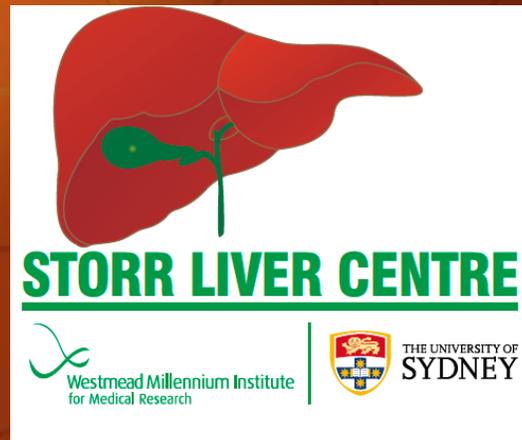


Towards NAFLD to MAFLD – importance of steatosis in the current paradigm shift

Professor Mohammed Eslam



Disclosures

- I have received honoraria payment from Sanofi

Overview

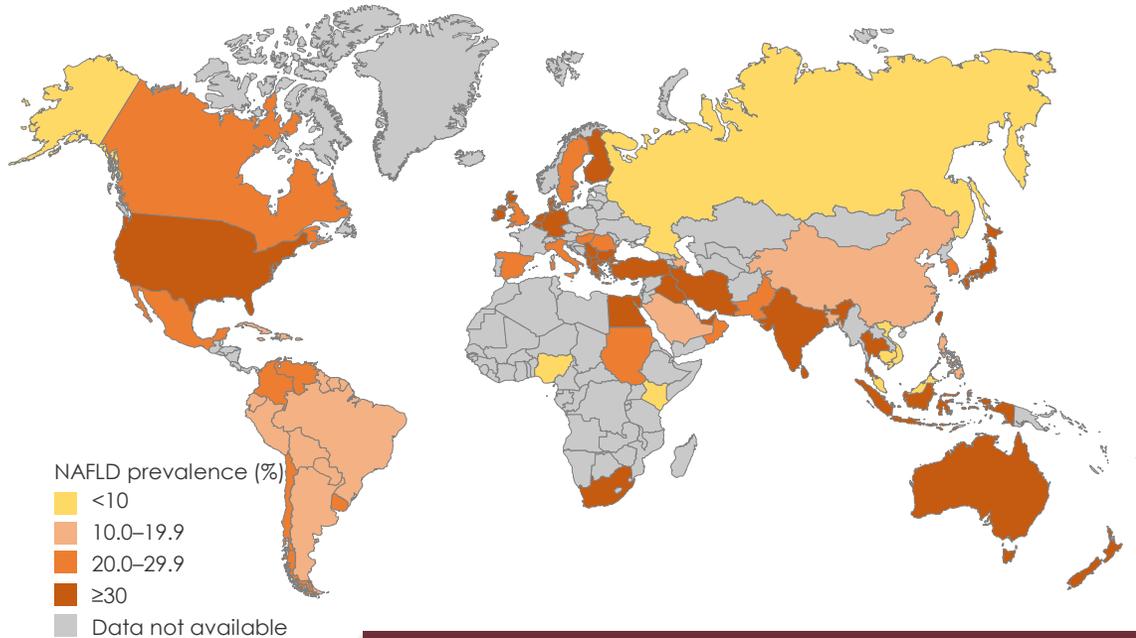
- 1 Prevalence of metabolic-associated fatty liver disease (MAFLD)
- 2 Problems with the old terminology
- 3 Coming up with a name
- 4 Coming up with a definition: from concepts to an algorithm
- 5 MAFLD: moving from concept to practice
- 6 The future

MAFLD, metabolic-associated fatty liver disease

Non-alcoholic fatty liver disease (NAFLD): the magnitude of the problem

25% of the world's population have NAFLD¹

40% of the NAFLD population is not obese^{2,3}



NO FDA approved drug to date

FDA, Food and Drug Administration; NAFLD, non-alcoholic fatty liver disease

1. Younossi Z, et al. Nat Rev Gastroenterol Hepatol 2018;15(1):11–20; 2. Ye Q, et al. Lancet Gastroenterol Hepatol 2020;5(8):739–52;

3. Eslam M, et al. Lancet Gastroenterol Hepatol 2020;5(8):713–15

Is NAFLD the right name for fatty liver disease associated with metabolic dysfunction?

NAFLD, non-alcoholic fatty liver disease

Is NAFLD the right name?

The terminology 'non-alcoholic' trivialises and stigmatises the disease; there is a need to distance disease from obesity, alcohol etc.

What is the safe limit of alcohol?

Does not define an individual's phenotype with enough precision to develop targeted therapies; hence, poor responses and trial failure

Problems with the terminology of NAFLD¹

Does not capture the heterogeneity of the patient population with regard to drivers and disease modifiers

