Title: Use of non-invasive diagnostic tools for non-alcoholic steatohepatitis: a qualitative exploration of challenges and barriers

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Abbreviations

ACO: Accountable care organization

ALT: Alanine aminotransferase

AST: Aspartate aminotransferase

FIB-4: The Fibrosis-4 Index for Liver Fibrosis

HCPs: Health care providers

IDN: Integrated delivery network

MCO: Medicaid managed care organization

NAFLD: Non-alcoholic fatty liver disease

NASH: Non-alcoholic steatohepatitis

NITs: Non-invasive tests

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EAT received consulting fees from Boehringer, Gilead Sciences, Pfizer, Novo Nordisk, Alexion, Orphalan and Intercept Pharmaceuticals. LV received consulting fees from Gilead Sciences, Pfizer, Astra Zeneca, Novo Nordisk, Intercept pharmaceuticals, Diatech Pharmacogenetics, IONIS, Boehringer Ingelheim; speaker's fee from MSD, Gilead Sciences, AlfaSigma, AbbVie, Viatris; received support for attending meetings and/or travel from Gilead Sciences; holds a patent (planned, issued or pending) with Takeda, and participated on Data Safety Monitoring Boards or Advisory Boards for Intercept, Pfizer, Gilead Sciences, Novo Nordisk, Boeringher Ingelheim. MT received consulting fees from GE Healthcare, Boehringer Ingelheim and GSK; speaker's fee from Echosens, Siemens healthcare, Norgine and Tillotts Pharma; has a planned patent for a non-invasive marker for hepatic inflammation; and has an unpaid leadership or fiduciary role in the Alcohol & Society non-governmental

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Data Availability Statement

Data supporting the findings of this study may be available upon reasonable request to the corresponding author. However, due to privacy and ethical restrictions, the data are not publicly available, and any data containing identifying information cannot be shared.

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Ethics approval statement

The study protocol and related documents were reviewed by an independent ethics-review board (VERITAS IRB). The board granted approval for the study in February 2021.

Patient consent statement

Not applicable.

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Clinical trial registration

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Abstract

Background & Aims: Non-invasive tests (NITs) are underutilized for diagnosis and risk stratification in non-alcoholic fatty liver disease (NAFLD), despite good accuracy. This study aimed to identify challenges and barriers to the use of NITs in clinical practice.

Methods: We conducted a qualitative exploratory study in Germany, Italy, United Kingdom, and United States. Phase 1 participants (primary care physicians, hepatologists, diabetologists, researchers, healthcare administrators, payers, and patient advocates; n=29) were interviewed. Phase 2 participants (experts in NAFLD; n=8) took part in a group discussion to validate and expand on phase 1 findings. Finally, we triangulated perspectives in a hybrid deductive/inductive thematic analysis.

Results: Four themes hindering the use of NITs emerged: 1) limited knowledge and awareness; 2) unclear referral pathways for patients affected by liver conditions; 3) uncertainty over the value of NITs in monitoring and managing liver diseases; and 4) challenges justifying system-level reimbursement. Through these themes, participants perceived a stigma associated with liver diseases, and primary care physicians generally lacked awareness, adequate knowledge, and skills to use recommended NITs. We identified uncertainties over the results of NITs, specifically to guide lifestyle intervention or to identify patients that should be referred to a specialist. Participants indicated an ongoing need for research and development to improve the prognostic value of NITs and communicating their cost-effectiveness to payers.

Conclusions: This qualitative study suggests that use of NITs for NAFLD are limited due to several individual and system-level barriers. Multi-level interventions are likely required to address these barriers.

Keywords: elastography, steatotic liver disease, Fibrosis-4 (FIB4) score, cirrhosis, Enhanced Liver Fibrosis (ELF) score, magnetic resonance imaging (MRI)

Lay summary

- Primary care providers have limited knowledge of non-invasive tests and referral of patients at risk of or with advanced liver fibrosis is suboptimal.
- There is an ongoing stigmatization of liver diseases and a low perceived confidence to support patients with lifestyle modifications.
- The cost-benefit value of non-invasive tests is unclear to system payers.

