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## **Global research initiative for patient screening on MASH (GRIPonMASH) protocol: rationale and design of a prospective multicentre study**

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# BMJ Open Global research initiative for patient screening on MASH (GRIPonMASH) protocol: rationale and design of a prospective multicentre study

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## ABSTRACT

**Introduction** The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) may be as high as 38% in the adult population with potential serious complications, multiple comorbidities and a high socioeconomic burden. However, there is a general lack of awareness and knowledge about MASLD and its progressive stages (metabolic dysfunction-associated steatohepatitis (MASH) and fibrosis). Therefore, MASLD is still far underdiagnosed. The 'Global Research Initiative for Patient Screening on MASH' (GRIPonMASH) consortium focuses on this unmet public health need. GRIPonMASH will help (primary) healthcare providers to implement a patient care pathway, as recommended by multiple scientific societies, to identify patients at risk of severe MASLD and to raise awareness. Furthermore, GRIPonMASH will contribute to a better understanding of the pathophysiology of MASLD and improved identification of diagnostic and prognostic markers to detect individuals at risk.

**Methods** This is a prospective multicentre observational study in which 10 000 high-risk patients (type 2 diabetes mellitus, obesity, metabolic syndrome or hypertension) will be screened in 10 European countries using at least two non-invasive tests (Fibrosis-4 index and FibroScan). Blood samples and liver biopsy material will be collected and biobanked, and multiomics analyses will be conducted.

**Ethics and dissemination** The study will be conducted in compliance with this protocol and applicable national and international regulatory requirements. The study initiation package is submitted at the local level. The study protocol has been approved by local medical ethical committees in all 10 participating countries. Results will be made public and published in scientific, peer-reviewed, international journals and at international conferences.

**Registration details** NCT05651724, registration date: 15 Dec 2022.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Multicentre European study embedded in clinical practice.
- ⇒ Implementation of accepted European guidelines.
- ⇒ Stimulate collaboration between primary and secondary care.
- ⇒ Liver biopsies only in a subset of patients.

## INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD)<sup>1</sup> is a disease with increasing prevalence, associated with metabolic and cardiovascular morbidity.<sup>2–5</sup> The estimated global prevalence of MASLD is now over 38%.<sup>6</sup> Patients with comorbidities such as type 2 diabetes mellitus (T2DM), obesity, metabolic syndrome and hypertension are at an increased risk for MASLD. Prevalence estimates range up to 55% in people with T2DM and up to 75% for people with obesity.<sup>7–9</sup> Overall, the socioeconomic burden and costs of MASLD are high.<sup>10 11</sup> Despite its prevalence and associated risks, MASLD is often underdiagnosed.

The progressive stages of the MASLD spectrum are metabolic dysfunction-associated steatohepatitis (MASH) and MASH with progressive liver fibrosis, which can eventually lead to liver cirrhosis, liver failure and hepatocellular carcinoma.<sup>12</sup> Approximately 20–25% of MASLD patients develop MASH. The estimated prevalence of MASH in the general European adult population is 6–7%.<sup>13</sup> Again, a much higher prevalence has been suggested in those with T2DM (up to 65%) and obesity

(up to 30%).<sup>14</sup> The severity of MASH is determined by the presence and stage of liver fibrosis, a key determinant of liver-related complications and both liver-related and all-cause mortality.<sup>4 15</sup> The gold standard for a confirmatory MASH diagnosis and staging is histology by liver biopsy, although non-invasive tests (NITs) are increasingly being used as diagnostic and prognostic tools as well.<sup>16 17</sup>

MASLD is usually asymptomatic and is often not detected until patients enter the progressive stages and/or develop complications, whereas, in the early stages, the disease is reversible. In the USA, MASH is already the leading cause of liver transplants in women, and the second most common cause in men.<sup>18</sup> Therefore, timely diagnosis and staging of MASLD is important to identify the growing group of patients at increased risk of liver-related and cardiovascular complications. A multidisciplinary approach should be initiated in these patients, which may include intensive lifestyle intervention,<sup>19</sup> participation in therapeutic trials and, in selected cases, bariatric surgery.<sup>20</sup> The first drug for this indication (resmetirom) has been approved by the Food and Drug Administration (FDA) in March 2024.<sup>21</sup>

Several scientific societies have proposed patient care pathways for implementation in clinical practice to identify patients with severe MASLD.<sup>22–24</sup> The European Association for the Study of Liver (EASL), the European Association for the Study of Diabetes (EASD) and the European Association for the Study of Obesity (EASO) jointly developed NAFLD clinical practice guidelines in 2016.<sup>16</sup> In 2021 the first ‘*Clinical Practice Guidelines on Non-invasive tests for Evaluation of Liver Disease Severity and Prognosis*’ were published,<sup>23</sup> which proposed a diagnostic flow chart using concordant NITs to screen patients at risk. NITs are generally categorised as blood-based diagnostics (that can be either algorithms based on liver enzymes or specific serum markers, usually combined) or imaging-based techniques (ie, ultrasound, MRI and transient elastography). In June 2024, an updated guideline was published: ‘*EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD)*’ reflecting the new nomenclature and recent developments in the field.<sup>25</sup> While the aforementioned and multiple other international guidelines from scientific societies<sup>16 25–28</sup> urge screening individuals at high risk of developing progressive stages of MASLD, these recommendations have not been broadly implemented.<sup>29–31</sup> There are several reasons for this: MASLD is a silent disease, there is a lack of awareness among professionals for MASLD and its associated risks,<sup>32</sup> and no pharmacological therapeutic intervention is available in Europe yet.

To assist (primary) healthcare providers to implement the patient care pathway as suggested by the EASL,<sup>23 25</sup> the ‘Global Research Initiative for Patient Screening on MASH’ (GRIPonMASH) study has been designed. Within this study, high-risk patients identified at primary care practices or attending hospital outpatient clinics will be screened for the presence of MASLD, liver fibrosis and

(at-risk) MASH using at least two NITs in 10 European countries. Additional published and exploratory NITs will also be investigated.<sup>33</sup> Furthermore, a central biobank will be set up and multiomics will be applied to gain a better understanding of the pathophysiology of MASLD-MASH and to evaluate diagnostic and prognostic markers to identify patients at risk. Simultaneously, GRIPonMASH aims to promote awareness and implementation of screening among (primary) healthcare providers, thereby improving clinical care.