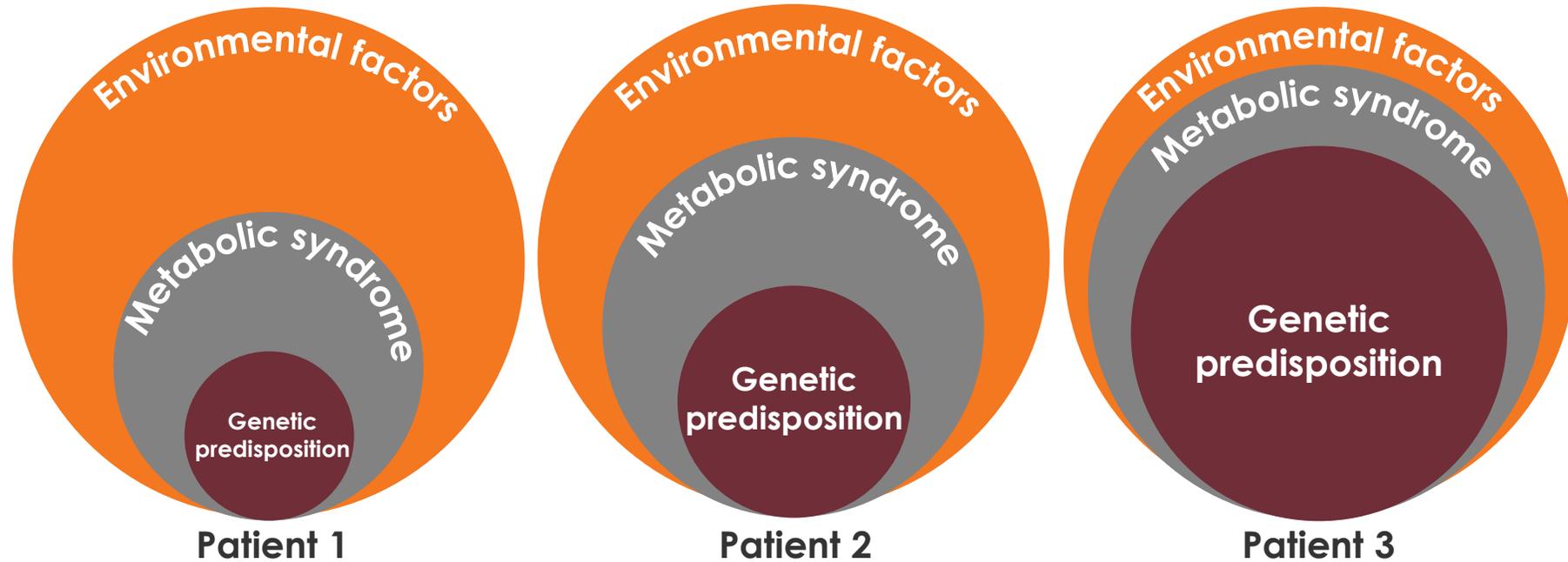
There is a lack of patient awareness, public health response and funding for NAFLD

NAFLD diagnosis is based on exclusion. There is a need to diagnose using **positive** criteria as NAFLD can coexist with other liver diseases; synergistic on outcomes

NAFLD, non-alcoholic fatty liver disease

1. Eslam M, et al. Gastroenterology 2020;158(7):1999–2014.e1

Heterogeneity in outcomes



- Impact on clinical trials as they do not take into account patient heterogeneity¹
- Response rates are suboptimal (10–20% greater than placebo)¹

1. Eslam M, et al. Gastroenterology 2020;158(7):1999–2014.e1

Lack of public health response and underfunding: could it be due to the negative impact of the 'NAFLD' name?



- 29 European countries were surveyed in a study examining public health response to NAFLD¹
 - None of the participating countries had written strategies or action plans for NAFLD¹



- NAFLD is not considered in the screening guidelines of diabetes or other related diseases¹



- Liver diseases are underfunded¹

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis
1. Lazarus JV, et al. J Hepatol 2020;72(1):14–24

Does your country have a national NAFLD/NASH strategy/action plan?

1 Yes

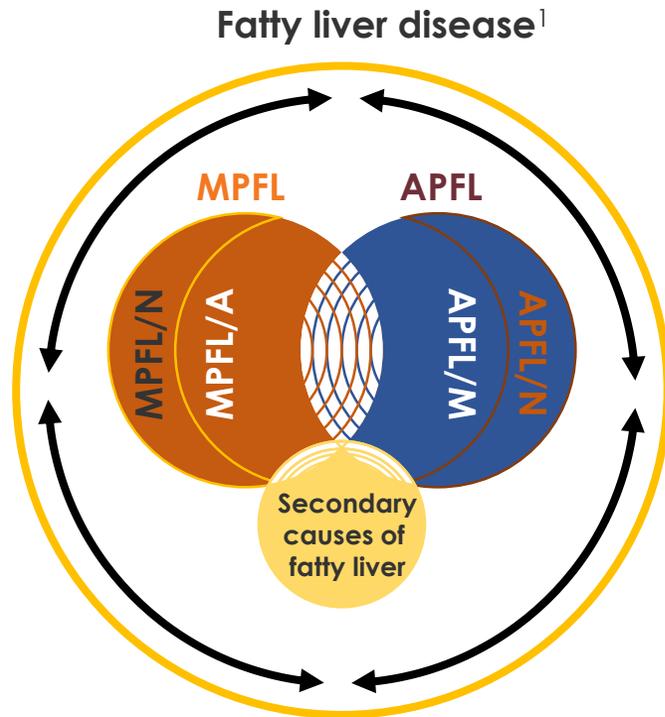
2 No

3 Unsure

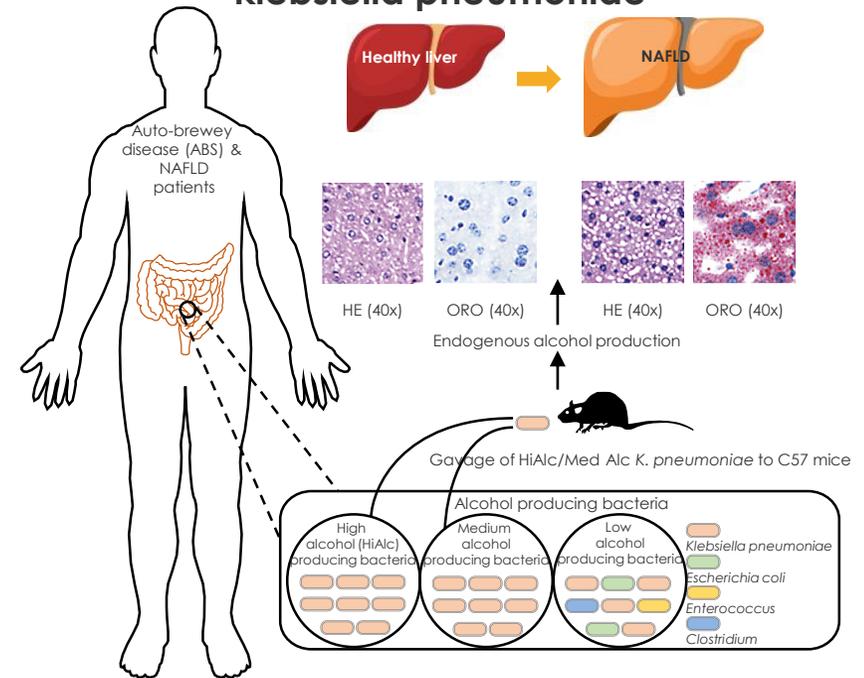
The way to MAFLD?