Introduction

Despite its association with obesity and other markers of metabolic disease, non-alcoholic fatty liver disease (NAFLD) is often left unrecognized due to its asymptomatic nature.[1] A recent study of patients with a BMI >25 kg/m2 and elevated alanine transaminase (ALT) in the United States (US) showed that 95% of those affected by NAFLD were unaware of their condition.[1] Lack of awareness of NAFLD amongst the general population, and even clinicians and public health officials, are of equal concern in countries like Germany, Italy and the United Kingdom (UK), where the incidence of NAFLD is expected to grow.[2]

The timely identification and management of NAFLD is crucial, as this condition can progress into more serious diseases, including non-alcoholic steatohepatitis (NASH), advanced fibrosis, and hepatocellular carcinoma (HCC) – the latter two conditions are potentially irreversible and could lead to death.[1] Although liver biopsies are still considered the standard for a conclusive diagnosis of NASH, and the assessment of advanced fibrosis, they are used selectively due to their invasive nature. Risk stratification, beginning with the application of non-invasive tests (NITs) by primary care physicians can enhance the quality of healthcare delivered to patients.[3]

NITs include, but are not limited to, the fibrosis-4 (FIB-4) score, NAFLD fibrosis score (NFS), aspartate-aminotransferase-to-platelet ratio (APRI), enhanced liver fibrosis (ELF) test, transient elastography (TE) and magnetic resonance elastography (MRE).[4] Studies have demonstrated that the FIB-4 score, vibration-controlled transient elastography (VCTE) and MRE accurately stratify patients affected by NAFLD based on risk of experiencing a serious liver-related event (e.g., development of liver cirrhosis, hepatic decompensation, extrahepatic complications).[5-7] Of particular relevance for primary care physicians is the FIB-4 score,

which is blood-based and uses clinical information routinely collected in many practices, thus incurring limited cost.

Evidence suggests that when primary care physicians identify patients at risk of serious liver-related events via NITs and refer them to specialists, diagnosis of the condition increases four-fold, making NITs a cost-effective tool.[8, 9] Unfortunately, global integration of NITs is encumbered by non-adherence to guidelines in practice,[10, 11] national differences in diagnostic practices,[12] and a lack of uniform recommendations for the use of specific NITs over others.[13] In some countries a lack of reimbursement for promising commercial tests renders them inaccessible to some patients, even when recommended.[14, 15] Many universally recognized approaches to NAFLD and NASH management are not part of HCP practice due to a lack of knowledge, time or reimbursement for these practices.[4, 16]

Considering the prognostic value of NITs, this study aimed to further explore factors that hinder or challenge the implementation and use of NITs for NAFLD, NASH and advanced fibrosis in routine clinical practice, especially those that can be effectively addressed through educational and behavioural interventions. This exploration focused on uncovering convergences across targeted countries and medical specialties. The secondary objective was to generate recommendations for overcoming these barriers and create a path for optimal in-practice use of NITs.

Methods

Study design

This study was performed from an interpretivist viewpoint,[17] using a hybrid of deductive and inductive reasoning approach to qualitative analysis.[18] This approach was considered as an appropriate first step to explore potential challenges and barriers to the implementation of NITs, from the perspectives of both the average and expert-level professional involved in the use, research, advocacy and implementation of NITs in NAFLD, NASH or advanced fibrosis. The study employed two phases of data collection and analyses: Phase 1 consisted of semi-structured, in-depth interviews with individuals representing the professions of interest, to better understand the challenges and barriers, brought forward by the facilitator from the literature, or by the participants as they responded to a mix of pre-determined and spontaneous questions.[19] The number of interviews (n=29) was determined a priori to reach data saturation,[20] based on previous experience conducting similar studies.

Phase 2 consisted of a two-hour expert workgroup discussion between clinicians and researchers, with renowned expertise in the field of NAFLD, NASH and advanced fibrosis, to review phase 1 findings,[21] provide further meaning and context to the perspectives identified, and offer recommendations for enhanced use and implementation of NITs. Findings from both phases were triangulated by identifying common and discordant themes, relationships and elucidations from all collected data, in the context of current literature, to capture a more complete understanding of the phenomena.[22, 23] The Standards for Reporting Qualitative Research (SRQR)[24] protocols were used to report findings of this study. The study protocol and related documents were granted approval by an independent ethics-review board (VERITAS IRB), in February 2021.

