD steatosis) 78%
- **Impact on Clinical trials**
  - To what extent would a change in name ONLY (without a change in definition), impact the interpretation of clinical trial results?
    (Hinder: 18%, no impact 72%, enhance: 10%)

Areas Without Consensus (<67%) Up to R4

- Disease definition
  - Current **definition** of NAFLD/NASH is sufficiently flawed to warrant consideration of a definition change (66% agree/somewhat agree)
  - 'Metabolic dysfunction' is a clearly defined clinical entity (56%)
  - **Impact on clinical trials/biomarkers**
  - Impact of change in **BOTH name and definition** on the interpretation of clinical trial results **WHICH USED the original definition of NASH?** (hinder: 60%, no impact:21%, enhance: 19%)
  - Impact of a **change in name ONLY** (without a change in definition), on the current timeline of biomarker approval? (Delay 25%, No impact 63%, Accelerate 12%)
  - Impact of a **change in disease definition** (e.g. allowing greater alcohol consumption) on the current timeline of biomarker approval? (Delay 59%, No impact 25%, Accelerate 15%)
- Disease classification
  - Those with steatosis without Met RF should be characterized separately (81%)
  - The term 'metabolic dysfunction' highlights a central aspect of disease pathophysiology (86%)

Over-Arching Term – R3

	% 1st or 2nd Choice	% of 1st Choices	% of 2nd Choices	% of 3rd Choices
Fatty Liver Disease	**72**	46	26	28
Steatotic Liver Disease	**95**	48	47	6
Lipogenic/Lipotoxic Liver Disease	**34**	7	27	66

Discussion with Steering Committee:

- Most popular as 1st or 2nd
- To avoid stigma if possible, SLD recommended as overarching term

Summary and Next Steps

- Name change – clear consensus
- Stigma with both ‘non-alcoholic’ and ‘fatty’
- Over-arching term: Steatotic liver disease
- Definition **will not** include more liberal alcohol intake and **will have** a ‘metabolic qualifier’
- Awaiting finalization
  - Replacement term and acronym for NAFLD
  - Specifics of the revised definition