MAFLD, metabolic-associated fatty liver disease

Towards a more accurate nomenclature for fatty liver disease



Fatty liver disease caused by high-alcohol-producing *klebsiella pneumoniae*²

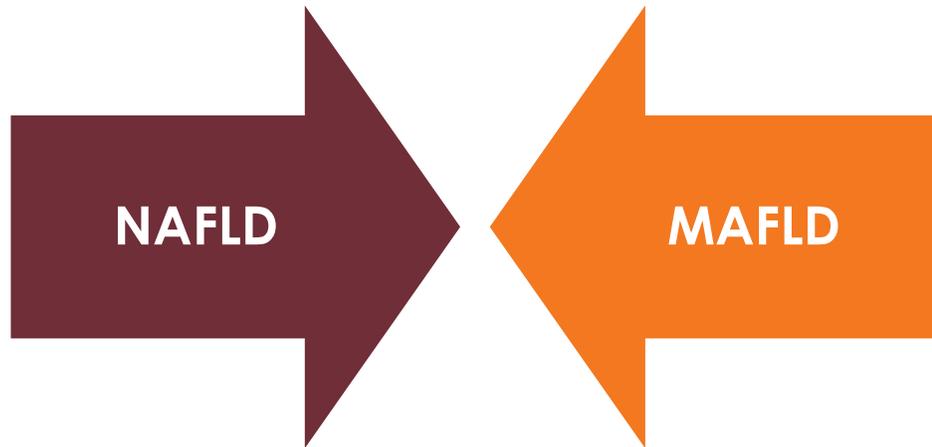


ABS, auto-brewery disease; APFL, alcohol predominant fatty liver; APFL/M and APFL/N, alcoholic predominant fatty liver with metabolic dysfunction or with no metabolic dysfunction; HE, haematoxylin and eosin stain; HiAlc/MedAlc, high/medium-alcohol-producing bacteria; MPFL, metabolic dysfunction predominant fatty liver; MPFL/A and MPFL/N, metabolic dysfunction predominant fatty liver with, and without alcohol intake that is anything more than ceremonial; NAFLD, non-alcoholic fatty liver disease; ORO, oil red O stain

1. Eslam M, et al. *Gastroenterology* 2019;157(3):590-3; 2. Yuan J, et al. *Cell Metab* 2019;30(4):675-88.e7

From NAFLD to MAFLD: expert opinion

- Expert opinions were gauged using the Delphi method¹
- 72.4% of participants supported the term MAFLD¹



The International Consensus Panel (in alphabetical order)¹

- Arun Sanyal (USA)
- Brent Neuschwander-Tetri (USA)
- Claudio Tiribelli (Italy)
- David E. Kleiner (USA)
- Elizabeth Brunt (USA)
- Elisabetta Bugianesi (Italy)
- Hannele Yki-Järvinen (Finland)
- Henning Grønbaek (Denmark)
- Helena Cortez-Pinto (Portugal)
- Jacob George (Australia)
- Jiangao Fan (China)
- Luca Valenti (Italy)
- Manal Abdelmalek (USA)
- Manuel Romero-Gomez (Spain)
- Mary Rinella (USA)
- Marco Arrese (Chile)
- Mohammed Eslam (Australia)
- Pierre Bedossa (France)
- Philip N Newsome (UK)
- Quentin M Anstee (UK)
- Rajiv Jalan (UK)
- Ramon Bataller (Spain)
- Rohit Loomba (USA)
- Silvia Sookoian (Argentina)
- Shiv K Sarin (India)
- Stephen Harrison (USA)
- Takumi Kawaguchi (Japan)
- Vincent Wai-Sun Wong (Hong Kong)
- Vlad Ratziu (France)
- Yusuf Yilmaz (Turkey)
- Zobair Younossi (USA)

MAFLD, metabolic-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease

1. Eslam M, et al. Gastroenterology 2020;158(7):1999–2014.e1

Endorsement of MAFLD by regions with the highest prevalence of MAFLD

The Asian Pacific Association for the Study of the Liver (APASL) clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease¹

APASL, 2020

MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease²

International Consensus Panel, 2020

Nomenclature and definition of metabolic-associated fatty liver disease: a consensus from the Middle East and North Africa³

Middle East and North Africa Expert Review Panel, 2021

The Latin American Association for the Study of the Liver (ALEH) position statement on the redefinition of fatty liver disease⁴

ALEH, 2021

The sub-Saharan Africa position statement on the redefinition of fatty liver disease: From NAFLD to MAFLD⁵

Sub-Saharan Africa Experts, 2021

Endorsing the redefinition of fatty liver disease⁶

Malaysian Society of Gastroenterology and Hepatology, 2021

The Chinese Society of Hepatology position statement on the redefinition of fatty liver Disease⁷