Inclusion and purposive sampling criteria

Phase 1 inclusion criteria were for participants to: 1) be a primary care physician, hepatologist, diabetologist, researcher, healthcare administrator, payer or representative of an organization involved in reimbursement or patient advocacy in NAFLD; 2) work or practice within Germany, Italy, UK or USA; 3) have at least five years (if a healthcare provider) or three years (if other role) in given role; 4) have experience using, reimbursing, researching or advocating for NITs in the field of NAFLD; and 5) treat at least 15 (if a primary care physician) or 20 (if a hepatologist or diabetologist) patients per month affected by NAFLD. Purposive sampling was used to ensure maximum variance in final sample selected demographics (regions within countries, years of practice, practice settings).[25] The criteria for Phase 2 was to have a recognized expertise in the field of NAFLD and non-invasive assessment of liver disease.

Recruitment

Potential candidates of Phase 1 were identified from three sources: EASL membership list, online research panel of healthcare professionals [26], and organizations with a known role in reimbursement or advocacy for patients with liver disease in the studied regions (see Figure 1). Through this process, a total of 318 potential candidates were identified as likely to meet inclusion criteria's (based on country, profession, and specialty), and were contacted via email invitations. Additional recruitment efforts were made through announcements on EASL's social medias and snowball sampling (asking candidates to forward invitations to others in their network). The total estimated reach was over 1,000 individuals. The eligibility of all who followed the secure URL link in the invitation or announcement, was confirmed by applying inclusion criteria previously described. Once quota (n=29) was met, enrolment was

closed. For phase 2, the principal investigators (PI, co-authors EAT, LV, MT, all appointed by EASL) formed an expert workgroup by recruiting five expert hepatologists (co-authors AMA, JVL, MN, MR, and FT). Each PI listed three candidates from a list of 2021 International Liver Congress (ILC) delegates, forming a list of five after excluding duplicates and balancing gender and countries.

Data collection

Semi-structured interview guides, with open-ended questions and potential probes depending on profession (see Supplementary Material 1 for examples) were developed to support moderators during the 45-minute interviews in phase 1. Interview guides were designed to collect detailed insights on the experiences, perspectives and opinions held by participants across pre-determined areas of exploration, while allowing expert moderators to investigate unexpected but relevant topic areas brought forward by the participants. Expert moderators (including co-author SP) were professional interviewers with graduate-level degrees and experience conducting qualitative research in healthcare, and were briefed prior to data collection on the study, the interviewing process and the guide. All participants' identities were anonymized. Interviews were conducted between July and August 2021. Phase 2 data was collected during an expert workgroup discussion in September 2021, facilitated by educational experts, including co-author SP, in collaboration with the study PI/clinical experts (co-authors EAT, LV, MT). Synthesized findings from phase 1 were shared during the first 30 minutes of the meeting, and the remaining 90 minutes were used for the discussion, focusing on interpretations of phase 1 findings, and recommendations to address identified challenges and barriers. The interviews and expert workgroup discussion were

conducted in English, via a secured conference platform, recorded with participants' consent, and transcribed.

Data analysis, integration, and trustworthiness

Direct content and thematic analyses were used in phases 1 and 2 to identify and provide insight into common perceptions, opinions and experiences reported by participants.[27] Qualitative data was subject to a hybrid of deductive and inductive coding, categorizing transcript content into distinct topics explored as part of the interviews, using NVivo (QSR International Pty Ltd., version 12.0, 2020). The final coding tree and additional notes on the coding process can be found in Supplementary Material 2. Coded content was reviewed and organized into themes, examined for their relevance and contribution to the objectives of this study.[28] Perspectives captured across both phases were triangulated to enhance the accuracy and trustworthiness of the findings, providing a multi-faceted exploration of the themes.[23]

Results

A total of 335 participants opened the link to the screener included in the email invitations or social media announcements in relation to Phase 1 of the study. Twenty-nine participants from Germany, Italy, UK, and USA participated in phase 1 interviews (table 1). Data saturation occurred after approximately twelve interviews. Participants representing clinicians reported mainly working in academic hospitals. A larger proportion (72%) of participants reported working in an urban setting (see figure 2). Across categories, 38% of participants

had 3-10 or 11-20 years of practice experience, and 24% had over 21 years of experience. The gender balance of participants was 38% female, 62% male.

Barriers to the implementation of NITs

Participants reported challenges, barriers and gaps affecting the optimal provision of care for patients with NAFLD, NASH and advanced fibrosis, including the use of NITs in clinical practice. Figure 3 conceptualizes identified challenges, barriers, and gaps in four main spheres: 1) use of NITs by clinicians; 2) interprofessional collaboration; 3) patient communication and engagement; and 4) system-level decisions. The following sections describe each of these four spheres in more detail. Table 2 presents these challenges, barriers, and gaps by country. Table 3 presents selected quotes articulating what many participants had shared within each theme for the purpose of providing an example.