## METHODS AND ANALYSIS

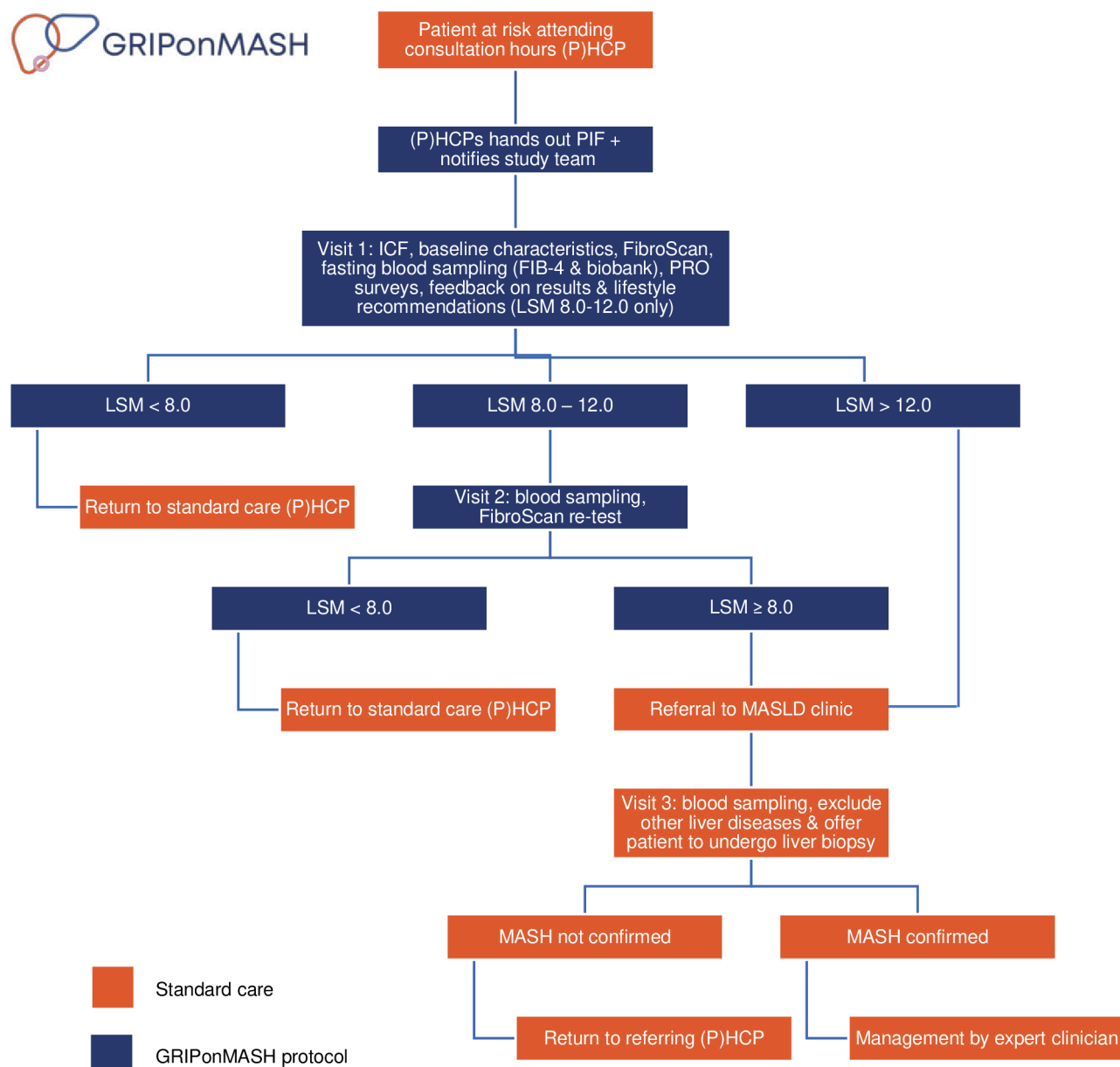
### Study design

In this prospective multicentre, observational study, the implementation of a transmural patient care pathway will be promoted. The study will initially employ two NITs: (1) the most commonly used blood-based diagnostic, the Fibrosis-4 index (FIB-4); and (2) liver stiffness measurement by vibration-controlled transient elastography (LSM by VCTE) using the FibroScan. In total, 10 000 adult patients at high risk of developing MASLD and MASH (ie, having T2DM, metabolic syndrome, obesity or arterial hypertension) will be screened. See figure 1 for an overview of the study design.

### Patient care pathway and return to standard care

Participants will be recruited at consultation hours at participating primary care centres and outpatient clinics. Prospective participants will be invited to the Centre of Excellence (CoE) for the first visit. Informed consent will be obtained from all individual participants included in the study (Master Patient Information File is included as online supplemental material I). Participants will be instructed to arrive at each visit after an overnight fast. The assessments of the first visit include baseline clinical characteristics, blood sampling, a FibroScan examination and a lifestyle assessment (by patient-reported outcome (PRO) surveys and an optional 24-hour dietary recall). The participants and referring (primary) healthcare providers will receive feedback on the FibroScan results and the next steps to take according to the patient care pathway. When the LSM by VCTE results are indeterminate (LSM 8–12 kPa), lifestyle recommendations will be provided to the participant.

The patient care pathway provides three management options based on the LSM by VCTE results. Option 1: if the FibroScan examination indicates low risk of advanced fibrosis (LSM <8 kPa), the participant returns to standard care. Option 2: when the FibroScan examination is indeterminate (LSM 8–12 kPa), the FibroScan examination and blood sampling will be repeated after 12 weeks (visit 2). Depending on the retest, the participant either returns to standard care (if LSM <8 kPa) or will be referred to a specialist at the MASLD clinic for detailed analysis (if LSM ≥8 kPa). Alternative diagnoses will be excluded as described in the EASL guideline,<sup>16 25</sup> blood will be sampled and a liver biopsy is offered to definitively



**Figure 1** Overview of study design and patient flow. FIB-4, Fibrosis-4 index; GRIPonMASH, Global Research Initiative for Patient Screening on MASH; ICF, informed consent form; LSM, liver stiffness measurement by vibration-controlled transient elastography; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; (P)HCP, (primary) healthcare provider; PIF, patient information folder.

diagnose the presence of MASH and the fibrosis stage, following local clinical care protocols (visit 3). If MASH is not confirmed after detailed analysis, the participant will return to their referring care provider. If MASH is confirmed, the participant will stay at the MASLD clinic for follow-up and possible treatment according to the most recent local guidelines. Patients fulfilling the criteria to undergo bariatric surgery should receive this recommendation if the procedure is available in the participating country/CoE. If during the study, pharmaceutical therapies become available for this indication, these should be prescribed following current local practice. Option 3: when the FibroScan examination indicates advanced fibrosis (LSM >12 kPa), the participant will be

referred to a specialist at the MASLD clinic for detailed analysis according to local clinical care protocols (visit 3). In these cases, a liver biopsy is also strongly advised, unless there is already evidence of liver decompensation. The clinical follow-up of patients at the MASLD clinic is part of standard clinical care, including the local reading of liver biopsies.