The Chinese Society of Hepatology, 2021

Looking for a new name for non-alcoholic fatty liver disease in Spanish: esteatosis hepática metabólica⁸

HEPAmet Registry, The Spanish Association for the Study of the Liver (AEEH) and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), 2021

MAFLD, metabolic-associated fatty liver disease

1. Eslam M, et al. *Hepatology* 2020;14(6):889–919; 2. Eslam M, et al. *Gastroenterology* 2020;158(7):1999–2014.e1; 3. Shiha G, et al. *Gastroenterol Hepatol* 2021;6(1):57–64; 4. Mendez-Sanchez N, et al. *Gastroenterol Hepatol* 2021;6(1):65–72; 5. Spearman CW, et al. *J of Hepatol* 2021;74(5):1256–1258; 6. Tan S, et al. *Gastroenterol Hepatol* 2021;6(3):163; 7. Nan Y, et al. *J Hepatol* 2021; doi: <https://doi.org/10.1016/j.jhep.2021.05.003>; 8. Romero-Gómez M and Ampuero J. *Rev Esp Enferm Dig* 2021;113(3):161–163

What do others think?

Four Twitter polls

From NAFLD to MAFLD:
Nurse and allied health
perspective, 2021¹

Redefining fatty
liver disease: an
international patient
perspective, 2021²

MAFLD, metabolic-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease
1. Clayton M, et al. Liver Int 2021;41(4):683–91; 2. Shiha G, et al. Gastroenterol Hepatol 2021;6(1):73–9

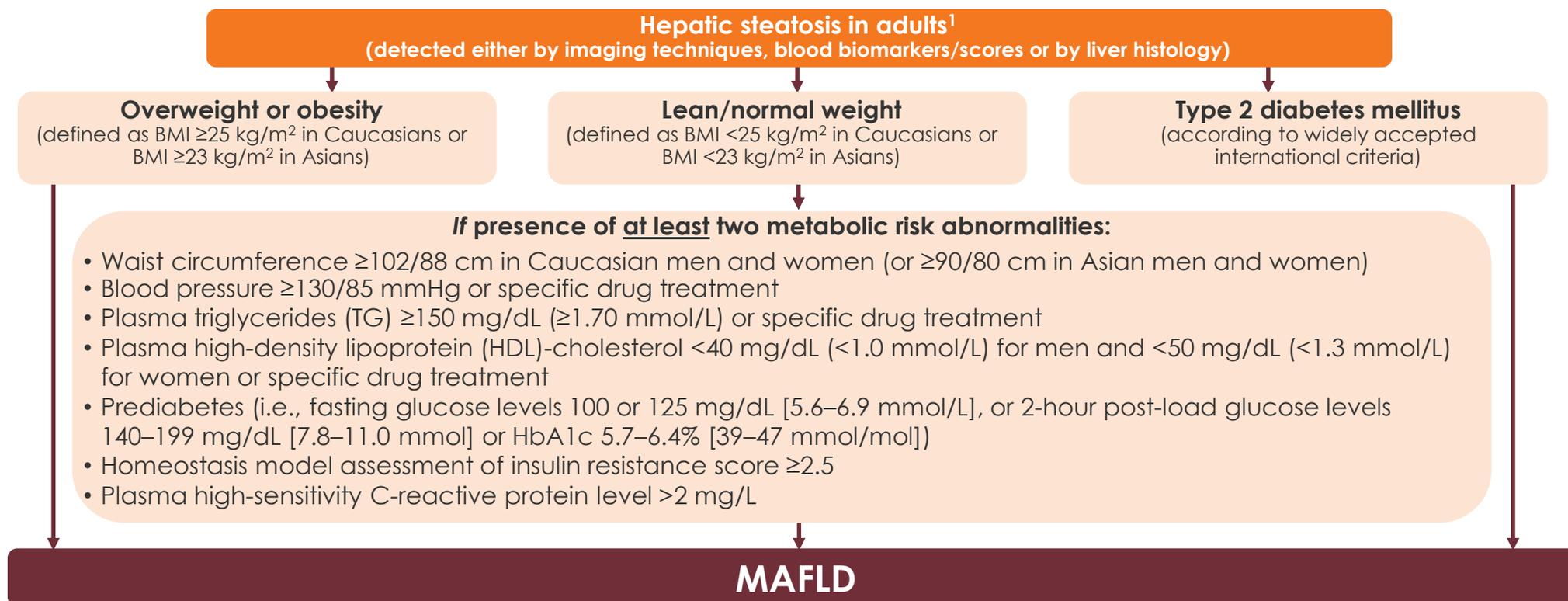
Before today, how familiar were you with the concept of MAFLD?

- 1 I was familiar with it and actively used the terminology
- 2 I was familiar with it but did not use the terminology
- 3 I was not at all familiar

MAFLD: redefinition of fatty liver disease More than just rebranding!