1) *Use of NITs by clinicians: limited knowledge and awareness of liver diseases, relevant updated guidelines, and NITs*

Participants expressed the sentiment that liver diseases are subject to a lack of societal awareness and stigma that may pose a barrier to HCPs communicating effectively with patients regarding their condition. The need for HCPs treating patients with liver disease to modify their approach to reduce potential stigmatization was brought forward in both phases of the study (see Table 3, Quote A). A lack of knowledge of available and emerging NITs, and sub-optimal skills to interpret the results based on limited and outdated knowledge of

clinical practice guideline recommendations were reported by phase 1 primary care physicians, diabetologists, payers and researchers (see Table 3, Quote B).

2) *Interprofessional collaboration: unclear referral pathways for patients with liver conditions*

The lack of knowledge related to NITs for the diagnosis of NASH and NAFLD, especially among primary care physicians, was reported to partially explain poor referrals of patients with markers of liver disease and/or fibrosis to specialists. Both phase 1 and phase 2 participants acknowledged a current lack of consensus internationally on what tools to use in primary care versus secondary care, and what should warrant a referral to secondary care. Specialists suggested low confidence in the ability of primary care physicians to request referrals based on relevant liver enzyme test results, and a need for greater education and tools available to them to apply guideline recommendations (see Table 3, Quotes C-E).

A lack of clarity on processes for optimal co-management was cited as a barrier to collaboration with other HCPs, whether through referrals as seen above, or within the context of a multidisciplinary team. Interprofessional collaboration in the care of patients with NASH and NAFLD was reported as falling behind, compared to other disease areas (such as diabetes). Inadequately defined roles and responsibilities of healthcare team members were reported by specialists, primary care physicians, patient advocates, and researchers to be a system-wide issue that ultimately impacts patients' care (see Table 3, Quote F).

3) *Patient communication and engagement: uncertainty over the value of NITs in the monitoring and management of liver diseases*

A prevalent belief in the community that NITs might not be useful in the absence of effective pharmacological agents for NAFLD, NASH and advanced fibrosis was reported by phase 1 participants (see Table 3, Quote G). Participants reported that the role of lifestyle modifications as a critical strategy to limit progression of NASH and NAFLD was under-emphasized. Physicians from phase 1 were particularly concerned with what they perceived as patients' resistance to change, and unwillingness to do what it takes to adopt a healthier lifestyle that can improve liver health (see Table 3, Quote H).

Physicians included in this study (i.e., primary care, diabetology and hepatology) perceived their lack of expertise in behavioural change as a key barrier to eliciting healthy behaviours amongst their patients and did not mention referring patients to dieticians or physiotherapists. This barrier was a frequent reason for their perceived uncertainty for using NITs in the monitoring of liver health status, in conjunction with a preventative approach to liver health. A sense of discouragement was noted amongst multiple stakeholders regarding the ability of patients to change their health behaviours if already affected by chronic conditions like obesity and diabetes. Phase 1 and 2 participants reported that the previously mentioned stigmatization of the disease was impacting optimal patient engagement in dialogues related to lifestyle modifications and could impact HCPs' confidence in initiating discussion on these topics with their patients. Phase 1 participants also reported that clinicians might lack the skills and access to resources to facilitate lifestyle modifications and promote behavioural changes. Using NITs to support an open dialogue with patients about liver health, and

taking a preventative approach, was mentioned by participants in both phases as not only yielding potential benefits for patients' health and quality of life, but also cost saving for public health systems (see Table 3, Quote I).

4) System-level decisions: reimbursing of NITs

Participants specified that there are enduring needs to improve NITs in terms of precision, validity, and better prognostic value. Without these improvements, the risks of using NITs could in some cases outweigh their benefits (see Table 3, Quote J). The perception that greater evidence is needed to justify the use of NITs was suggested as an explanation for suboptimal reimbursement at the system level in some countries. Participants reported challenges justifying NIT cost-effectiveness based either on the available evidence for their impact on early diagnosis, or when an available option is impractical due to excessive costs of patented tools. For these reasons, aiming to support further studies that demonstrate cost-effectiveness was seen as a prominent factor to contribute to establishing optimal reimbursement policies moving forward.

