CLDF

Chronic Liver Disease Foundation

3RD ANNUAL

LIVER CONNECT

CONFERENCE

NASH CONNECT

Evolving NAFLD Models of Care and Future Perspectives

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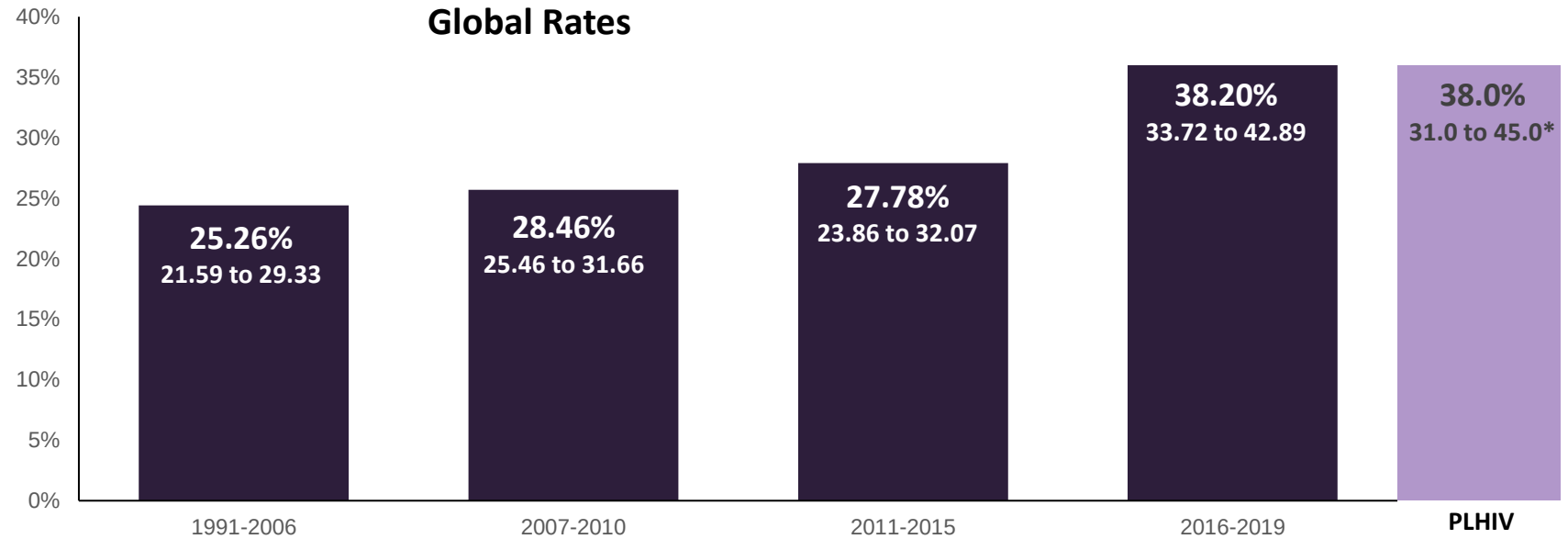
CUNY SPH GRADUATE SCHOOL OF PUBLIC HEALTH & HEALTH POLICY

Research grants to my institution from AbbVie, Gilead and MSD. Speaker fees from AbbVie, CEPHEID, Genfit, Gilead Sciences, Janssen, Intercept, MSD, Novavax and Novo Nordisk, unrelated to today’s talk.

Global NAFLD Prevalence is on the Rise

Data are displayed as prevalence (95% CI)



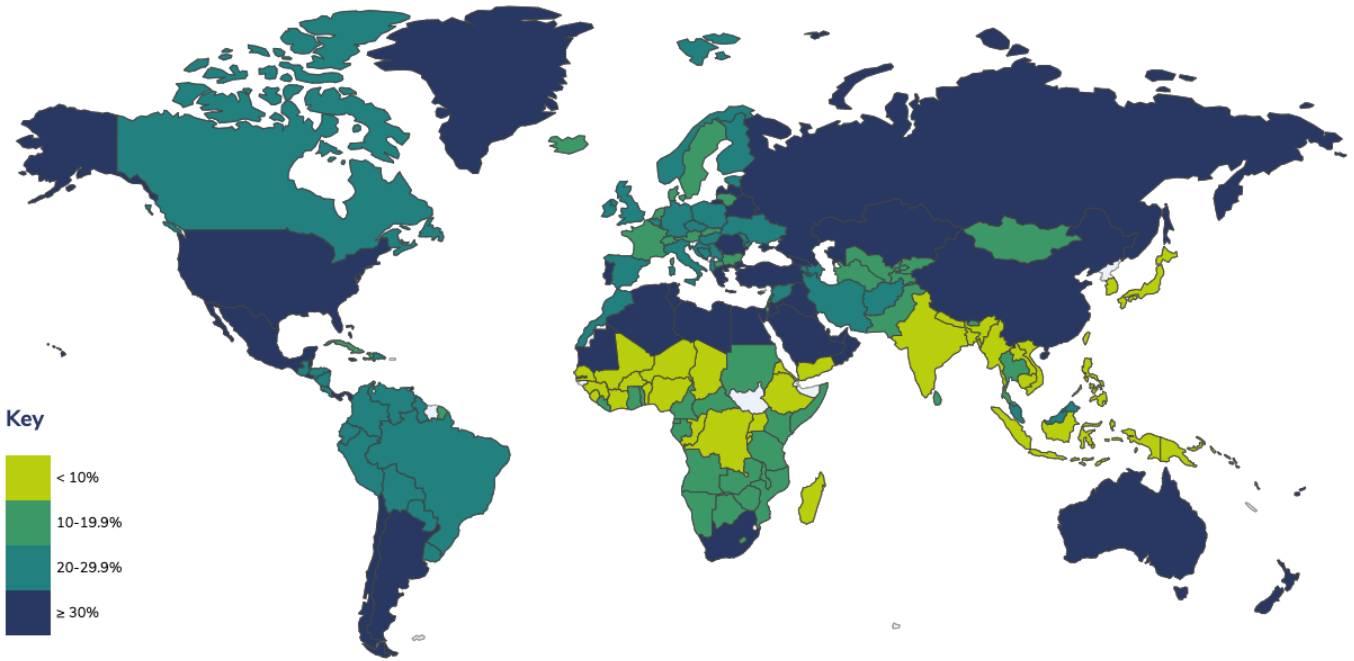
Survey year (Middle year of data collection)

Pooling of NAFLD prevalence estimates and ultrasound-defined NAFLD.