### Long-term follow-up

All participants will be included in a long-term follow-up programme. The European guidelines recommend retesting patients at risk every 1–5 years.<sup>23 25</sup> At 3 years and 5 years after the inclusion date, all participants are invited for a follow-up visit which includes a FibroScan



examination, fasted blood sampling, lifestyle assessment and a follow-up questionnaire.

### Study duration

The expected study duration is 8 years, from June 2023 to March 2031. After the prescreening by the (primary) healthcare provider, a participant should attend the first visit at the CoE within 4 weeks. Within 2 weeks, the referring care provider should receive feedback from the CoE with the results of the first visit and recommendation for follow-up according to the patient care pathway. In the case of LSM >12 kPa at visit 1, the participants should receive an appointment with the specialist at the MASLD clinic within 16 weeks for further detailed analysis and a possible liver biopsy. In the case of LSM ≥8 kPa at retest (visit 2), the participants should receive an appointment with the specialist at the MASLD clinic within 30 weeks for further detailed analysis and a possible liver biopsy. If available, earlier consultation is allowed. Participants should be fully evaluated within a period of 8 months after referral, and feedback needs to be sent to the referring care provider.

### Study population

This study will be conducted in adult patients (over 18 years of age) with a current or prior diagnosis of at least one of the following four conditions: T2DM, metabolic syndrome, obesity or arterial hypertension. Participants must meet the following inclusion criteria: (1) being willing to provide written informed consent; (2) 18–75 years of age; (3) either diagnosed with or currently being treated for at least one of the earlier mentioned conditions according to the criteria provided in [table 1](#).

A participant who meets any of the following criteria will be excluded from participation in this study: (1) patient with known hepatitis B, C or HIV or any other liver condition (like haemochromatosis, sarcoidosis, Wilson's disease, etc); (2) patient with any other condition that may lead to liver fibrosis or cirrhosis; (3) patient engages in (excessive) alcohol use (defined as: >3 units/day (30 g/day) in men and >2 units/day (20 g/day) in women; (4) patient with history or evidence of any other clinically significant condition or planned or expected procedure that in the opinion of the investigator, may compromise

**Table 1** Inclusion criteria, based on criteria for diagnosis of type 2 diabetes mellitus, obesity, arterial hypertension and metabolic syndrome

Condition	Criteria								
Type 2 diabetes mellitus	At least two times a fasting glucose >7.0 mmol/L Or elevated non-fasting glucose >11.1 mmol/L 2 hours after OGTT Or HbA1c ≥48 mmol/mol (≥6.5%) <i>Or being actively treated for previously diagnosed type 2 diabetes by a HCP</i>								
Obesity	Body mass index (BMI) ≥30 kg/m <sup>2</sup> Or waist circumference: <i>Caucasian: male ≥94 cm, female ≥80 cm</i> <i>South-Asian/Chinese: male ≥90 cm, female ≥80 cm</i> <i>Japanese: male ≥85 cm, female ≥90 cm</i>								
Arterial hypertension	Systolic blood pressure (BP) ≥140 mm Hg and/or diastolic BP ≥90 mm Hg <i>Or being actively treated for previously diagnosed arterial hypertension by a HCP</i>								
Metabolic syndrome	Central obesity defined with waist circumference (see above) <i>if BMI is ≥30 kg/m<sup>2</sup>, central obesity can be assumed and waist circumference does not need to be measured.</i> And any two of the following: <table border="1"> <tr> <td>Raised triglycerides</td><td>≥ 150 mg/dL (1.7 mmol/L) <i>or specific treatment for this lipid abnormality</i></td></tr> <tr> <td>Reduced HDL cholesterol</td><td>&lt; 40 mg/dL (1.03 mmol/L) in men &lt; 50 mg/dL (1.29 mmol/L) in women <i>or specific treatment for this lipid abnormality</i></td></tr> <tr> <td>Raised BP</td><td>Systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg <i>or treatment of previously diagnosed hypertension</i></td></tr> <tr> <td>Raised fasting plasma glucose (FPG)</td><td>FPG ≥100 mg/dL (5.6 mmol/L) 2 hour OGTT ≥7.8 mmol/L or previously diagnosed type 2 diabetes <i>(if above &gt;5.6 mmol/L or 100 mg/dL, an oral glucose tolerance test is strongly recommended, but is not necessary to define presence of the syndrome)</i></td></tr> </table>	Raised triglycerides	≥ 150 mg/dL (1.7 mmol/L) <i>or specific treatment for this lipid abnormality</i>	Reduced HDL cholesterol	< 40 mg/dL (1.03 mmol/L) in men < 50 mg/dL (1.29 mmol/L) in women <i>or specific treatment for this lipid abnormality</i>	Raised BP	Systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg <i>or treatment of previously diagnosed hypertension</i>	Raised fasting plasma glucose (FPG)	FPG ≥100 mg/dL (5.6 mmol/L) 2 hour OGTT ≥7.8 mmol/L or previously diagnosed type 2 diabetes <i>(if above &gt;5.6 mmol/L or 100 mg/dL, an oral glucose tolerance test is strongly recommended, but is not necessary to define presence of the syndrome)</i>
Raised triglycerides	≥ 150 mg/dL (1.7 mmol/L) <i>or specific treatment for this lipid abnormality</i>								
Reduced HDL cholesterol	< 40 mg/dL (1.03 mmol/L) in men < 50 mg/dL (1.29 mmol/L) in women <i>or specific treatment for this lipid abnormality</i>								
Raised BP	Systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg <i>or treatment of previously diagnosed hypertension</i>								
Raised fasting plasma glucose (FPG)	FPG ≥100 mg/dL (5.6 mmol/L) 2 hour OGTT ≥7.8 mmol/L or previously diagnosed type 2 diabetes <i>(if above &gt;5.6 mmol/L or 100 mg/dL, an oral glucose tolerance test is strongly recommended, but is not necessary to define presence of the syndrome)</i>								
HCP, healthcare provider; HDL, high-density lipoprotein; OGTT, oral glucose tolerance test.									

the patient's safety or ability to be included in this study; (5) the patient is an employee or contractor of the facility that is conducting the study or is a family member of the investigator, subinvestigator or any sponsor personnel; (6) the patient is not able to understand the details of the protocol and/or is not able to provide written informed consent; (7) the patient is pregnant or breastfeeding; (8) the patient underwent bariatric surgery in the last 12 months.