Recommendations to facilitate the use of NITs

In response to many of the above concerns, participants of the expert work group discussion offered recommendations to facilitate the adoption and implementation of NITs. These recommendations are summarized in Table 4. Among these recommendations, experts considered that improving primary care physicians and diabetologists' familiarity with available guidelines would support knowledge of liver diseases, a first step in establishing an

awareness and understanding of available and emerging NITs (e.g., notifications in electronic health record system). Increasing knowledge was also recommended as a pathway to building HCPs skill base in effective approaches to improving patient education and awareness of NITs. This recommendation was intended to support patients during diagnosis specifically, since understanding test results and the value of lifestyle modifications may improve adoption of NITs. To enhance the use of NITs, it was recommended that greater clarity be sought regarding the role of primary versus secondary care when interpreting test results, and how these results ought to be used in optimal patient referral. In addition to referrals, effective interprofessional collaboration was highlighted as a crucial element for integrating NITs. Just as primary care physicians are important partners in monitoring and encouraging lifestyle changes, hepatologists should be part of a multidisciplinary team, due to the prevalence of patients with metabolic disorders who are at-risk of NASH progression. Further system-level improvements to NIT integration were recommended in several countries where insurance is needed to access clinically relevant diagnostic NITs, whether due to their cost or their reimbursement status in a public system. Systems-level improvements to NITs allude to improvements in terms of reimbursement, costs, willingness-to-pay, and the evidence base used by decision-makers to promote or halt use of NITs (e.g., prognostic, and diagnostic accuracy and calibration, health economy analyses).

Discussion

This exploratory qualitative study undertaken in four countries highlights the current need for primary care physicians' education and patient focused education to address the four identified themes which limit use of NITs for NASH and advanced fibrosis: 1) limited

knowledge and awareness of liver diseases, relevant updated guidelines and NITs; 2) unclear referral pathways for patients affected by liver conditions; 3) doubts regarding the value of NITs in monitoring and managing liver diseases in the absence of effective medical treatments; and 4) system-level limitations to reimbursing NITs.

The need to enhance knowledge and guideline-recommended use of NITs in both primary and secondary care is supported by further literature. For example, a 2016 survey of UK gastroenterologists/hepatologists (n=116) revealed that recommended NITs, such as ratio calculations between aspartate transaminase (AST) and alanine transaminase (ALT) are not routinely performed in primary care, and less than 50% of specialists surveyed used tests such as FIB-4 and FibroScan®.[29] Another survey in 2021 of liver health experts in the tertiary level setting across 24 countries showed variability in the cut-offs used for FIB-4, liver stiffness by VCTE (FibroScan®) and the NAFLD Fibrosis Score, suggesting a knowledge gap of the appropriate cut-off to be used.[30] The importance of undertaking such research is further underscored in a recent article describing global research priorities in the field of fatty liver diseases.[31]

Our study strengthens this point as interviews with participants indicated potential gaps in knowledge and skills affecting physicians' ability to use and interpret NITs for the evaluation of NASH and advanced fibrosis, despite the presence of clinical guidelines providing readers with recommended cut-offs to assess likelihood of advanced fibrosis and cirrhosis.[32, 33] Our study provided additional context as to *why* NITs are poorly implemented, including: low societal awareness regarding liver diseases in general and constrained capacity (both human and financial) to promote and monitor the effectiveness of lifestyle modifications as a preventative and therapeutic intervention for liver diseases. These educational gaps and

systemic barriers have wider clinical implications on patient health outcomes, as they can limit the timely and effective identification of patients at risk of fibrosis and cirrhosis, who could most benefit from a rigorous, medically assisted, non-pharmacological interventions preventing or slowing disease progression.

While previous studies have raised the importance of enhancing screening of NAFLD in primary care to optimize referral to hepatology,[8, 34] our study suggests that referral pathways for patients affected by NAFLD are unclear. Since our study was conducted in 2021, the perceptions captured may not reflect the current clinical reality, in which many more updated clinical practice guidelines by the European Association for the Study of the Liver (EASL), the American Gastroenterological Association (AGA) and the Association for the Study of Liver Diseases (AASLD), amongst others, have been published and publicly available to guide the appropriate management of NASH, including risk stratification of liver diseases and recommended referral pathways from primary to secondary care.[33, 35, 36] These recommendations align with national guidelines published in 2022,[37-40] or described in community pathways.[41] Future studies should assess the impact of these updated guidelines on the current referral of patients affected by NAFLD to secondary care, and investigate how current perspectives on referral compare to those captured in our study.