Source: Younossi ZM *et al.* The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. *Hepatology*. 2023.
*Manzano-Nunez R. *et al*. Uncovering the NAFLD burden in people living with HIV from high- and middle-income nations: a meta-analysis with a data gap from Subsaharan Africa. *JIAS*. 2023.

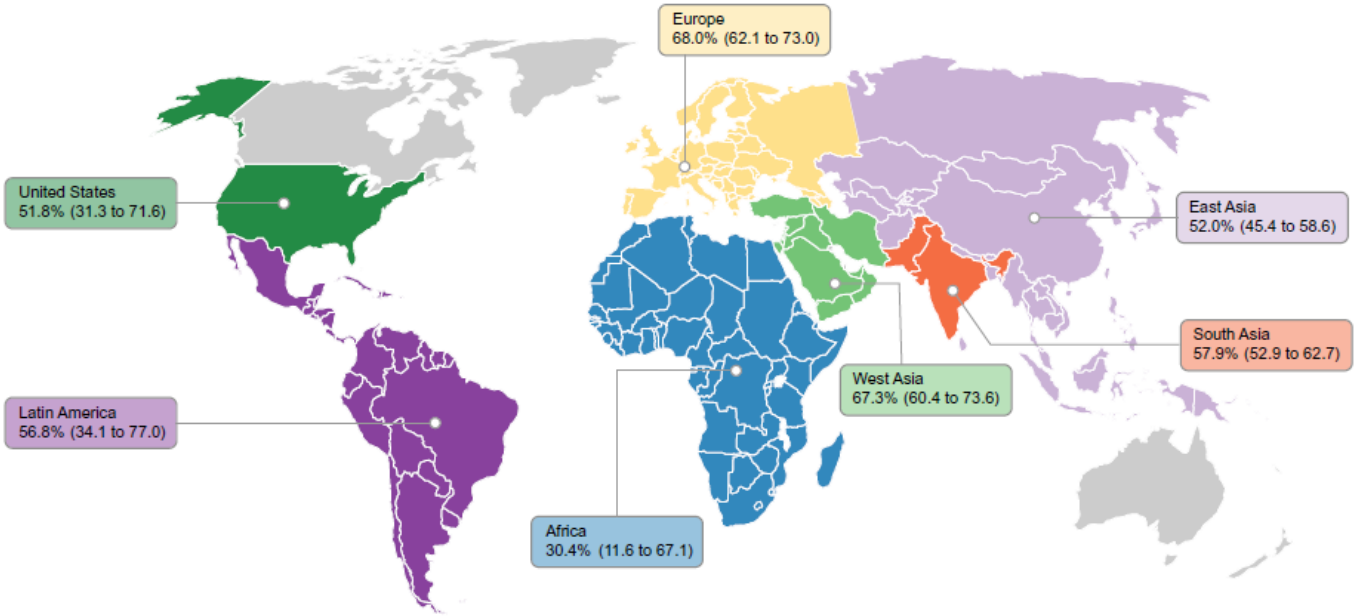
Obesity and Metabolic Syndrome Are Major Drivers of the Increase in NAFLD

Obesity prevalence map



Source: World Obesity Federation: https://data.worldobesity.org/region/who-africa-region-2/#data_prevalence.

Global NAFLD and NASH Prevalence in Patients With T2DM

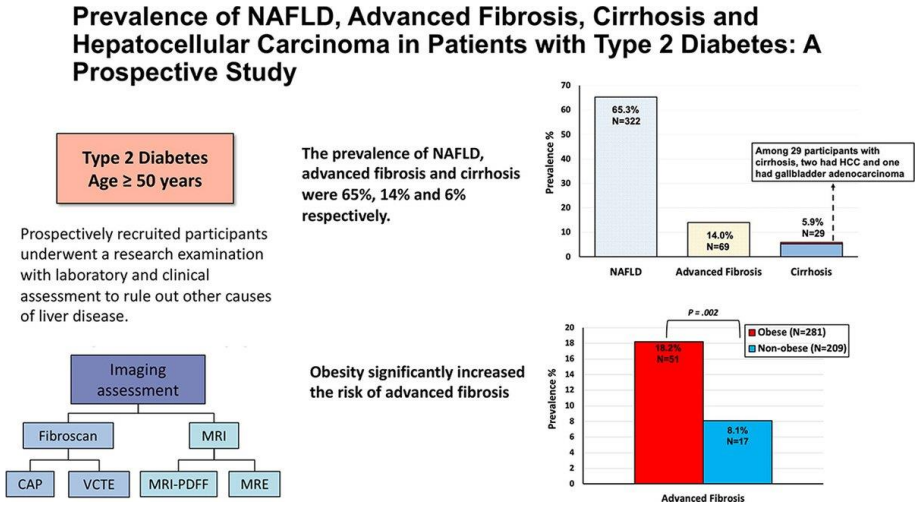


- 55.5% have NAFLD
- 37.3% have NASH
- 17.0% have advanced fibrosis

Source: Younossi ZM et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. *J Hepatol*. 2019;71:793.