MAFLD, metabolic-associated fatty liver disease

MAFLD: adults diagnostic criteria



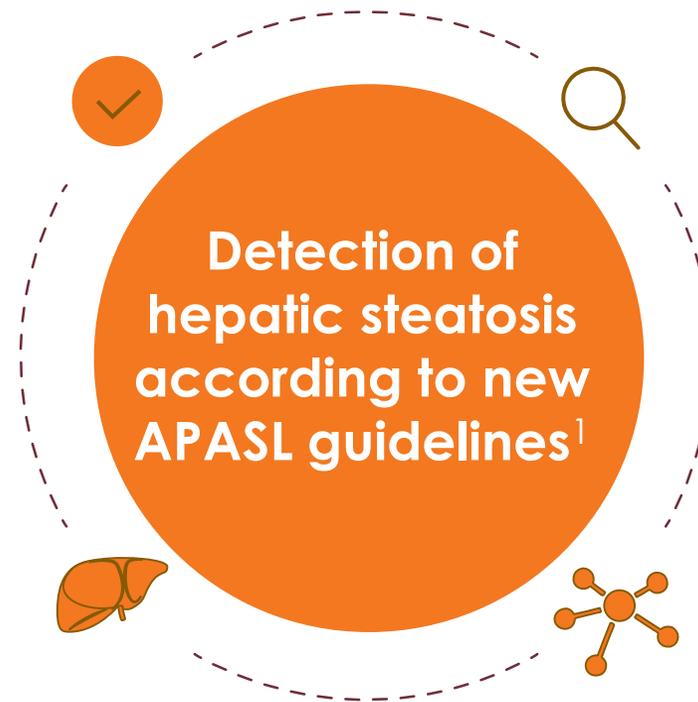
BMI, body mass index; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; MAFLD, metabolic-associated fatty liver disease; TG, triglyceride
1. Eslam M, et al. J Hepatol 2020;73(1):202–9

Diagnosis of MAFLD is based on the detection of hepatic steatosis

Routine imaging such as abdominal ultrasonography is usually sufficient for the detection of hepatic steatosis¹

Magnetic-resonance imaging (MRI)-based techniques are considered the gold standard to quantify liver fat but it is not recommended for routine clinical practice¹

APASL, Asian Pacific Association for the Study of the Liver; MAFLD, metabolic-associated fatty liver disease
1. Eslam M, et al. Hepatol Int 2020;14(6):889–919



Controlled attenuation parameter measurement by vibration-controlled transient elastography (VCTE) is more sensitive than ultrasonography¹

Serum biomarkers and scores such as the fatty liver index (FLI) may be used as an alternative method for the diagnosis of steatosis¹

The changing spectrum of fatty liver diseases (FLD)

Changing scenario of FLD classification¹

(A) Categorization of FLD subtypes

(B) Quantification of hepatic fat content



ALD, alcoholic liver disease; FLD, fatty liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis

1. Valenti L, et al. Liver Int 2020;40(5):1016–17

MAFLD: moving from concept to practice

MAFLD, metabolic-associated fatty liver disease

MAFLD vs NAFLD: hepatic fibrosis

- MAFLD definition is **more practical** for identifying patients with FLD at high risk of disease progression¹
- This definition allows physicians to consider the whole patient rather than focusing on a particular organ¹
- MAFLD helps in identifying a homogenous group of patients with FLD associated with metabolic dysfunction: existence of non-metabolic dysfunction NAFLD = 4.74%¹

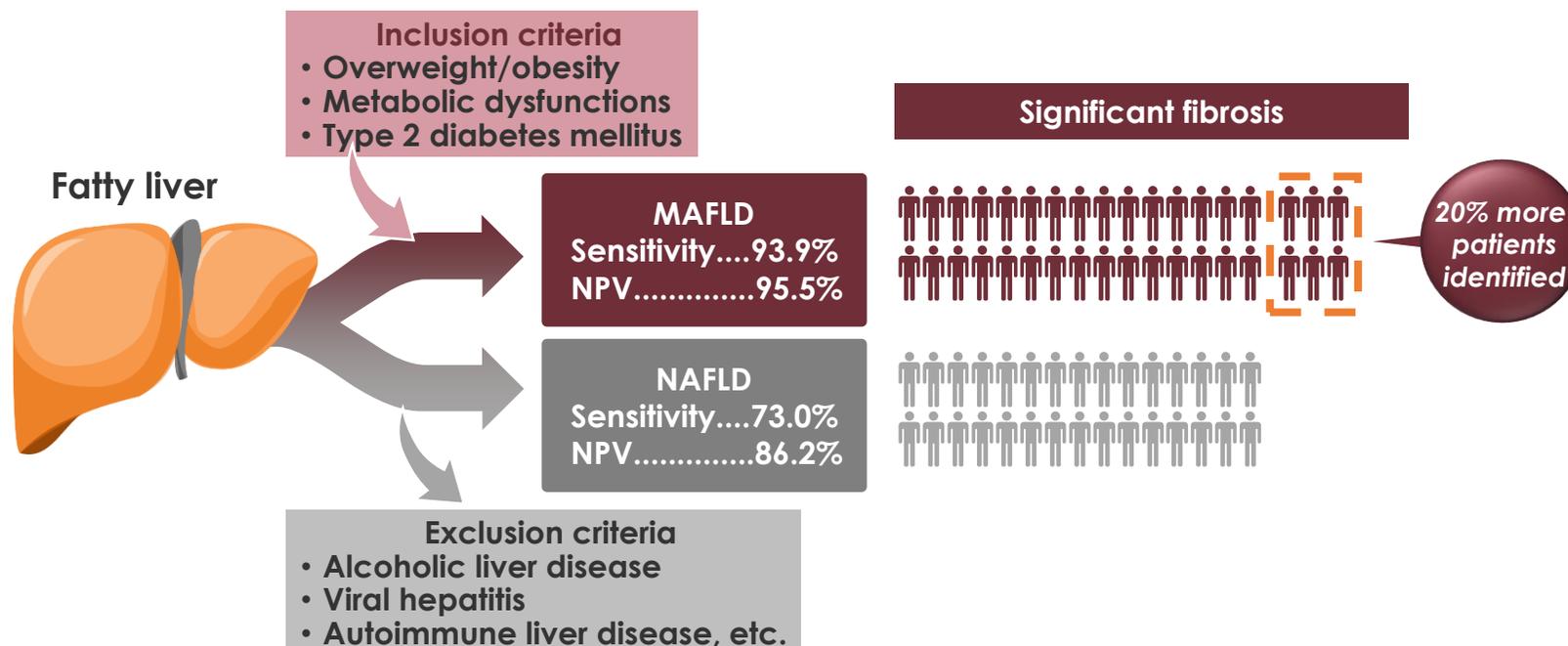
13,083 cases with US and lab data; NHANES III
 MAFLD was diagnosed in 4087/13,083 (31.24%)
 NAFLD in 4347/13,083 (33.23%) amongst the overall population¹