Unfortunately, our study identified that clinicians perceive a lack of available medical treatments for NAFLD, as an underlying causality to the limited use of NITs, despite current guidelines (including those available at the time of data collection) stating that lifestyle modifications, consisting of diet and exercise changes led by a registered dietician and exercise physiologist, respectively, are the recommended standard of care for patients affected by NASH,[36] and the AGA recommends similar non-pharmacological interventions for

NAFLD.[39] These preventative and therapeutic interventions are expected to remain key in the management of liver diseases in the future, even after medical therapies become available in the field.[42] Our study found that clinicians perceived having limited capacity to enact behavioural change amongst patients. However, patients may be more motivated than clinicians think, as suggested by a recent study where a majority (88%) of NAFLD patients surveyed demonstrated desire to be more active, though almost half (47%) felt they lacked education and resources from their provider to support them.[43]

Our study findings suggest a need to raise awareness amongst both physicians and patients when it comes to existing resources available in their region, leveraging the expertise of multiple disciplines, to support lifestyle modifications based on best-practice.[43]

Overall, the results of our study suggest, as others have,[44] that a lack of knowledge of NAFLD and NASH hinder the translation of available guidelines into clinical practice. Thus, publication of guidelines should be complemented with the development and deployment of activities to help alleviate potential barriers to their implementation in practice. In order to further translate knowledge into practice, real-word studies and the development of a thinktank with all key stakeholders, to identify the most promising strategies to involve patients in research surrounding non-invasive diagnostic tools, an identified barrier,[44] may prove beneficial. Poor public awareness of the importance of liver health in general, and of NAFLD, NASH, and advanced fibrosis in particular, alongside underdiagnosis by HCPs and a lack of reimbursement for testing may be addressed through public health campaigns and policy advocacy as well as outreach to payers and administrators. Evidence of the cost-effectiveness of combining non-invasive diagnosis with behavioural/lifestyle modifications should be included in messaging.[45]

Recent studies show that systemic changes are urgently needed to raise awareness and transform health policies regarding NAFLD at the population and community levels, and the findings of this study concur.[11, 46] However, they also suggest that significant gaps in knowledge and skills about NITs persist, and that care for NASH suffers from a lack of clear consensus on best practices. A new study with a larger sample size should be performed to describe the extent and magnitude of these barriers, and an assessment of the precise educational needs of various HCPs at the country level. Our explorative study suggests that educational programs, evidence-based awareness and dissemination campaigns, and policy level changes will support the implementation of new non-invasive diagnostic tools, while other systemic barriers did not come up. For example, only one participant in phase 1 expressed concern of “medicalizing” patients by introducing liver disease as an additional worry. Since only one participant mentioned this, we did not include it as common theme, but larger qualitative studies may have identified a need for better evidence on the negative consequences of early detection of liver disease as an important barrier (e.g., to what extent screening for fibrosis causes overdiagnosis, anxiety about own health, futile invasive investigations; or out of pocket healthcare costs).

Strengths and Limitations

While multiple countries and professions involved in the use and implementation of NITs were included within this two-phase qualitative exploratory research study, the sample size was too small to identify unique challenges, barriers, and gaps affecting each country, individually. However, this was not the aim of this exploratory research study, which aimed to better understand the meaning and context of potential factors hindering the use and

implementation of NITs, poorly understood within the published evidence. Interview coding indicated data saturation reach after the 12th interview, which means that the twenty-nine interviews of 45-minutes in length completed for this exploratory research study was more than sufficient in sample size. The inclusion of multiple countries and professions was a strength of the study and done for the purpose of triangulation, which is a method of comparing and contrasting insights obtained from multiple sources, viewpoints and analyses to enhance the trustworthiness of reports.[23] Future studies could seek to validate the findings by collecting the insights of other experts, such as health economists to map barriers related to cost-effectiveness of using NITs in primary care, and the role of differences in willingness-to-pay in different health care systems. An exploratory study design was determined most suitable at the time of conceptualization, as little evidence was present in the literature with respect to the investigated topic area. Now that this study has identified emerging themes constituting meaningful barriers from the perspective of relevant stakeholders in the space of NAFLD and NASH, authors recommend further research endeavours to validate the presence of identified barriers in larger, more targeted samples, leveraging the power of quantitative research methodologies (e.g., surveys) to increase the strength and specificity of evidence. In addition, while generating potential recommendations to address identified barriers to the use and implementation of NITs were an important component of this research study, determining the hierarchy of priority needs and/or determine consensus among the expert working group members, such as via the Delphi method,[47] were beyond the scope of the study. Another shortcoming is the possibility of some recommendations being uniform worldwide, while others may need to be adapted regionally; we could not explore this concept with the limited number of phase 1 and 2 participants. The study's recommendations are not exhaustive and merit further reflection amongst the community to ensure identified barriers