Prevalence of NAFLD, Advanced Fibrosis, Cirrhosis and Hepatocellular Carcinoma in People With T2DM

- US study: 1 out of 7 diabetics have advanced liver fibrosis.
- If they are obese, 1 out of 5.
- With these numbers, SCREENING of liver fibrosis should be mandatory in people with type 2 diabetes mellitus (T2DM).
- 2012: Loomba et al “Diabetes is strongly associated with risk of NASH, fibrosis, and advanced fibrosis. Family history of diabetes, especially among nondiabetics, is associated with NASH and fibrosis in NAFLD.” (Hepatology)



Source: Ajmera V et al. A prospective study on the prevalence of NAFLD, advanced fibrosis, cirrhosis and hepatocellular carcinoma in people with type 2 diabetes. *J Hepatology*. 2022.

Current ADA Guidelines on NAFLD

4. Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Medical Care in Diabetes—2019*

Diabetes Care 2019;42(Suppl. 1):S34–S45 | https://doi.org/10.2337/dc19-S004

4. Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Medical Care in Diabetes—2022*

Diabetes Care 2022;45(Suppl. 1):S46–S59 | https://doi.org/10.2337/dc22-S004

Recommendation

4.14 Patients with type 2 diabetes or prediabetes and elevated liver enzymes (alanine aminotransferase) or fatty liver on ultrasound should be evaluated for presence of nonalcoholic steatohepatitis and liver fibrosis. **C**

UF UNIVERSITY of FLORIDA College of Medicine

Slide courtesy of Dr Ken Cusi.

Source: Cusi K et al. Time to include non-alcoholic steatohepatitis in the management of patients with type 2 diabetes. *Diabetes Care*. 2020;43(2):275-279.

NAFLD as a Cardiovascular Risk Factor

Journal of Hepatology 2018 vol. 68 | 335–352

Hypertension, diabetes, atherosclerosis and NASH: Cause or consequence?

Amedeo Lonardo[1], Fabio Nascimbeni[1], Alessandro Mantovani[2], Giovanni Targher[2,*]

Arteriosclerosis, Thrombosis, and Vascular Biology

CURRENT OPINION

Cardiovascular risk in patients with nonalcoholic fatty liver disease: looking at the liver to shield the heart

Curr Opin Lipidol 2020;31:364-366.

Kenneth Cusi[a,b] *and Eddison Godinez Leiva*[b]

AHA SCIENTIFIC STATEMENT

Nonalcoholic Fatty Liver Disease and Cardiovascular Risk: A Scientific Statement From the American Heart Association

P. Barton Duell, MD, Chair; Francine K. Welty, MD, Vice Chair; Michael Miller, MD; Alan Chait, MD; Gmerice Hammond, MD, MPH; Zahid Ahmad, MD; David E. Cohen, MD, PhD; Jay D. Horton, MD; Gregg S. Pressman, MD; Peter P. Toth, MD, PhD; on behalf of the American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Hypertension; Council on the Kidney in Cardiovascular Disease; Council on Lifestyle and Cardiometabolic Health; and Council on Peripheral Vascular Disease

Source: Duell et al, Arterioscler *Thromb Vasc Biol*. 2022 Jun;42(6):e168-e185.

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Slide courtesy of Dr Ken Cusi.

Source: Duell P et al. Nonalcoholic fatty liver disease and cardiovascular risk: a scientific statement from the American Heart Association. *Arterioscler Thromb Vasc Biol*. 2022;42(6):e168-e185.

Implications for Management and Care Pathway

NAFLD

- Minimal metabolic assessments:
  - Hyperglycaemia
  - Dyslipidaemia
  - Hypertension
  - Obesity
- Further workup for cardiovascular disease and other conditions as appropriate

Obesity and/or diabetes

- Work up for NAFLD and liver fibrosis as appropriate
- If cirrhosis, will also benefit from screening for liver cancer and varices

Treatments that benefit both NAFLD and concurrent metabolic conditions

- Lifestyle intervention
- Metabolic drugs
- Bariatric surgery

The Economic Impact of NAFLD and NASH

- Two studies found that in **Europe** alone, the annual economic burden of **NAFLD and NASH** is **estimated at ~€35 and ~€20 billion**, respectively, in direct medical costs, and ~€191 billion in societal costs due to loss of quality-adjusted life-years for NAFLD.
- Another **European** study found that the total economic costs of NASH were €8,548-19,546 million.
  - Of these, health system costs were €619-1292 million.
  - Total wellbeing costs were €41 536-90 379 million.
- In the **United States**, NAFLD has annual direct medical costs of about $103 billion.
- Patients with NASH have been reported to have a similar level of health-related quality of life, work productivity and activity impairment to individuals with T2DM but have reported worse mental status and a higher level of health resource use including emergency care and hospitalisation.

Sources: Younossi ZM et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. *Hepatology*. 2016;64:1577-1586; O'Hara J et al. Cost of non-alcoholic steatohepatitis in Europe and the USA: The GAIN study. *JHEP Rep*. 2020;2(100142); Schattenberg JM et al. Disease burden and economic impact of diagnosed non-alcoholic steatohepatitis in five European countries in 2018: A cost-of-illness analysis. *Liver Int*. 2021;41(6):1227-1242; Balp M-M, Krieger N, Przybysz R, et al. The burden of non-alcoholic steatohepatitis (NASH) among patients from Europe: A real-world patient-reported outcomes study. *JHEP Reports*. 2019; 1(3): 154-61.