Variables	NAFLD (n =4347)	MAFLD (n=4087)	P-value
DM (%)	1092 (25.12)	1171 (28.65)	< 0.001
Hypertension (%)	1343 (30.89)	1463 (35.8)	< 0.001
HbA1c (%)	5.83 ± 1.44	5.91 ± 1.48	0.009
NFS score	-2.18 ± 1.52	-2.05 ± 1.51	< 0.001
FIB4 score	1.01 ± 0.84	1.06 ± 1.35	0.033
BARD score	2.52 ± 0.93	2.64 ± 0.97	< 0.001

BARD, body mass index, aspartate aminotransferase/alanine aminotransferase ratio, and diabetes; DM, diabetes mellitus; FIB4, fibrosis-4; FLD, fatty liver disease; HbA1c, glycated hemoglobin; MAFLD; metabolic-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; NFS, non-alcoholic fatty liver disease fibrosis score; NHANES, national health and nutrition examination survey
 1. Lin S, et al. Liver Int 2020;40(9):2082–9

MAFLD vs NAFLD: hepatic fibrosis

Comparison of the diagnostic accuracy of the MAFLD definition vs existing NAFLD criteria to identify patients with significant liver fibrosis (n=765, Japan)¹

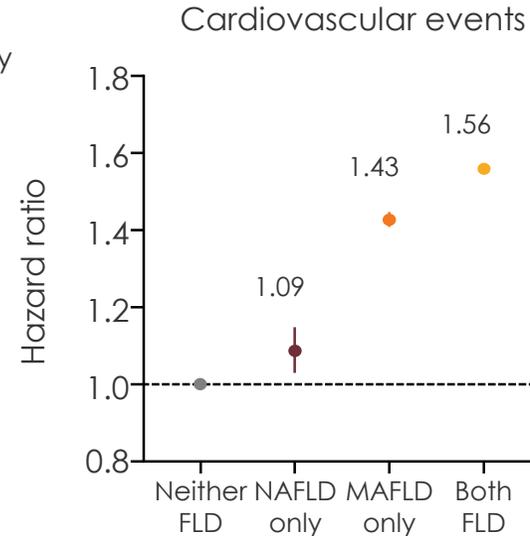
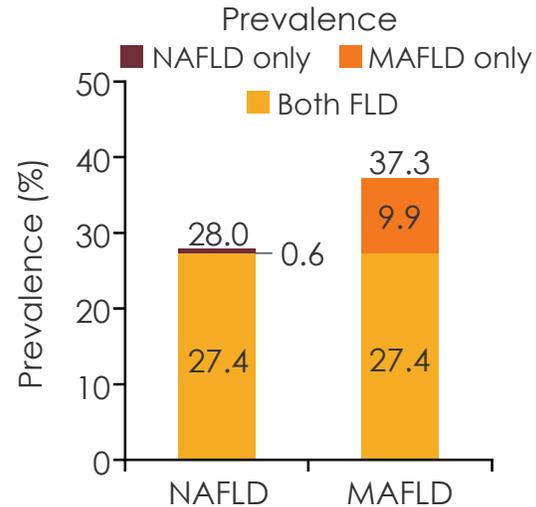
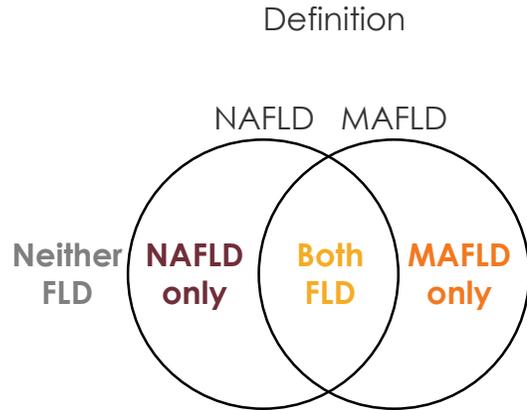


MAFLD metabolic-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; NPV, negative predictive value

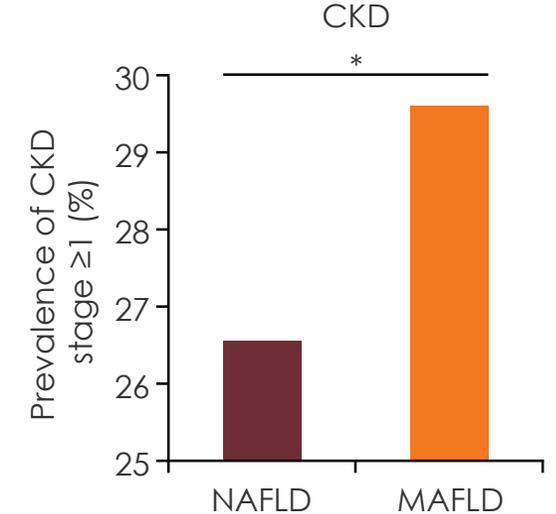
1. Yamamura S, et al Liver Int 2020;40(12):3018-30