### Study sites

The 10 selected countries are: Belgium, Czech Republic, France, Germany, Greece, Italy, Portugal, Romania, Spain and The Netherlands. In each country, clinics defined as CoE and several satellite primary care centres will be recruited. The general aim is to recruit 1–2 CoEs per country depending on the local size and distribution of primary care centres and CoEs. CoEs should fulfil the following criteria: (1) CoE should be able to perform liver biopsies; (2) CoE should have personnel trained to carry out FibroScan examinations. XL probe needs to be available to be used when indicated by FibroScan; (3) CoE should be able to store blood and liver samples for a limited time; (4) CoE should be able to arrange shipment of samples by courier services to the central biobank; (5) CoE should have sufficient access to (at least two) primary care centres willing to participate in GRIPon-MASH including at least 100 patients per practice; (6) the team of CoE should at least comprise: one internist/diabetologist or endocrinologist, one gastroenterologist/hepatologist.

### Biobank

The collected liver and blood samples will be shipped to a central biobank at UMC Utrecht, the Netherlands. Participants will be asked to approve the biobanking of their blood, DNA and liver samples for a total of 15 years, since we foresee rapid developments in available diagnostic tools and multiomics methods. Some samples will be used for prespecified central assessments. We aim to analyse the remaining samples over the next decade using any novel scientific advances.

### Sample size estimation

The primary objectives of this study are to establish the prevalence of MASLD, at-risk MASH and liver fibrosis based on FibroScan examinations in high-risk patients, to compare the prevalence between countries and assess the added value of a 2-step pathway (see [table 2](#)). As such, this study should be considered a pilot study helping to implement clinical guidelines and consolidate patient care pathways. We estimate that including 1000 patients per country will give a realistic reflection of the situation per country and that it will provide enough power to determine differences between included countries and diagnostics (see [figure 2](#)).

### Study procedures

Randomisation, blinding and treatment allocation will not occur in this study, as participants will follow the flow

of the patient care pathway. Treatment of T2DM, metabolic syndrome, obesity and/or arterial hypertension will continue according to routine care.

### Baseline characteristics

At the first visit, the following data will be recorded: age, gender, ethnicity, primary diagnosis for inclusion and date of diagnosis, comorbidities, short medical history, short family history and current medication use. A short physical exam will be performed including: height, weight, waist circumference and blood pressure. If the participant does not recall medication use, the investigator will request this information from the care provider. Results of recent (not older than 6 months) laboratory measurements of urine albumin/creatinine ratio and presence of microalbuminuria will be requested from the care provider, if available.

### FibroScan examination

All patients will undergo a FibroScan (Echosens, France) examination to assess simultaneously LSM by VCTE and controlled attenuation parameter (CAP). The measurements will be carried out in participants fasting for at least 3 hours and after a 5-minute resting time in the supine position on the examination bed by a trained and certified staff member of the CoE. [Tables 3 and 4](#) provide the cut-off values that will be used to interpret LSM and CAP, respectively. CAP can be used to estimate steatosis and LSM to estimate fibrosis. Type of probe used and validity of measurements will also be recorded.

The recommendations for the next steps in the patient care pathways are based on the LSM by VCTE results, which provides an indication of the fibrosis stage of the participant. The referring care provider will be informed about the results and recommendations following a predefined format.

### Blood sampling and processing

All blood samples will be collected after an overnight fast. At visit 1, 47.5 mL of blood will be drawn and processed to allow biobanking, direct central analysis and local measurements. 6 mL blood, four plasma aliquots and seven serum aliquots will be biobanked. Two serum aliquots and 2 mL of blood in a PAXgene tube will be shipped directly to central analysis. The CoE will perform local measurements of aspartate aminotransferase (AST) level, alanine transaminase (ALT) level, platelet count and HbA1c. At visit 2, 8.5 mL of blood will be drawn and processed into one plasma aliquot and two serum aliquots for biobanking and 1 PAXgene tube for central analysis. At visit 3 and the follow-up visits, 16.5 mL of blood will be drawn and processed into two plasma aliquots and three serum aliquots for biobanking and 1 PAXgene tube for central analysis. Each CoE will receive 'biobank kits' including tubes and preprinted labels to ensure high-quality sample collection that is comparable across sites. The samples processed for biobanking will be stored

