



# Practice guidance documents for the diagnosis and management of non-alcoholic fatty liver disease—recent updates and open questions

Volker M. Lauschke<sup>1,2,3^</sup>

<sup>1</sup>Dr Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart, Germany; <sup>2</sup>Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden; <sup>3</sup>University Tübingen, Tübingen, Germany

*Correspondence to:* Prof. Volker M. Lauschke, PhD. Dr Margarete Fischer-Bosch Institute of Clinical Pharmacology, Auerbachstr. 112., 70 376 Stuttgart, Germany; Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden; University Tübingen, Tübingen, Germany. Email: volker.lauschke@ikp-stuttgart.de.

*Comment on:* Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, *et al.* AASLD Practice Guidance on the clinical assessment and management of non-alcoholic fatty liver disease. *Hepatology* 2023;77:1797-835.

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Primarily driven by an increasingly sedentary lifestyle and hypercaloric nutritionally imbalanced diets, non-alcoholic fatty liver disease (NAFLD) has emerged as the most prevalent liver disease in the US and Europe. NAFLD constitutes an umbrella term that includes a spectrum of disease from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH), NASH fibrosis and NASH cirrhosis that are all characterized by  $\geq 5\%$  of all hepatocytes being steatotic in patients with little alcohol intake and no apparent alternative causes. The American Association for the Study of Liver Diseases (AASLD) has recently provided an updated comprehensive guidance document that provides 29 actionable statements to improve diagnosis and patient management of adult NAFLD in clinical practice taking into account the recent advances in risk assessment and therapeutic measures (1).

The new document provides an update of the previous AASLD practice guidance from 2018 (2). For patients with incidental findings of hepatic steatosis, AASLD recommends evaluation of metabolic comorbidities, alcohol intake as well as the exclusion of other etiologies, such as genetic disease, nutrient deficiencies or exposure to drugs known to impact hepatic *de novo* lipogenesis or  $\beta$ -oxidation. One important innovation of the update

is the algorithm for risk stratification in patients with a clinically suspected or established NAFLD. The main purpose of this evaluation is to exclude advanced fibrosis using a test with high negative predictive value (NPV). To this end, the AASLD recommends the fibrosis 4 (FIB-4) score as a non-invasive blood-based test that exhibited consistently good prognostication in secondary or tertiary care settings across studies (3). These recommendations align well with guidelines from the Asian Pacific Association for the Study of the Liver (APASL) that recommend either non-invasive tests or liver stiffness measurements (LSM) for the exclusion of advanced fibrosis (4). However, correlation of FIB-4 with LSM showed high rates of false negatives up to 46% in patients with multiple risk factors, indicating that the reliance on FIB-4 for specialist referrals might be problematic (5,6). In contrast, the algorithm recommended by the European Association for the Study of the Liver (EASL) additionally suggests referral to gastrointestinal specialist centers for every patient with steatosis and liver enzyme abnormalities, which the AASLD guidance considers unreliable as they are frequently normal in patients with advanced liver disease (7). It remains to be determined, which process provides increased patient benefits.

<sup>^</sup> ORCID: 0000-0002-1140-6204.

**Table 1** Comparison of important recommendations regarding the NASH diagnosis and management issued by major international societies

| Recommendation                                      | AASLD   | EASL   | APASL   |
|---|---|--|---|
| Risk groups recommended for NAFLD screening         | Diabetics and patients with complicated obesity, family history of cirrhosis or moderate-to-high alcohol consumption  | Diabetics and all individuals with persistently abnormal liver enzymes, obesity or MetS  | Diabetics and all individuals who are overweight, obese or have been diagnosed with MetS  |
| Screenings recommended for patients with steatosis  | Diabetes  | Features of MetS, evaluation of CVD  | Features of MetS, evaluation of CVD and cardiovascular risk   |
| Identification of steatosis                         | Standard ultrasound not recommended to identify hepatic steatosis. Steatosis should be identified using CAP or MRI-PDFF   | Ultrasound is recommended as first-line. MRS is the only quantitative method, but not recommended in clinical practice   | Ultrasound is recommended as first-line. Alternatives are CAP and transient elastography. MRS and MRI-PDFF not recommended in clinical practice |
| Identification of NASH                              | Serum and imaging-based methods not yet fit for routine clinical practice   | NASH has to be diagnosed by a liver biopsy   | NASH has to be diagnosed by a liver biopsy. Exclusion using elastography or blood biomarkers and scores of fibrosis                             |
| Identification of fibrosis                          | FIB-4 risk assessment recommended. Advanced fibrosis or cirrhosis needs to be confirmed by liver biopsy   | NFS, FIB-4, ELF or FibroTest with or without transient elastography. Advanced fibrosis or cirrhosis needs to be confirmed by liver biopsy  | NFS, FIB-4, ELF or FibroTest with or without transient elastography. Advanced fibrosis or cirrhosis needs to be confirmed by liver biopsy       |
| Dietary & lifestyle recommendations                 | Hypocaloric diet & increased physical activity; abstinence from alcohol in NASH fibrosis  | Hypocaloric diet free of processed food, as well as food and beverages high in added fructose. Increased physical activity   |   |
| Endorsements of pharmacological treatments for NASH | Semaglutide (for patients with T2DM/obesity), pioglitazone (for patients with T2DM) or vitamin E  | Pioglitazone (also off-label) or vitamin E   | No firm recommendations   |
| Bariatric surgery                                   | Useful measure to improve the histological lesions of NAFLD. Decompensated cirrhosis is absolute exclusion criterion  | Useful measure to improve the histological lesions of NAFLD. No recommendation regarding the use in cirrhosis  | Useful measure to improve the histological lesions of NAFLD. Individualized decision in cirrhotic patients                                      |
| Therapeutic measures for dyslipidemia               | Statins, omega-3 FAs, icosapent ethyl or fibrates   | Statins, omega-3 FAs   | Statins should be considered in all patients with NAFLD and hyperlipidemia  |
| Follow-up   | Low risk patients with steatosis: every 2–3 years; in patients with prediabetes, T2DM or 2 or more metabolic risk factors: 1–2 years; patients with biopsy confirmed fibrosis: annually | NAFL patients without worsening of metabolic risk factors: 2–3-years; patients with NASH and/or fibrosis: annually; patients with NASH cirrhosis: every 6 months; if indicated on a case-by-case basis, liver biopsy could be repeated after 5 years |   |