A Public Health Emergency

A global issue
NAFLD affects >30% of people around the world

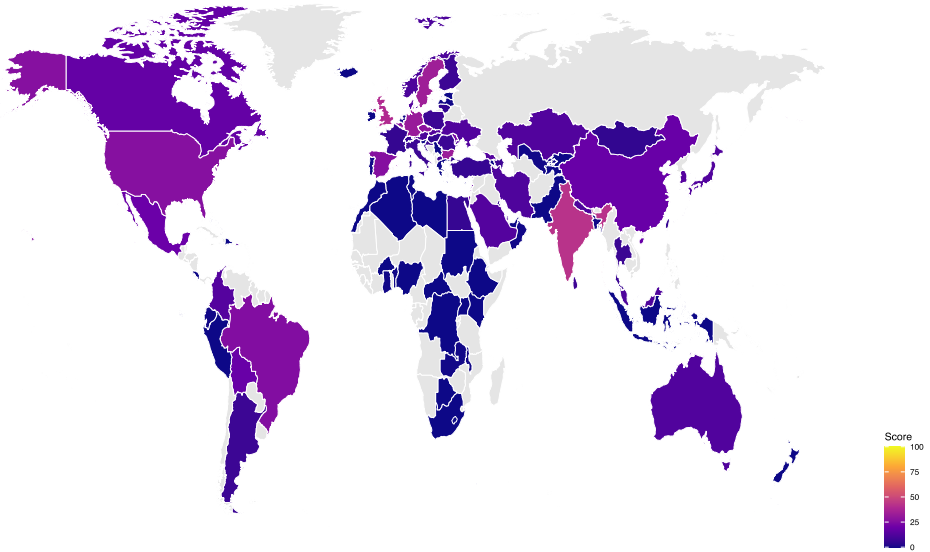
A significant impact
NAFLD has serious health, economic and social implications

A complex challenge
NAFLD requires us to work across disciplines and sectors to find solutions

A silent condition
NAFLD has received little attention from policy-makers or the public health community

Photo credit: The World Obesity Federation.

A Global Review of NAFLD and NASH Related Policies



- **None of the 102 countries was found to be well prepared to address NAFLD.**
- Close to a third of countries received an overall score of zero.
- The results can assist countries in identifying priority actions to improve their NAFLD preparedness.
- We can use the index to track national, regional and global progress over time.

Source: Lazarus JV et al. The global NAFLD policy review and preparedness index: Are countries ready to tackle the challenge?. *J Hepatology*. 2021;76(4):771-780.

Key Strategies and Policies for Addressing NAFLD

- National or sub-national NAFLD/NASH strategy + the inclusion of NAFLD/NASH in the national or sub-national strategies of key diseases or conditions related to NAFLD/NASH

Region	NAFLD/NASH Strategy	Obesity	Alcohol	CVD	Liver disease	Diabetes	Healthy habits/nutrition
East Asia & Pacific	0/12 (0%)	0/11˜ (0%)	0/11˜ (0%)	0/11˜ (0%)	0/12 (0%)	0/11˜ (0%)	0/11˜ (0%)
Europe & Central Asia	0/42 (0%)	2/40˜ (5%)	1/39˜ (3%)	1/40˜ (3%)	1/41˜ (2%)	0/38˜ (0%)	1/39˜ (3%)
Latin America & Caribbean	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)
Middle East & North Africa	0/14 (0%)	0/13˜ (0%)	0/14 (0%)	0/13˜ (0%)	0/14 (0%)	0/13˜ (0%)	0/14 (0%)
North America	0/2 (0%)	0/2 (0%)	0/2 (0%)	0/2 (0%)	0/2 (0%)	0/2 (0%)	0/2 (0%)
South Asia	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/4˜ (0%)
Sub-Saharan Africa	0/15 (0%)	0/14˜ (0%)	0/14˜ (0%)	0/14˜ (0%)	0/13˜ (0%)	0/14˜ (0%)	0/13˜ (0%)
Total	**0/102 (0%)**	**2/97˜ (2%)**	**1/97˜ (1%)**	**1/97˜ (1%)**	**1/99˜ (1%)**	**0/95˜ (0%)**	**1/95˜ (1%)**

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; CVD, cardiovascular disease. ˜Denominator for each variable adjusted to remove missing values and responses of “don’t know”.

Source: Lazarus JV et al. (2021). The global NAFLD preparedness index: are countries ready to tackle the challenge? https://www.journal-of-hepatology.eu/article/S0168-8278(21)02168-1/fulltext.

Wilton Park and EIU Collaborations

Wilton Park

- The first-ever event taking a broad public health approach to NAFLD
- 50 experts and practitioners, including from the World Health Organization (WHO), discussing how to tackle the challenge of NAFLD
- Event report outlines some of the key steps and action for a NAFLD roadmap
- A global research and action agenda focus at the 3rd event in **Oct 2022**