**Table 2** Primary and secondary objectives, subobjectives and associated outcome measures

Primary objective		
Objective	Subobjectives	Outcome measures
To implement a transmural patient care pathway, to identify patients with MASLD and its progressive form of MASH in primary care centres and clinics in 10 European countries	Prevalence of liver steatosis and MASLD estimated by FibroScan CAP in patients at risk	Steatosis stage deduced from CAP measurement with FibroScan MASLD definition (CAP >280 and 1 out of 5 cardiometabolic risk factors)
	Prevalence of liver fibrosis estimated by FibroScan LSM in patients at risk	Fibrosis stage deduced from LSM by VCTE measurement with FibroScan
	Prevalence of at-risk MASH estimated by FAST score in patients at risk	At-risk MASH deduced from FAST score
	Prevalence of MASH in patients at risk (in subset only)	MASH diagnosis confirmed by histology (NAS/SAF criteria) on liver biopsy
	Comparison of the prevalence of liver steatosis, MASLD, liver fibrosis and (at-risk) MASH between the participating countries	Prevalence (see above) stratified per country
	Added value of a 2-step pathway (FIB-4+FibroScan) as compared with FibroScan only for detection of high-risk patients	Number of patients at risk identified by FIB-4 in comparison to numbers found using LSM by VCTE with FibroScan and numbers found in combination
Secondary objectives		
Objective	Subobjectives (if applicable)	Outcome measures
To gain a better understanding of the pathophysiology of MASLD and to identify markers that will help to detect patients at risk (by applying a multi-omics approach)	Build/validate a diagnostic model to identify MASH patients in a high-risk population	Possible model parameters are all baseline clinical characteristics reported in the electronic case report form.
	Explore genotypes related to MASH in different European countries.	Genomic (GWAS) and proteomics analysis on collected blood samples
	Explore (non-invasive) metabolite biomarkers identifying MASH in patients at risk.	Mass-spectrometry based metabolomic and lipidomic analyses and fluxomics analysis on collected blood samples, both targeted and untargeted approaches
	Prevalence of comorbidities and associated therapies (especially for cardiovascular disease) in patients with MASH compared with those without, in high-risk patient populations.	Prevalence of comorbidities in patients at risk and patients diagnosed with MASLD/MASH
	Identify prognostic factors/biomarkers for complications in patients with MASLD and MASH at 5 years.	Disease progression and liver-related and non-liver related complications
Evaluate Patient Reported Outcomes (PRO) from baseline throughout follow-up		PRO surveys at baseline and follow-up
Confirm high risk of liver fibrosis based on second FibroScan examination after lifestyle recommendations (in subset only)		Revisited FibroScan examination (CAP and LSM by VCTE) 12 weeks after first FibroScan and after lifestyle recommendations
To evaluate changes in CAP, LSM by VCTE and FAST scores over time.		Repeated CAP, LSM by VCTE and FAST measurement over time
CAP, controlled attenuation parameter; FAST, FibroScan aspartate aminotransferase; GWAS, genome-wide association studies; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, Metabolic dysfunction-associated steatotic liver disease; NAS, NAFLD activity score; SAF, Steatosis, Activity and Fibrosis score; VCTE, vibration-controlled transient elastography.		

locally at  $-80^{\circ}\text{C}$  and then be shipped from the CoE to the central biobank in batches.

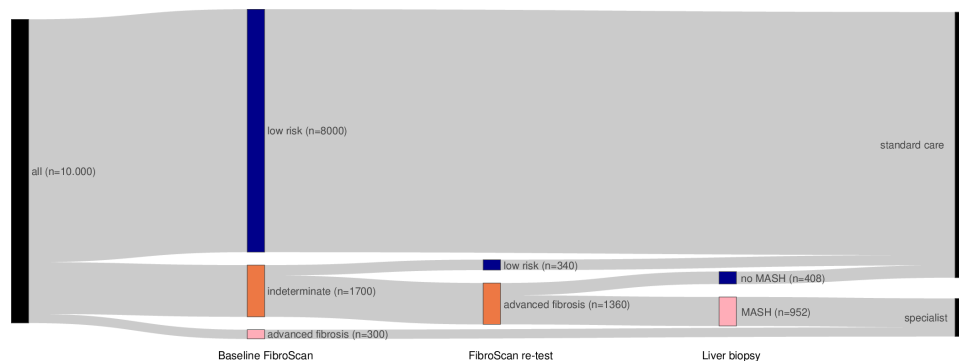
#### Fibrosis-4 index

The FIB-4 is a widely used blood-based diagnostic.<sup>23 34 35</sup> The FIB-4 index is an algorithm based on age, AST, ALT and platelet count and is calculated at baseline using the

following formula:  $\text{FIB-4} = (\text{age (years)} \times \text{AST (U/L)}) / (\text{platelet count (} 10^9/\text{L)} \times \text{square root(ALT (U/L))})$ .

#### FibroScan-AST score

The FibroScan-AST (FAST) score is an algorithm combining the FibroScan examination results (LSM by VCTE and CAP) with a blood marker (AST) to identify



**Figure 2** Expected patient flow through patient care pathway. Based on estimates available in the literature, in the total at-risk population of 10 000 participants, we expect 80% to score LSM <8 kPa (low risk), 17% is expected to score LSM =8–12 kPa (indeterminate) and 3% LSM >12 kPa (advanced fibrosis) on screening with FibroScan. We assume at least 80% will have LSM ≥8 kPa at the re-test. Of those who will be offered liver biopsy, we expect that for 70% MASH diagnosis will be confirmed on biopsy. In theory, this leads to approximately 950 biopsy-confirmed diagnoses of MASH. However, considering reluctance for invasive testing and loss to follow-up, we expect to identify approximately 500 confirmed MASH patients in this study and thus, on average, 50 per country. LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis.

patients with active fibrotic-MASH, also referred to as at-risk MASH.<sup>36</sup>

### Liver biopsy

Liver biopsies will be carried out according to local procedures at the participating CoE. The CoE will prepare: (1) slides for local reading according to local standard operating procedures; (2) three unstained slides to allow central reading and digital pathology assessment; and (3) snap freeze liver tissue with liquid nitrogen to allow metabolomic analysis. These tissue samples will be temporarily stored at the CoE before shipment to the central biobank. A panel of 2 independent and well-trained pathologists will execute the central reading. The histopathological features of MASH (steatosis, hepatocyte ballooning and lobular inflammation) will be assessed using the NAFLD activity score (NAS) criteria<sup>37</sup> and Steatosis, Activity and Fibrosis (SAF) score,<sup>38</sup> and the fibrosis stage will be determined.

### Baseline laboratory measurements (central)

The following variables will be measured centrally for each participant. Metabolic panel: total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), apolipoprotein B, glucose and creatinine. Liver enzymes: ALT, AST, bilirubin (direct and total), gamma-glutamyltransferase and alkaline phosphatase. Other: lipoprotein (a), insulin, sex hormone-binding globulin, free thyroxine,

tri-iodothyronine, thyroid stimulating hormone, albumin and globulins.

### Genetic and proteomic analysis (central)

DNA will be extracted from the biobanked full blood samples. Genetic analyses of patients will be accomplished by genome-wide association studies (GWAS). Targeted and untargeted proteomics analysis will be used to identify serological protein biomarkers.

### Metabolomic, lipidomic and fluxomic analysis (central)

Metabolomic, lipidomic and fluxomic studies will be performed on the liver biopsy and fasted blood samples. Metabolites including lipids will be extracted from EDTA plasma samples and analysed using mass-spectrometry (MS) based metabolomics and lipidomics methods. A global metabolomics high-resolution platform will be used, allowing the targeted and untargeted/global analyses of a wide range of hundreds of small molecules including amino acids, central energy and carbon metabolism, but also exogenous molecules, dietary chemicals, microbiome-derived metabolites, environmental chemicals, commercial products and drugs. A lipidomics platform allows the analysis of more than 20 lipid classes including diglycerides, triglycerides, phospholipids, ceramides, sphingolipids and many more. A targeted MS/MS platform will be used covering more than 300 modified free fatty acids

**Table 3** Cut-off values for CAP<sup>25 47 48</sup>

CAP (dB/m)	Indication of steatosis stage
248–267	S1
268–279	S2
≥280	S3
CAP, controlled attenuation parameter.	