MAFLD vs NAFLD: extrahepatic manifestations

Cardiovascular disease¹ 9,584,399 participants



Chronic kidney disease²



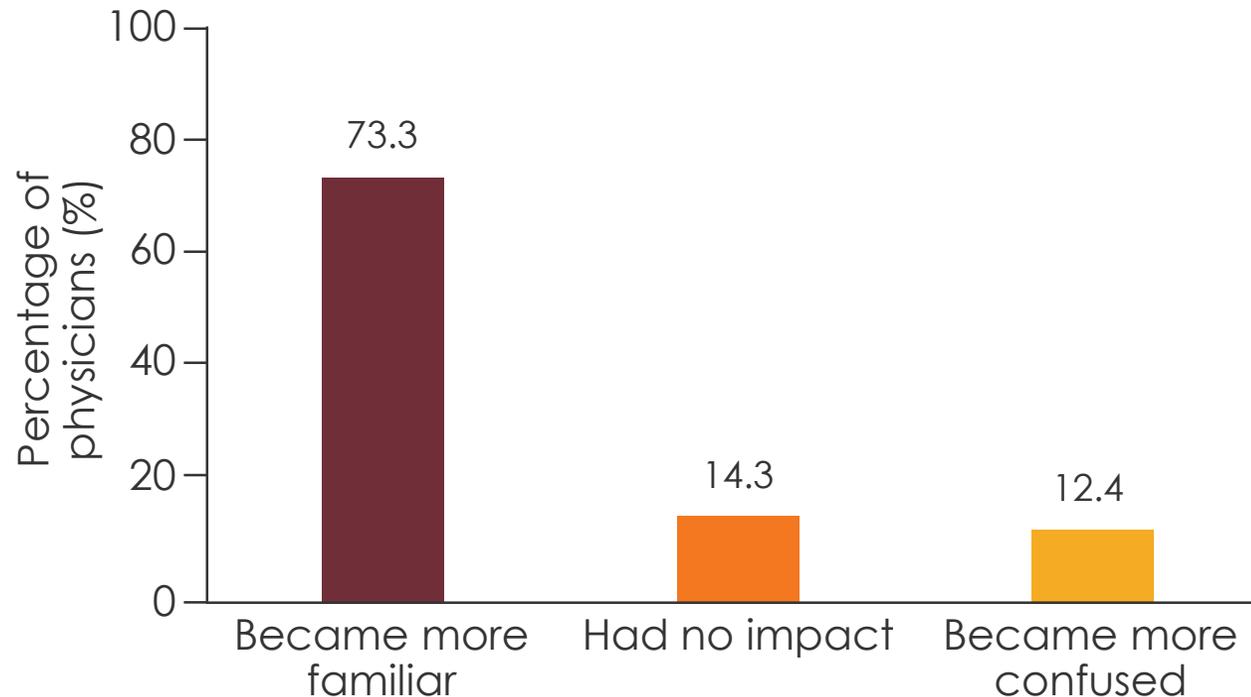
MAFLD may better identify fatty liver with high cardiovascular risk

Clinical Gastroenterology
and Hepatology

CKD, chronic kidney disease; FLD, fatty liver disease; MAFLD, metabolic-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease
1. Lee H, et al. Clin Gastroenterol Hepatol 2020; doi: 10.1016/j.cgh.2020.12.022. [Epub ahead of print]; 2. Sun DQ, et al. Metabolism 2021;115:154433

Change from NAFLD to MAFLD increases the awareness of fatty liver disease in primary care physicians and specialists

Effects of name change from NAFLD to MAFLD on physicians' understanding of the disease¹



MAFLD, metabolic-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease
1. Fouad Y, et al. J Hepatol 2021;74(5):1254–1256

Change from NAFLD to MAFLD may improve patients' health-related quality of life (HRQoL)

- NAFLD causes impairment of HRQoL¹



Patient perspective:²

Reframing the disease to MAFLD removes the negative connotations of NAFLD which may have a positive effect on patient care and therefore, HRQoL



Nurse and allied health perspective:³

Reframing the disease to MAFLD aids understanding and improves nurse-patient communication, thereby improving patient care and HRQoL

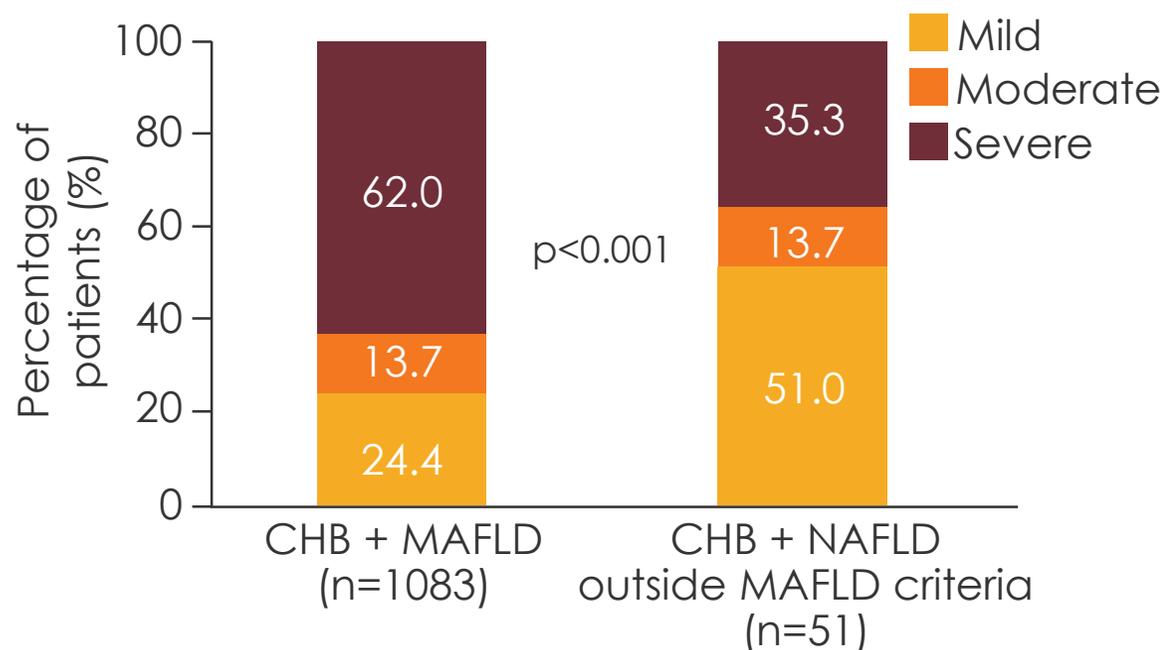
HRQoL, health-related quality of life; MAFLD, metabolic-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease

1. Golabi P, et al. Health Qual Life Outcomes 2016;14(18); 2. Shiha G, et al. Gastroenterol Hepatol 2021;6(1):73–9; 3. Clayton M, et al. Liver Int 2021;41(4):683–91

MAFLD and viral hepatitis

MAFLD and CHB¹

Distribution of severity of hepatic steatosis



MAFLD and CHC²

The proposed criteria for diagnosis of MAFLD is well validated and easily applicable to the entire spectrum of disease including non-obese subjects

CHB, chronic hepatitis B; CHC, chronic hepatitis C; MAFLD, metabolic-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease

1. Mak LY, et al. J Hepatol 2020; 73(6):1573–1574; 2. Fouad Y, et al. medRxiv 2020; doi:10.1101/2020.08.20.20176214

The APASL guidelines for the management of MAFLD



Ideally, an effective therapy should:

- Reduce **steatosis** and **liver injury**
- Improve **metabolic sequelae**
- Improve **cardiovascular risk**¹



Hence, lifestyle modification including **dietary change**, **weight loss**, and **structured exercise intervention** remains the first-line and cornerstone therapy for this condition¹

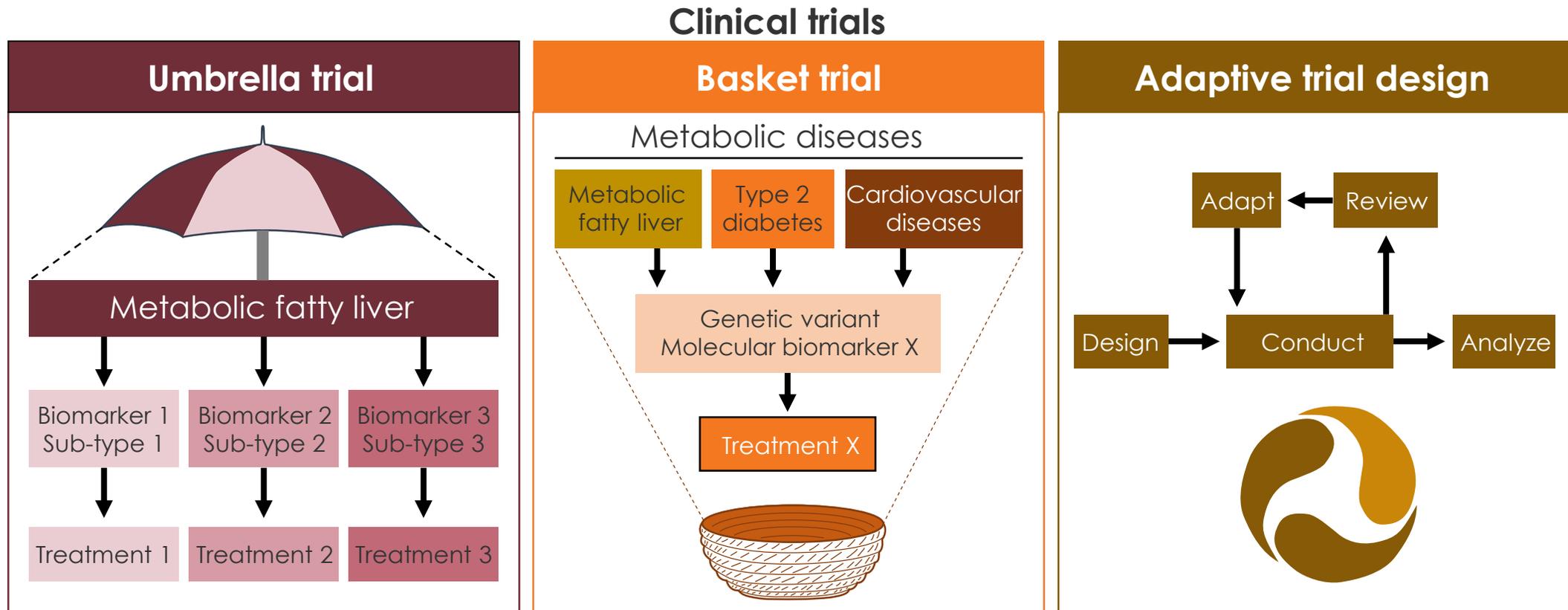
APASL, The Asian Pacific Association for the Study of the Liver; MAFLD, metabolic-associated fatty liver disease

1. Eslam M, et al. Hepatol Int 2020;14(6):889–919

MAFLD: the future

MAFLD, metabolic-associated fatty liver disease

Innovative clinical trials for MAFLD¹



MAFLD, metabolic-associated fatty liver disease
1. Eslam M, et al. Gastroenterology 2020;158(7):1999–2014.e1

Summary

- 1 MAFLD prevalence: 1 in 4 people globally
- 2 Problems with the old terminology: numerous
- 3 Coming up with a name: consensus process
- 4 Coming up with a definition: from concepts to an algorithm
- 5 Validity for clinicians: first evidence of superiority is in!
- 6 The future: bright

MAFLD, metabolic-associated fatty liver disease



Thank you!!!
Down-under: Sydney