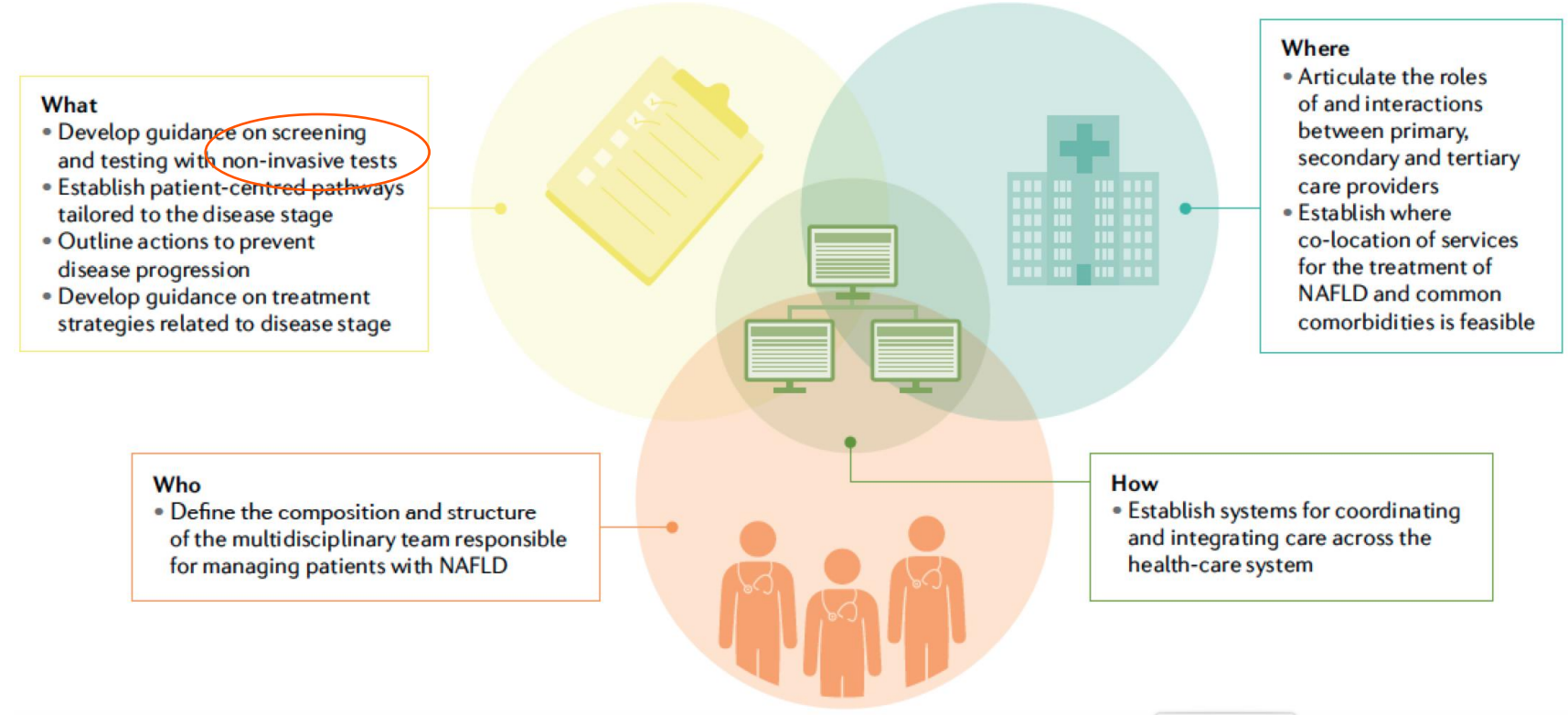
https://www.wiltonpark.org.uk/wp-content/uploads/2021/02/WP1736V3-Report.pdf

The Economist Intelligence Unit

- A deep dive into the opportunities and challenges for addressing NAFLD in Asia, Latin America and the Middle East
- 55 regional experts engaging in 14 workshops over 12 months
- Report details key calls to action across a range of areas, from models of care (MoCs), to integration of NAFLD into non-communicable disease (NCD) activities
- Regional experts are now taking these recommendations forward

https://eiuperspectives.economist.com/healthcare/nafld-sounding-alarm-global-public-health-challenge

Eight Recommendations for Improving MoCs of NAFLD and NASH Patients

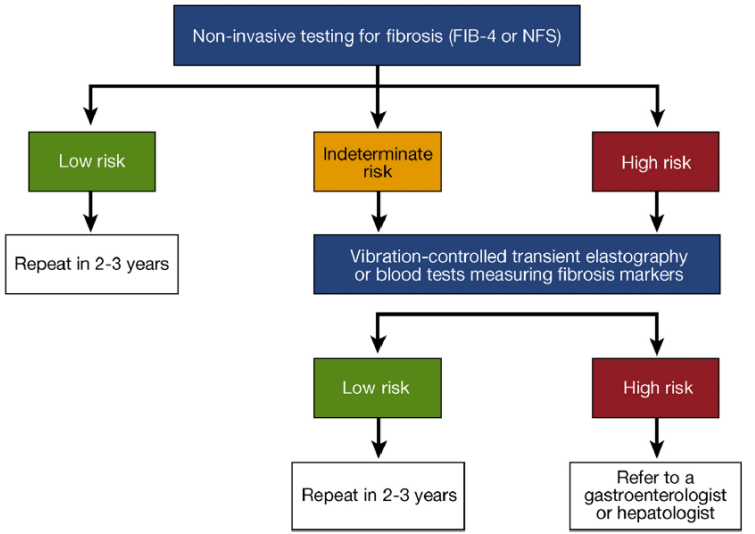


Source: Lazarus et al. Defining comprehensive models of care for NAFLD. *Nature Reviews Gastro Hep*. 2021;18:717-729.

A Multidisciplinary Approach for the Management of NAFLD

Preparing for the NASH Epidemic: A Call to Action

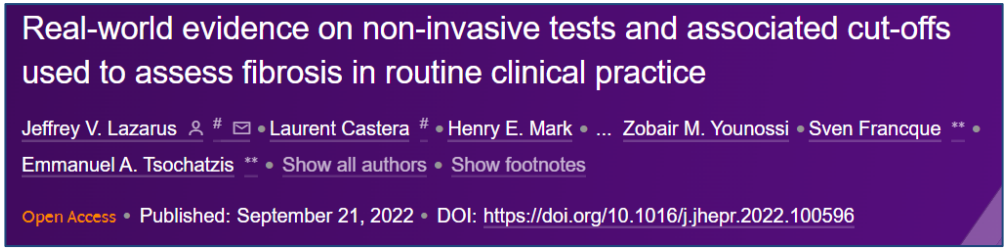
Fasiha Kanwal,[1] Jay H. Shubrook,[2] Zobair Younossi,[3] Yamini Natarajan,[4] Elisabetta Bugianesi,[5] Mary E. Rinella,[6] Stephen A. Harrison,[7] Christos Mantzoros,[8] Kim Pfotenhauer,[9] Samuel Klein,[10] Robert H. Eckel,[11] Davida Kruger,[12] Hashem El-Serag,[13] and Kenneth Cusi[14]



Algorithm for risk stratification in patients with NAFLD/NASH. FIB-4, Fibrosis-4 Index; NFS, NAFLD fib

Source: Cusi K et al. Preparing for the NASH epidemic: A call to action. *Gastroenterology*. 2021;161:1030-1042.