**Table 4** Cut-off values for LSM by VCTE<sup>25 48 49</sup>

LSM by VCTE (kPa)	Indication fibrosis stage
< 8	Low risk of advanced fibrosis
8–12	Indeterminate risk
> 12	Advanced fibrosis
LSM, liver stiffness measurement; VCTE, vibration-controlled transient elastography.	



acting as bioactive lipid mediators both locally and systemically which are involved in immunology (innate immunity), inflammation, chemotaxis, cell survival, cell proliferation and differentiation. Fluxomic measurement based on metabolites labelled, for example, with  $^{13}\text{C}$ -glucose or  $2\text{H}_2\text{O}$  will be performed in vitro and in vivo to quantify metabolic fluxes and elucidate pathophysiological mechanisms.

### Biomarker analysis (central)

For the identification of novel circulating biomarkers, a panel of (potential) biomarkers will be identified in vitro by using liver-on-a-chip tools. Additionally, potential novel biomarkers (ie, PLIN-2 (HeparDx), PRO-C3, PRO-C6, oxidised LDL, glucagon, gastric inhibitory polypeptide, glucagon-like peptide-1, FICE34 and TLM3) will be measured.

### Lifestyle phenotyping

Lifestyle will be phenotyped in seven different areas: diet, water consumption, alcohol consumption, physical activity, smoking, sleep and endocrine environmental disruptors. The following self-reported questionnaires are used: diet will be assessed using the Mediterranean Diet Score (PREDIMED)<sup>39</sup>; water consumption will be obtained with one question; alcohol consumption, apart from wine in the PREDIMED, will be obtained with a maximum of 3 semiclosed questions; physical activity will be recorded using the International Physical Activity Questionnaire – Short Form<sup>40</sup>; smoking habits will be obtained with a maximum of 8 multiple and semiclosed questions; sleep quality will be obtained with the Brief version of the Pittsburgh Sleep Quality Index<sup>41</sup>; endocrine disrupting chemical exposures will be evaluated using six questions. Additionally, in CoEs with a dietitian and resources available, a 24-hour dietary recall will be annotated by an interviewer on 2 days (most recent regular weekday and 1 weekend day).

### Lifestyle recommendations

Lifestyle recommendations will be provided based on current clinical guidelines for MASLD/MASH patients.<sup>25 42</sup> A member of the study team will recommend participants adhere to a healthy dietary pattern and level of physical activity. The aim of the lifestyle recommendations is to lose 5% weight (ideally 10%); however, losing weight should not be the participant's ultimate goal but rather their adherence to a healthy lifestyle.

### Long-term follow-up (at 3 years and 5 years)

A follow-up questionnaire has been designed to inquire about the disease status and comorbidities, possible liver-related and non-liver related complications and changes in medication of the participant. At follow-up visits at 3 years and 5 years, the FibroScan examination will be repeated. At the same visit, the follow-up questionnaire should be completed by the research team who will request the necessary information from

the participant's care provider. At both time points, the participants will be asked to complete the lifestyle assessment again.

### Data management

Clinical data will be captured using an electronic case report form (eCRF), and only authorised staff at the CoE will be allowed to enter data into the eCRF. All eCRF data should be verifiable to a source at the CoE or accessible by the site staff, except if direct entry was allowed. Participants are identified by a code; only the local investigators will have the key. The investigator(s) will be responsible for ensuring eCRF data completeness and accuracy. Source data verification and data quality will be assessed by remote eCRF reviews, statistical checks and inperson monitor visits. Data from the eCRF and other sources (ie, central analyses, Liver Health Management platform) will be encoded and stored in a central study database (Data Science Platform).

### Statistical analysis

R software will be used for statistical analysis, and  $p$  values  $< 0.05$  (2-tailed) are considered statistically significant. By default, parametric testing will be employed. In case of not normally distributed variables, non-parametric tests will be employed. Before analysis, we will assess the degree and possible reasons for missingness and apply appropriate methods to handle missing data, that is, multiple imputation.

As the primary objective is the implementation of a patient care pathway (see table 2), primarily descriptive statistics will be used instead of hypothesis testing. Prevalence of MASLD, liver steatosis, fibrosis and (at-risk) MASH will be reported for each country. The prevalence will be compared between countries using one-way analysis of variance (ANOVA) (or Kruskal Wallis test). The overlap in numbers of patients at risk identified by the 2 NITs will be reported as well.

For the secondary objectives, the following statistical methods will be used: diagnostic modelling using logistic regression and machine learning (ML)/artificial intelligence (AI) approaches; associations in GWAS and proteomics data will be analysed using logistic regression; associations between MASH diagnosis by histology and (non-invasive) metabolite (bio)markers will be analysed using logistic regression; prevalence of comorbidities will be estimated in total group of patients at risk with/without MASLD, the difference between the groups will be analysed using one-way ANOVA (or Kruskal Wallis test); prognostic modelling using logistic regression and ML/AI approaches; mixed linear modelling will be implemented to assess changes in PRO over time; difference between first and second LSM by VCTE measurements will be assessed using a paired t-test (or Wilcoxon signed rank test); mixed linear modelling will be implemented to assess the repeated measurements of CAP, LSM by VCTE and FAST over time.

## Ethics and dissemination

The study will be conducted in compliance with this protocol and applicable national and international regulatory requirements (including Declaration of Helsinki). The study initiation package is submitted at the local level. The study protocol has already been approved by local medical ethical committees in all 10 participating countries: Netherlands (Medical Research Ethics Committees United, A23.273/R22.057), Germany (Etik-Kommission Landesärztekammer Rheinland-Pfalz, 2022–16602 and Ärztekammer des Saarlandes, 185/24), Spain (Comités Éticos de Investigación de los Hospitales Universitarios Virgen Macarena y Virgen del Rocío, 1631-N-22), Belgium (Ethische Commissie Universitair Ziekenhuis Antwerpen, EDGE 002626 and Comité d’Ethique C Hôpital Erasme-ULB, SRB2023083), Portugal (Comissao de Etica do Centro Académico de Medicina de Lisboa, 203/23), Greece (Research Ethics and Deontology Committee of HUA, r-3549/08.10.2024), Romania (Comisia de Etica a Spitalului Municipal Sacele, 7201/13.11.2024), Czech Republic (Etická komise Všeobecné fakultní nemocnice v Praze, 152/24s Grant), Italy (Comitato Etico Territoriale Lazio AREA 3, ID 7135) and France (Comité de protection des personnes Ouest IV, 2025-A00083-46). Results will be made public and published in scientific, peer-reviewed, international journals and at international conferences.