are properly addressed. This paper aimed to facilitate reflections within the community and provide guidance for barriers worth further investigation, especially those that can be feasibility addressed at the individual-level without an intervention at the institutional level (e.g., knowledge of NITs by clinicians).

Conclusions

With the publication of the 2021 update of the EASL guidelines for the use of non-invasive tests for evaluation of liver disease severity and prognosis, as well as several other national guidelines, it is important to understand and anticipate barriers to the implementation of recommendations in clinical practice. This two-phase qualitative exploratory research study contributed to this effort, shedding light on factors that can facilitate or hinder the use of clinically relevant NITs by multiple stakeholders from four countries (Germany, Italy, the UK, and USA) involved in the care of patients with NAFLD, NASH and advanced fibrosis. Findings indicated a need to address the low societal awareness and stigmatization of NAFLD, efficient referral of patients from primary to secondary care, engagement of patients in optimal monitoring and management of their liver disease and reimbursement of NITs within health systems. The insights generated by this exploratory research study are relevant for the identification of clinicians' educational needs, including those of primary care physicians and diabetologists. Further validation of needs within larger sample sizes and using quantitative research methods is recommended to contribute to the development of evidence-based continuing medical education, and performance improvement interventions aimed at addressing these needs.

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Tables & Figures

Table 1. Phase 1 demographics – Profession by country (n=29)

Profession	**Germany**	**Italy**	**UK**	**USA**	**Total**
Diabetologists	1	1	1	1	4
Hepatologists	1	1	1	1	4
Primary care physicians	1	2	2	1	6
Patient advocates	1	1	1	1	4
Clinical researchers	0	1	1	2	4
Basic researchers	0	1	1	2	4
Healthcare administrators & payers	0	1	1	1	3
					N=29

Table 2. Identified challenges, barriers and gaps by country.

Sphere	Identified challenges, barriers, and gaps by country	Germany	Italy	UK	USA
1. Use of NITs by clinicians	Low awareness and stigmatization of NAFLD	x	x		
	Sub-optimal knowledge of NITs		x	x	x
	Sub-optimal skills interpreting the results of NITs	x	x	x	x
2. Interprofessional collaboration	Lack of clear referral pathways between primary and secondary care	x		x	x
	Sub-optimal definitions of roles and responsibilities of various professions involved in NAFLD			x	x
3. Patient communication and engagement	Attitude that uses of NITs is not necessary in the absence of disease-modifying agents	x	x	x	x
	Sub-optimal skills to elicit and support lifestyle modifications by patients	x	x	x	x
4. System-level decisions	Sub-optimal reimbursement of NITs	x	x	x	x

Description: This table presents challenges, barriers and gaps to the optimal provision of care to patients affected by NAFLD, NASH and ALF reported by many participants across the 29 interviews thematically analysed. The last four columns indicate in which countries the findings were reported to be occurring.

Table 3. Representative quotes describing identified challenges and barriers.