NASH, non-alcoholic steatohepatitis; AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; APASL, Asian Pacific Association for the Study of the Liver; NAFLD, non-alcoholic fatty liver disease; MetS, metabolic syndrome; CVD, cardiovascular disease; CAP, controlled attenuation parameter; MRI-PDFF, magnetic resonance imaging–proton density fat fraction; MRS, magnetic resonance spectroscopy; FIB-4, fibrosis 4 calculator; NFS, NAFLD fibrosis score; ELF, enhanced liver fibrosis; T2DM, type 2 diabetes mellitus; FA, fatty acid.

While guidance by the different major societies aligns overall well, some further notable differences remain, particularly with regards to diagnostic modalities (*Table 1*). One major difference is the negative recommendation regarding the use of ultrasound for the detection of steatosis. The AASLD guidance recommends magnetic resonance imaging–proton density fat fraction (MRI-PDF) and elastography with controlled attenuation parameter (CAP) as methods of choice for the identification of steatosis whereas the use of ultrasound is explicitly not recommended due to its low sensitivity. In contrast, ultrasound is the preferred first-line diagnostic procedure for imaging of NAFLD both EASL and APASL, whereas MRI is not recommended for routine clinical practice due to its high cost, despite being recognized as the gold standard to quantify liver fat. Furthermore, for large-scale studies EASL and APASL endorse the use of serum biomarkers, such as the fatty liver index (FLI), NAFLD liver fat score (NAFLD-LFS), hepatic steatosis index (HSI), visceral adiposity index (VAI) and triglyceride-glucose (TyG) index, which can predict the presence, but not the severity, of steatosis with acceptable accuracy [positive predictive values (PPVs) of 99% and NPVs of 10–16%] (8).

Which points remain to be addressed?

The current guidance document focusses on adult NAFLD, whereas similar updated AASLD recommendations for the diagnosis and management of NASH in children and juveniles are currently lacking. The author refers to a separate upcoming guidance document for these patient groups, which is urgently needed.

- (I) There is furthermore ongoing discussion about the nomenclature of fatty liver disease. The APASL has abandoned the acronym NAFLD for the overarching term “metabolic (dysfunction) associated fatty liver disease (MAFLD)” that better reflects disease pathogenesis (9). While this change might help in the identification and recognition of disease subtypes, it would arguably be beneficial for both patients and clinicians if terminology could be standardized between the different societies and expert groups as soon as possible.
- (II) Genetic variants in multiple risk genes have been consistently associated with NAFLD onset and progression (10). Most pronounced are the effects of variations in *PNPLA3*, *TM6SF2*, *GCKR*, *MBOAT7* and *HSD17B13* with moderate-to-large effect sizes. However, their inclusion into personalized risk stratification algorithms is

currently not recommended in clinical practice by either AASLD or APASL. The European guidance does not endorse routine genetic testing for these variations either but recommends consideration of genotyping in selected patients and clinical studies. With increasing prevalence of medical genomics and direct-to-consumer genetic testing, more and more individuals with incident NAFLD diagnoses will have information about their genetic risk factors. Consequently, ongoing discussions about if and how such information can be included into individualized risk assessments are required, particularly in light of emerging prospective evidence indicating that integration of clinical fibrosis markers with polygenic risk scores can refine prediction of NAFLD, NASH fibrosis and hepatocellular carcinoma (11,12). Besides genetic factors, recent proteomic investigations revealed that plasma protein signatures can discriminate between NAFLD and NASH cirrhosis (13). Combined, these results exemplify the rapid development in NASH biomarker identification some of which will likely transpire into clinical guidance in the near future.

- (III) The new AASLD guidance emphasizes the need to manage common medical comorbidities, such as type 2 diabetes, hypertension and obesity with a prioritization of medicines that also might have benefits for NASH. These include pioglitazone for patients with diabetes, semaglutide for diabetes and obesity, vitamin E in patients without diabetes, as well as the use of statins, omega-3 fatty acids, icosapent ethyl or fibrates for the management of dyslipidemias. Multiple drugs are currently in late clinical stages of development. Arguably the most promising current candidates to be the first approved drug for NASH are the THR $\beta$  agonist resmetirom and the pan-PPAR agonist lanifibranor, which both show significant improvement with regards to NASH resolution and decrease in fibrosis (14). Based on these data it appears reasonable to assume that regulatory approvals of drugs for the treatment of NASH within the next 3–5 years are likely. Once available, NASH-specific pharmacotherapy can be expected to result in major impacts on patient management and clinical guidance. In these developments it will be imperative to maintain a patient-centric

focus that considers inter-individual differences in demographic factors, disease phenotypes and comorbidities. The current guideline's strong emphasis on the multidisciplinary of NAFLD patient care provides an excellent basis to integrate such developments with lifestyle and dietary measures in the future.

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