## Patient and public involvement

The draft protocol was reviewed and endorsed by Liver Patients International. The European Liver Patients Association, the European Atherosclerosis Society and the EASL have also endorsed the final project.

## DISCUSSION

Although several factors are involved in the progression from MASLD to MASH (environmental, dietary and genetic), the exact mechanisms behind MASLD development and progression remain unknown.<sup>43</sup> The widely used estimate of 38% worldwide prevalence of MASLD is based on a meta-analysis of studies from 2016 to 2019.<sup>6</sup> However, exact data about the prevalence in different European countries using accepted diagnostic tools like LSM by VCTE or the golden standard, liver biopsy, are still lacking. This study will provide prevalence estimates based on a large number of participants.

The patient care pathway used in this study is based on the 2021 and 2024 updates of the EASL clinical practice guidelines.<sup>23 25</sup> In contrast to these guidelines, in the current protocol, the two NITs (FIB-4 and FibroScan) will be performed in the same visit. Recently, there has been debate about the accuracy of FIB-4 to (pre)screen in the general population at primary care level,<sup>44</sup> as the index was validated and developed in secondary and tertiary care. This issue was acknowledged by the EASL in 2021, and they already advised not to base diagnoses on one single NIT, but to use concordant NITs instead.<sup>23</sup> Therefore,

in the current protocol, it was decided to perform the FibroScan and blood sampling for FIB-4 on the same day for each patient. We can then compare the added value of FIB-4 versus FibroScan and their prognostic capacity at follow-up within a population at risk identified at the primary care level and outpatient clinics and thereby either validate the guidelines or propose adjustments.

In line with the EASL Clinical Practice Guidelines, structured programmes aimed at lifestyle changes towards healthy diet and habitual physical activity are advisable.<sup>16</sup> The current study only includes lifestyle recommendations to a subset of participants as this would be feasible within current clinical practice. The level of adherence to the Mediterranean diet will be evaluated throughout the study. The Mediterranean diet is thought to be beneficial,<sup>45</sup> although evidence is still limited.<sup>46</sup> We also aim to build towards personalised lifestyle advice.

European experts have demonstrated that most countries in Europe are not yet ready to face the growing MASLD/MASH problem, because they lack guidelines, registries and multidisciplinary programmes.<sup>30</sup> Therefore, initiatives such as this study aimed at increasing knowledge and awareness of MASLD and MASH among professionals are essential. In addition, this study aims to integrate all levels of clinical care, which is much needed for the multidisciplinary management of MASLD.

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**Contributors** DEG and MCC conceptualised the study. VDDJ and MCC were the main authors of the manuscript and protocol. DEG, OHF and the members of the initial Julius Clinical-initiated Scientific Steering Committee (HC-P, SF, CM, MR-G, MET, AH, LS, JMS, JWMM, AG and VR) and Independent Advisory Board (JW and MA) critically reviewed the initial protocol. TH contributed to the lipidomics/metabolomics section and JV and MD to the liver biopsy section. CF-P, RB, GD, LM, VR and CS critically review the revised protocol. MCC is guarantor. This study is executed within the GRIPonMASH consortium; the consortium reviewed the protocol.