NITs to Assess Fibrosis Levels


Real-world evidence on non-invasive tests and associated cut-offs used to assess fibrosis in routine clinical practice

Jeffrey V. Lazarus # • Laurent Castera # • Henry E. Mark • ... Zobair M. Younossi • Sven Francque ** • Emmanuel A. Tsochatzis ** • Show all authors • Show footnotes

Open Access • Published: September 21, 2022 • DOI: https://doi.org/10.1016/j.jhepr.2022.100596

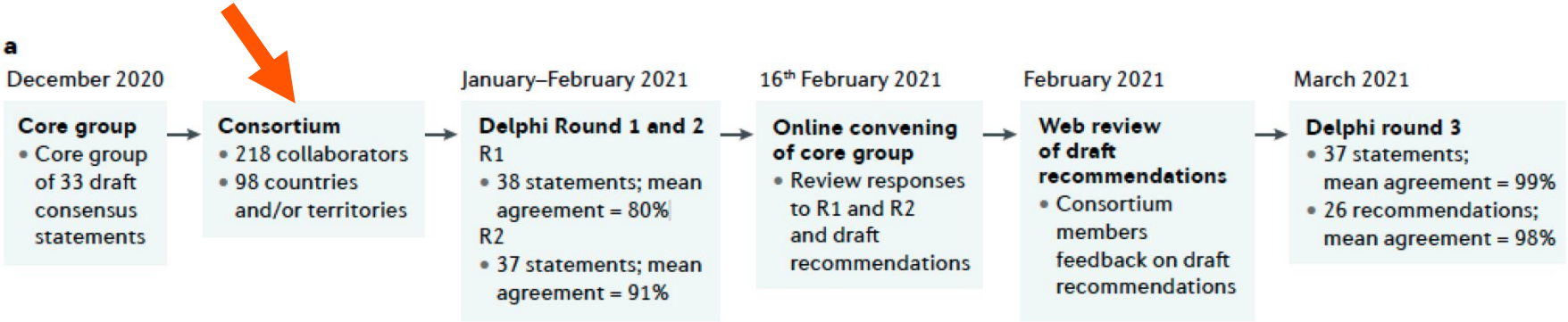
- Non-invasive tests (NITs) are valuable in identifying patients with NAFLD and fibrosis who require specialist care.
- Among 35 survey respondents, 14 different NITs were used, of which FIB-4 and transient elastography were the most common.
  - **Cut-offs used for the same NITs for NAFLD risk-stratification vary between clinicians.**
- Lower and upper cut-offs have important implications for test performance and clinical decision making.
- **Guidelines to standardise NIT cut-offs are needed** to improve and monitor consistency in risk-stratification in NAFLD.

JHEP Reports Innovation in Hepatology EASL

Source: Lazarus JV et al. Real-world evidence on non-invasive tests and associated cut-offs used to assess fibrosis in routine clinical practice. *JHEP Reports*. 2022;5(1):100596.

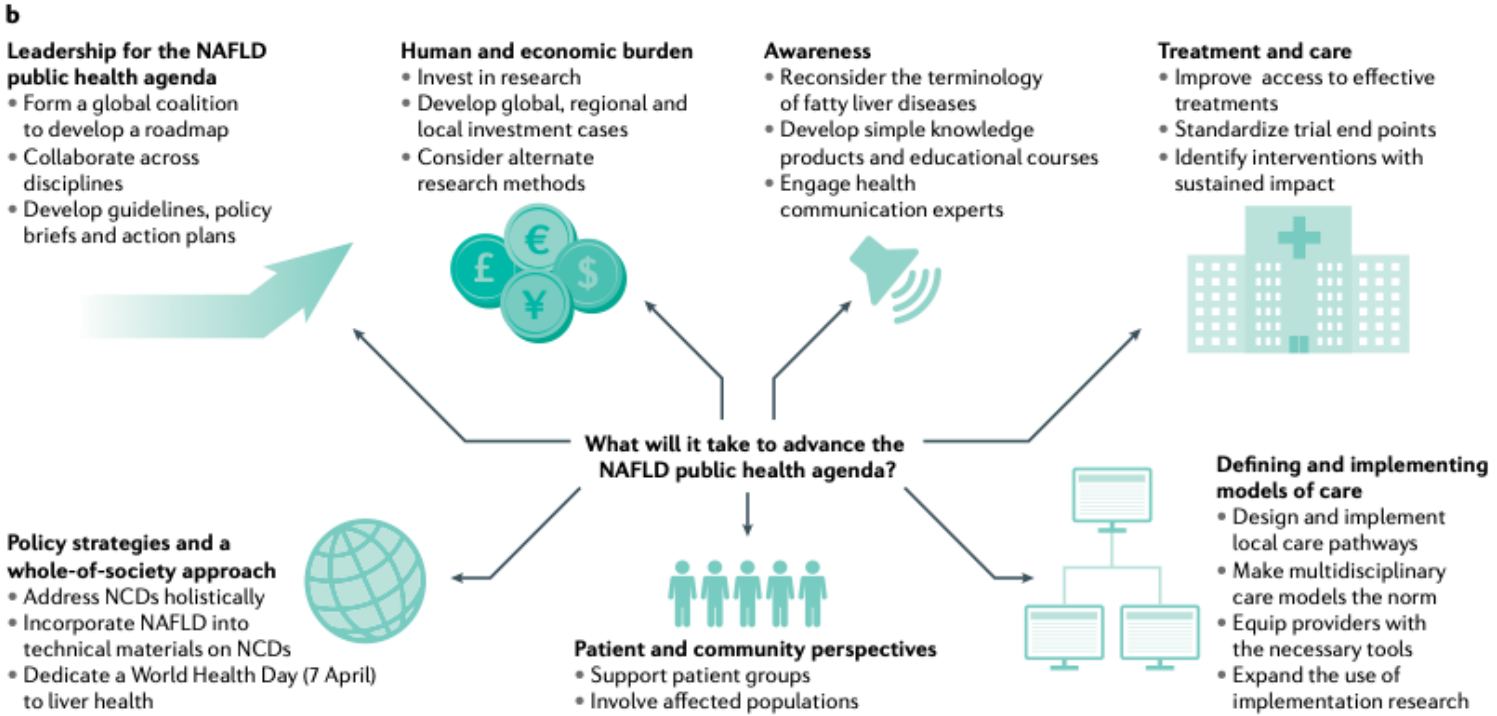
A Global Issue Needing a Global Response

- To support efforts to have a coordinated response, we set out to develop **a global NAFLD public health consensus statement** and a set of recommendations.
- The **Delphi process** employs a review and revision methodology that can result in relatively greater agreement among statements and recommendations over successive survey rounds, while also identifying areas of disagreement that may require special efforts going forward.
- We hope that this can form the basis of a global NAFLD roadmap.