Theme	Representative quote	
1) Use of NITs by clinicians: Knowledge and awareness factors hindering the use of non-invasive tests	A	*"Liver disease, as a whole, has got huge stigma associated with it. That comes both from people, obviously, alcohol has huge stigma associated with that, but also for people who are overweight. I think that means they don't want to talk about it as much, which means they don't get the help that they need. We have many examples of healthcare professionals behaving - stigmatizing the patients because of their way and their situation, etc. I think there's a lot of education that needs to be done in that area, as well."* --Patient advocate (Phase 1)
	B	*"I have no idea* [about emerging evidence for other biomarkers]. *You'd have to ask somebody who's technical about liver disease about that."* - Primary care physician, UK (Phase 1)
2) Interprofessional collaboration: Lack of clear referral pathways for patients with liver conditions	C	*"I think quite a few of the patients are currently cared for by the general practitioner who might notice that a patient has elevated liver enzymes such as ALT and AST but does not pay sufficient attention to this elevation."* - Diabetologist, Germany (Phase 1)
	D	*"It is very common to see patients referred very, very, very late in the process with presenting with a complication of cirrhosis [...] we need to get primary care doctors to understand, what an AST to ALT ratio means and why it matters and what some of the risk factors are or warning signs are before people decompensate."* -Expert work group participant (Phase 2)
	E	*"…We have not convinced the hepatological community that if [FibroScan] is broadly available to general practitioners, that this would be of benefit for the patient. Because we are not 100% sure that they will be able to translate the results of the FibroScan reliably and then benefit the patient."* - Hepatologist, UK (Phase 1)
	F	*"I think there's a lot of work to be done in terms of having better linking and better engagement between community and hospital in terms of diagnosing and staging liver disease. […] I think that area, that primary care, secondary care interface hasn't really been worked out just yet for fatty liver disease…"* - Diabetologist, UK (Phase 1)

3) Patient communication and engagement: Uncertainty over the value of NITs in the monitoring and management of liver diseases	G	*"... if there's no treatment, then there's a barrier to testing. Because what's the point? There's a perception, what's the point? I don't personally agree with that at all. I think there could be better research on this, because I think if you do tell someone that they've got the early stages but there's still time to reverse it, I think that's a huge incentive to make lifestyle changes."* - Patient advocate, UK (Phase 1)
	H	*"The difficulty is always the same. When you tell the patients about their problems, they often want a quick solution. They want you to find a way, a very easy way, with no side effects and stuff. But it's not always that easy."* - Primary care physician, Germany (Phase 1)
	I	*"…being more engaged in lifestyle behaviour changes [...] there are cost savings, because if the person progresses to the point where they're going to need expensive care, whether they're going to die on the way to the system, or they're going to be in this system, and we're going to know about it, we're going to be able to track it and say, well, 'What if we had known earlier'."* - Expert work group participant (Phase 2)
4) System-level decision: Reimbursing of NITs	J	*"With any new technology, new tests, new markers, anything like that, there's always going to be an element of it's new, we're not experienced with it. We need to be reassured that it actually works, because that's going to have a knock-on effect to the patients. If a non-invasive test tells that patient that we've got this disease, which they actually haven't, what are the implications for that patient?"* - Payer, UK (Phase 1)

Table 4. Recommendations to address identified challenges, barriers, and gaps to the use of NITs.

Recommendation	Prioritized audience
Build and reinforce knowledge based in relation to: • Current and upcoming non-invasive diagnostic tools and blood markers (especially FIB-4) for risk stratification • Best-practice and the 2021 EASL Clinical Practice Guidelines in the use and interpretation of non-invasive diagnostic tools and blood markers in NAFLD, NASH, or advanced fibrosis	• Primary care • Secondary care (non-hepatology) • Payers
Enhance skill and confidence in relation to: • Risk stratification for NAFLD • Identification of advanced fibrosis • Referral of patients to specialists • Options to prevent and treat NAFLD, NASH and ALF • Adherence to lifestyle changes and treatment	• Primary care
Address misperceptions in relation to: • The value in diagnosing advanced liver disease for surveillance purposes • The role of lifestyle changes to prevent complications and slow down progression	• Primary care • Secondary care (non-hepatology) • Payers (system) • Patient advocates
Enhance interprofessional collaboration though: • Better definition of roles and responsibilities of each provider involved in NAFLD, NASH and ALF • Greater dissemination of available guidelines and recommended cut-off for adequate patient referral by primary care • Use of electronic medical record system to recommend use of NIT and appropriate risk stratification	• Primary care • Secondary care • Payers (system) • Patient advocates
Improve access and affordability of NITs by sharing health economics evidence aiding implementation and reimbursement decisions by policymakers	• Primary care • Payers / health administrators

Fig. 1. Summary of the recruitment and data collection processes

Fig 2. Phase 1 demographics – Work setting, years of practice and location (n=29)

Fig 3. Conceptual framework of areas of barriers to NIT implementation

Description: This figure presents a summary of the key challenges, barriers and gaps to providing optimal care to patients affected by NAFLD, NASH and ALF, categorizing them under four main spheres which are inter-related.