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#### REFERENCES

- 1 Rinella ME, Lazarus JV, Ratzu V, *et al.* A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *Hepatology* 2023;78:1966–86.
- 2 Byrne CD, Targher G. NAFLD: a multisystem disease. *J Hepatol* 2015;62:S47–64.
- 3 Targher G, Byrne CD, Lonardo A, *et al.* Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: A meta-analysis. *J Hepatol* 2016;65:589–600.
- 4 Ekstedt M, Hagström H, Nasr P, *et al.* Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. *Hepatology* 2015;61:1547–54.
- 5 Driessen S, Francque SM, Anker SD, *et al.* Metabolic dysfunction-associated steatotic liver disease and the heart. *Hepatology* 2023.
- 6 Younossi ZM, Golabi P, Paik JM, *et al.* The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. *Hepatology* 2023;77:1335–47.
- 7 Quek J, Chan KE, Wong ZY, *et al.* Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2023;8:20–30.
- 8 Henry L, Paik J, Younossi ZM. Review article: the epidemiologic burden of non-alcoholic fatty liver disease across the world. *Aliment Pharmacol Ther* 2022;56:942–56.
- 9 Younossi ZM, Golabi P, de Avila L, *et al.* The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. *J Hepatol* 2019;71:793–801.
- 10 Schattenberg JM, Lazarus JV, Newsome PN, *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;41:1227–42.
- 11 Karlsen TH, Sheron N, Zelber-Sagi S, *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.
  - 12 Powell EE, Wong VWS, Rinella M. Non-alcoholic fatty liver disease. *Lancet* 2021;397:2212–24.
  - 13 Younossi ZM, Koenig AB, Abdelatif D, *et al.* Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016;64:73–84.
  - 14 Dufour J-F, Scherer R, Balp M-M, *et al.* The global epidemiology of nonalcoholic steatohepatitis (NASH) and associated risk factors—a targeted literature review. *Endocr Metab Sci* 2021;3:100089.
  - 15 Sanyal AJ, Van Natta ML, Clark J, *et al.* Prospective Study of Outcomes in Adults with Nonalcoholic Fatty Liver Disease. *N Engl J Med* 2021;385:1559–69.
  - 16 European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 2016;64:1388–402.
  - 17 Mózes FE, Lee JA, Vali Y, *et al.* Performance of non-invasive tests and histology for the prediction of clinical outcomes in patients with non-alcoholic fatty liver disease: an individual participant data meta-analysis. *Lancet Gastroenterol Hepatol* 2023;8:704–13.
  - 18 Nouredin M, Vipani A, Bresee C, *et al.* NASH Leading Cause of Liver Transplant in Women: Updated Analysis of Indications For Liver Transplant and Ethnic and Gender Variances. *Am J Gastroenterol* 2018;113:1649–59.
  - 19 Ratzliff V. Non-pharmacological interventions in non-alcoholic fatty liver disease patients. *Liver Int* 2017;37 Suppl 1:90–6.
  - 20 Ren M, Zhou X, Lv L, *et al.* Endoscopic Bariatric and Metabolic Therapies for Liver Disease: Mechanisms, Benefits, and Associated Risks. *J Clin Transl Hepatol* 2022;10:986–94.
  - 21 Harrison SA, Bedossa P, Guy CD, *et al.* A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. *N Engl J Med* 2024;390:497–509.
  - 22 Kanwal F, Shubrook JH, Adams LA, *et al.* Clinical Care Pathway for the Risk Stratification and Management of Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology* 2021;161:1657–69.
  - 23 Berzigotti A, Tsochatzis E, Boursier J. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. *J Hepatol* 2021;75:659–89.
  - 24 Srivastava A, Gailer R, Tanwar S, *et al.* Prospective evaluation of a primary care referral pathway for patients with non-alcoholic fatty liver disease. *J Hepatol* 2019;71:371–8.
  - 25 Tacke F, Horn P, Wai-Sun Wong V. EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J Hepatol* 2024;81:492–542.
  - 26 Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, *et al.* AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology* 2023;77:1797–835.
  - 27 Cusi K, Isaacs S, Barb D, *et al.* American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings: Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD). *Endocr Pract* 2022;28:528–62.
  - 28 LaBrecque DR, Abbas Z, Anania F, *et al.* World Gastroenterology Organisation global guidelines: Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *J Clin Gastroenterol* 2014;48:467–73.
  - 29 Anstee QM, Hallsworth K, Lynch N, *et al.* Real-world management of non-alcoholic steatohepatitis differs from clinical practice guideline recommendations and across regions. *JHEP Rep* 2022;4:100411.
  - 30 Lazarus JV, Palayew A, Carrieri P, *et al.* European “NAFLD Preparedness Index” - Is Europe ready to meet the challenge of fatty liver disease? *JHEP Rep* 2021;3:100234.
  - 31 Schattenberg JM, Anstee QM, Caussy C, *et al.* Differences between current clinical guidelines for screening, diagnosis and management of nonalcoholic fatty liver disease and real-world practice: a targeted literature review. *Expert Rev Gastroenterol Hepatol* 2021;15:1253–66.
  - 32 Driessen S, de Jong VD, van Son KC, *et al.* A global survey of health care workers' awareness of non-alcoholic fatty liver disease: The AwareNASH survey. *United European Gastroenterol J* 2023;11:654–62.
  - 33 Vali Y, Lee J, Boursier J, *et al.* Biomarkers for staging fibrosis and non-alcoholic steatohepatitis in non-alcoholic fatty liver disease (the LITMUS project): a comparative diagnostic accuracy study. *Lancet Gastroenterol Hepatol* 2023;8:714–25.
  - 34 Lazarus JV, Castera L, Mark HE, *et al.* Real-world evidence on non-invasive tests and associated cut-offs used to assess fibrosis in routine clinical practice. *JHEP Rep* 2023;5:100596.
  - 35 Grobbee EJ, de Jong VD, Schrieks IC, *et al.* Improvement of non-invasive tests of liver steatosis and fibrosis as indicators for non-alcoholic fatty liver disease in type 2 diabetes mellitus patients with elevated cardiovascular risk profile using the PPAR- $\alpha/\gamma$  agonist aleglitazar. *PLoS One* 2022;17:e0277706.
  - 36 Newsome PN, Sasso M, Deeks JJ, *et al.* FibroScan-AST (FAST) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study. *Lancet Gastroenterol Hepatol* 2020;5:362–73.
  - 37 Sheka AC, Adeyi O, Thompson J, *et al.* Nonalcoholic Steatohepatitis: A Review. *JAMA* 2020;323:1175–83.
  - 38 Nascimbeni F, Bedossa P, Fedchuk L, *et al.* Clinical validation of the FLIP algorithm and the SAF score in patients with non-alcoholic fatty liver disease. *J Hepatol* 2020;72:828–38.
  - 39 Martínez-González MA, García-Arellano A, Toledo E, *et al.* A 14-item Mediterranean diet assessment tool and obesity indexes among high-risk subjects: the PREDIMED trial. *PLoS One* 2012;7:e43134.
  - 40 Craig CL, Marshall AL, Sjöström M, *et al.* International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003;35:1381–95.
  - 41 Sancho-Domingo C, Carballo JL, Coloma-Carmona A, *et al.* Brief version of the Pittsburgh Sleep Quality Index (B-PSQI) and measurement invariance across gender and age in a population-based sample. *Psychol Assess* 2021;33:111–21.
  - 42 Franque SM, Marchesini G, Kautz A, *et al.* Non-alcoholic fatty liver disease: A patient guideline. *JHEP Rep* 2021;3:100322.
  - 43 Anstee QM, Darlay R, Cockell S, *et al.* Genome-wide association study of non-alcoholic fatty liver and steatohepatitis in a histologically characterised cohort\*. *J Hepatol* 2020;73:505–15.
  - 44 Graupera I, Thiele M, Serra-Burriel M, *et al.* Low Accuracy of FIB-4 and NAFLD Fibrosis Scores for Screening for Liver Fibrosis in the Population. *Clin Gastroenterol Hepatol* 2022;20:2567–76.
  - 45 Gepner Y, Shelef I, Korny O, *et al.* The beneficial effects of Mediterranean diet over low-fat diet may be mediated by decreasing hepatic fat content. *J Hepatol* 2019;71:379–88.
  - 46 Plaz Torres MC, Aghemo A, Lleo A, *et al.* Mediterranean Diet and NAFLD: What We Know and Questions That Still Need to Be Answered. *Nutrients* 2019;11:2971.
  - 47 Eddowes PJ, Sasso M, Allison M, *et al.* Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology* 2019;156:1717–30.
  - 48 Wong VW-S, Irls M, Wong GL-H, *et al.* Unified interpretation of liver stiffness measurement by M and XL probes in non-alcoholic fatty liver disease. *Gut* 2019;68:2057–64.
  - 49 Theel W, Boxma-de Klerk BM, Dirksmeier-Harincq F, *et al.* Evaluation of nonalcoholic fatty liver disease (NAFLD) in severe obesity using noninvasive tests and imaging techniques. *Obes Rev* 2022;23:e13481.