Source: Lazarus JV et al. Advancing the global public health agenda for NAFLD: a consensus statement. *Nature Reviews Gastro Hep*. 2022;19:68-70.

NAFLD Consensus Recommendations



Source: Lazarus JV et al. Advancing the global public health agenda for NAFLD: a consensus statement. *Nature Reviews Gastro Hep*. 2022;19:68-70.

The EASL-Lancet Commission: Protecting the Next Generation of Europeans Against Liver Disease Complications and Premature Mortality

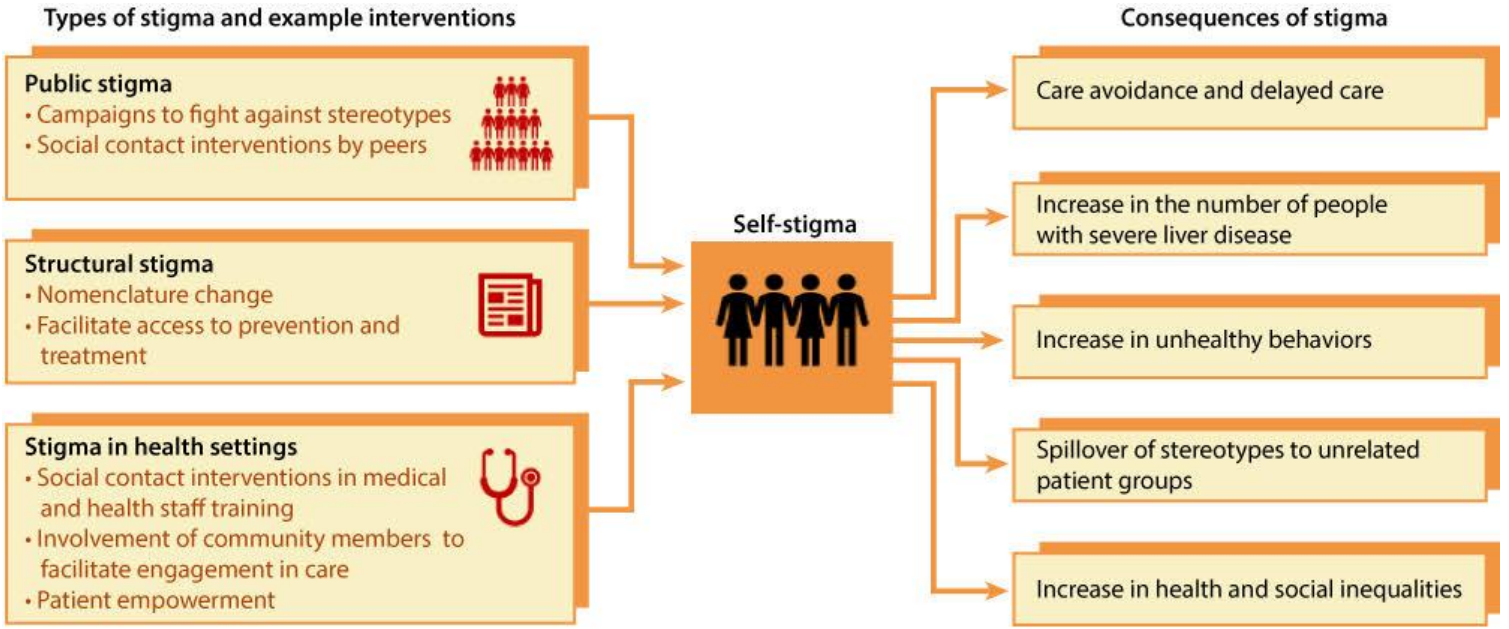
Fatty liver disease in Europe: estimated prevalence is on the rise.

Recommendations:

- **Recognise impact of** the **marketing** of alcohol and ultra-processed, high-sugar food and drinks to children
- **Advocate for improved health promotion** through access to healthy diets and physical activity
- The **endocrinologist should not miss NAFLD:** people with T2DM have a significantly increased risk of advancing liver fibrosis and hepatocellular carcinoma
- Develop **multi-stakeholder education programmes** to reduce all forms of stigma

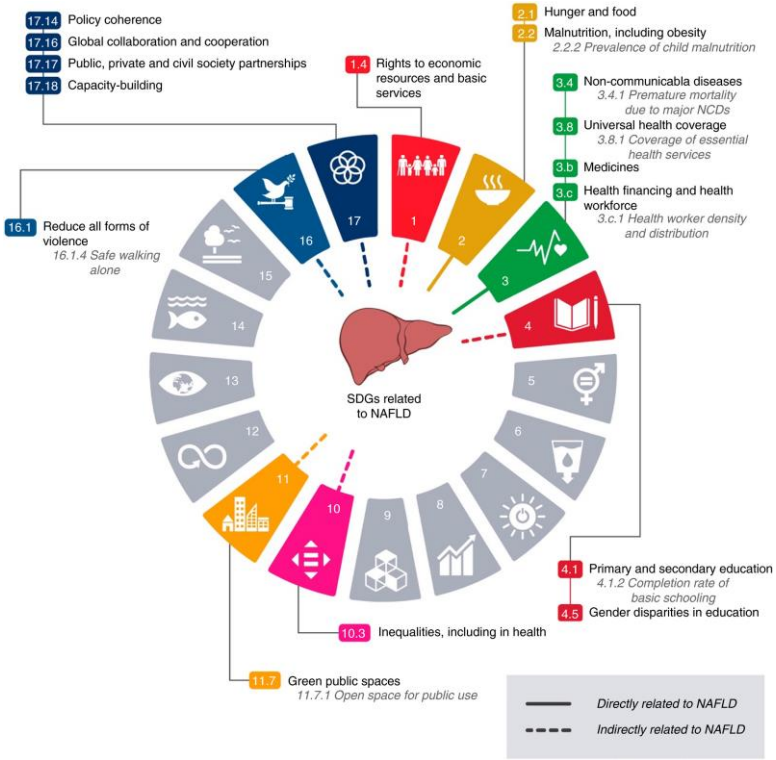
Source: Karlsen TH et al. The EASL-Lancet Liver Commission: protecting the next generation of Europeans against liver disease complications and premature mortality. *Lancet*. 2022;399:61-116.

Stigma



Source: Karlsen TH, et al. The EASL-Lancet Liver Commission: protecting the next generation of Europeans against liver disease complications and premature mortality. *Lancet*. 2022;399:61-116.

A Sustainable Development Goal Framework to Guide Multisectoral Action on NAFLD Through a Societal Approach



Source: Lazarus JV et al. A sustainable development foal framework to guide multisectoral action on NAFLD through a societal approach. *Alimentary Pharmacology & Therapeutics*. 2021;55(2):234-243.

Positioning NAFLD Within the NCD Agenda: Where Strategically Should NAFLD Sit in the NCD Agenda?

- Build partnerships and collaborations beyond the liver health community
- Establish a **collaborative response to NAFLD and other NCDs** via shared visions, common platforms
- Shared language across disciplines & understanding of the mutual benefits
- **Identifying where the NAFLD/NASH community can lead efforts and where it can support and amplify the work of others**
- World Obesity Day (4 March) to be used by the liver community to engage in and amplify their own and others' calls to action
- The national collaboration childhood obesity research (NCCOR) model could be useful to advance and coordinate NAFLD research and knowledge

Positioning NAFLD Within the NCD Agenda: What Alliances and Networks Need to Be Built or Strengthened to Advance This?

- **Engage with diabetes, obesity and heart disease communities**
- Engage with other key stakeholders: Paediatrics and adolescent health groups, primary care societies, cancer groups and HIV, food systems and nutrition societies
- Improve communication on NAFLD from professional organisations (diabetes , obesity)
- **Engage with and support a wide range of patient groups, including beyond the liver**
- Liver community to take the lead to establish collaborations with other disciplines and understand common benefits
- Liver community to support the international recognition of obesity as a disease
- **Use good quality data linking the prevalence of NAFLD to other diseases as tool for collaboration – metabolic syndrome**
- Cross-disciplinary research partnerships as tool for collaborations across organisations

Key Actions Advance the NAFLD Public Health Agenda

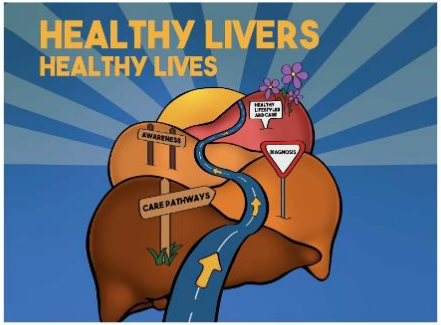
- An organised agenda that clearly sets out what research and action is required. This will be kicked off in Oct with global participation.
- Move the issue outside of the liver health space and make it part of others agendas (e.g., NCDs - obesity, diabetes).
- Establish multi-stakeholder collaborations across sectors and disciplines – and engage with WHO (globally and regionally).

Photo credit: The World Obesity Federation.

A Global Coalition “Healthy Livers, Healthy Lives”

- **Engagement of representatives from key medical associations** focused on the liver and other **key stakeholders** on the global fatty liver disease initiative.
- Transparent, inclusive global collaboration on **research and action priorities** for all stakeholders to take forward, in line with their own priorities, efforts and activities.
- **Discussion of:**
  - How to expand outside of the health/medicine space.
  - Plans for 2023 and beyond including:
    - Engagement at the EASL WHA side-event (May 2023).
    - EASL, INASL, ALEH, AASLD conferences.

Wilton Park



Report

Developing a research and action roadmap for fatty liver disease

Monday 17 – Wednesday 19 October 2022 | WP1957

In association with:

EASL

Final Thoughts

- We have a long way to go to make NAFLD a public health priority and ensure adequate responses from the local to the global level.
  - But there is cause for optimism…
- We have more momentum than ever and a growing coalition of experts across disciplines ready to advance this agenda.
- Together, we need to take the opportunity to shape the future of the NAFLD public health agenda!

Acknowledgements

The board of the EASL International Liver Foundation and in particular Massimo Colombo as well as Henry Mark and Marcela Villota at the secretariat, for the work on NAFLD/NASH.

A special thanks to the 218 experts who contributed to the NAFLD consensus statement (NRGH 2021) and to Quentin Anstee and Adam Palayew and the NAFLD survey country leads and team members of the global preparedness index (JHEP 2021).

Nancy Lee, Henry Mark and the team from Wilton Park and the thought leaders who participated in the Wilton Park care pathways meetings in 2020 (Models of Care in NRGH 2021) and the entire NAFLD Wilton Park thinktank steering committee. https://www.wiltonpark.org.uk/wp-content/uploads/2021/02/WP1736V3-Report.pdf

The Economist Intelligence Unit, including >50 participants and guest speakers from Asia, Latin America and the Middle East during the EASL International Liver Foundation engagement series in 2020-21. https://eiuperspectives.economist.com/healthcare/nafld-sounding-alarm-global-public-health-challenge

The ISGlobal Health Systems Research team

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