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REVIEW

Differences between current clinical guidelines for screening, diagnosis and management of nonalcoholic fatty liver disease and real-world practice: a targeted literature review

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ABSTRACT

Introduction: Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease and is associated with obesity and metabolic comorbidities. Liver steatosis can progress to nonalcoholic steatohepatitis (NASH) exhibiting a relevant risk of fibrosis and ultimately liver failure. To date, no approved treatment for NASH to reduce its clinical and humanistic burden has been developed.

Areas covered: We undertook a literature review to identify English language, national and international clinical guidelines for NAFLD regarding diagnosis, assessment and management, and determined their points of agreement and difference. Additionally, we investigated published literature relating to real-world management of NAFLD and NASH.

Expert opinion: National (China, England/Wales, Italy, the USA) and international society (Asia-Pacific, Europe, World Gastroenterology Organization) guidelines were identified and analyzed. All guidelines addressed identifying and diagnosing subjects with likely NAFLD, as well as assessment and management of individuals with risk factors for advanced disease, including fibrosis. Real-world practice reveals widespread suboptimal awareness and implementation of guidelines. In the absence of proven therapeutics, such gaps risk failure to recognize patients in need of specialist care and monitoring, highlighting the need for clear, easy-to-apply care pathways to aid in reducing the clinical and humanistic burden of NAFLD and NASH.

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nonalcoholic fatty liver disease; nonalcoholic steatohepatitis; clinical guidelines; literature review; liver fibrosis; real-world practice

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a major cause of chronic liver disease that is often underdiagnosed [1]. Although manageable and potentially reversible in its early stages, progressive liver steatosis can lead to nonalcoholic steatohepatitis (NASH) with advanced fibrosis (AF) and end-stage liver disease, which is rapidly becoming the leading indication for liver transplantation [1]. Importantly, patients with NASH also experience substantially impaired quality of life [2–4].

The incidence of NAFLD is increasing worldwide, with a prevalence of around 25%, and is associated with higher mortality rates than those in the general population [5–10]. Although adults are most commonly affected by NAFLD, with occurrence increasing with age, rates of childhood NAFLD are increasing, particularly in association with the occurrence of obesity [1,8,11,12].

Cardiometabolic comorbidities share epidemiological, pathophysiological and behavioral/lifestyle features with NAFLD, suggesting a close association with aspects of metabolic syndrome and insulin resistance [1,8,13–16]. Management of cardiometabolic conditions such as type 2 diabetes mellitus (T2DM) and metabolic syndrome using lifestyle modification and pharmacotherapy is a key component of NAFLD care [6,16,17].

Genetic background also plays a key role in determining the development and severity of NAFLD and NASH that may explain inter-individual variation in patterns of disease. Genome-wide association and large candidate gene studies have identified the I148M variant in the *patatin-like phospholipase domain-containing protein 3* (*PNPLA3*) gene as a common, strong genetic determinant of NAFLD, NASH, hepatic fibrosis, and hepatocellular carcinoma (HCC) [18,19]. Other single nucleotide polymorphisms (SNPs) that appear to play a moderate role in the NAFLD spectrum include those in the genes *TM6SF2, MBOAT7* and *GCKR* [20].

NAFLD is characterized by evidence of hepatic fat accumulation (steatosis), with or without chronic, mild inflammation, and where the role of other causative etiologies, such as viral

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Supplemental data for this article can be accessed here.

Article highlights

- Since the mid-2010s, national clinical guidance for the diagnosis, assessment, and management of NAFLD has been published for China, England/Wales, Italy, and the USA, as well as internationally from the Asia-Pacific, European, and global perspectives.
- All guidelines we reviewed provided recommendations for targeted, risk-based screening of individuals deemed likely to have NAFLD. Tests to screen patients who may have NAFLD included blood-based markers, imaging, and elastography techniques to exclude those at low risk of NASH and advanced fibrosis.
- To assess liver fibrosis, a key determining factor in risk of disease progression, FIB-4 and/or NFS scores were recommended in guidelines from China, Europe, Italy, and the USA.
- All guidelines provided recommendations for NAFLD management through lifestyle changes, principally weight loss through restriction of calorie intake and increased regular exercise.
- To date, no drugs have received regulatory approval for the treatment of NAFLD or NASH. However, all guidelines included weak recommendations for pharmacological support where considered necessary, although restricted to patients diagnosed with NASH with, or at risk of, fibrosis or disease progression.
- Despite the widespread availability of clinical guidelines, awareness and understanding of NAFLD, its diagnosis and management remain poor outside of specialists in hepatology. A lack of guidance and education is leading to low rates of diagnosis and therefore missed cases of serious, potentially life-threatening NASH and missed opportunities for intervention.
- The innovation of clear algorithms for sequential screening and diagnosis of NAFLD could help improve rates of identification and referral of at-risk individuals and improve standards of care.

hepatitis or excessive alcohol consumption, have been excluded [8]. Although steatosis itself is usually considered benign, evidence is accumulating that suggests it may contribute to NASH progression [1]. NASH is characterized by steatosis, ballooning degeneration, and lobular inflammation, which can progress to fibrosis, which is found in over half of patients with NAFLD, predisposing some individuals to cirrhosis and end-stage liver disease as well as being a HCC risk factor [1,8,9,21,22]. Although the incidence of NAFLD- and NASH-related HCC is low (0.44 and 5.29 per 1,000 person years, respectively), the high number of patients with NAFLD has led to HCC being the fifth most common cancer worldwide, as well as one of the two most frequent causes of cancer-related death [23,24].

Compared to NAFLD without NASH, a diagnosis of NASH is associated with shorter survival times, more cardiovascular events, and greater liver cancer mortality [21]. As well as being a leading cause of liver cirrhosis, NASH is associated with a substantial humanistic and economic burden that increases with advancing fibrosis levels. For example, end-stage liver disease accounts for between 56% and 90% of economic and wellbeing costs, and most NASH-related costs are due to use of secondary healthcare and the need for extensive diagnostic testing [4,22,25].

Screening and stratification of severity in large numbers of individuals are key components of efforts to combat disease progression. However, the complexity of NAFLD diagnosis and management is such that primary and specialist healthcare professionals play important roles, and multidisciplinary care is essential. Several international and national guidelines for diagnosing and managing NAFLD have been developed or updated in recent years [26–33]. Previously, inconsistencies between individual published guidelines for the diagnosis and treatment of NAFLD have been reported [34,35], as well as a paucity of country-specific guidance and supporting documentation to encourage guideline implementation [36]. This may go some way toward accounting for poor rates of NAFLD diagnosis and lack of screening for disease severity [5].

1.1. Objective of this review

The objective of this literature search and review was to determine areas of consistency in NAFLD clinical practice guidance and identify points of disagreement. A secondary objective was to investigate real-world practice patterns in NAFLD management based on published data.

2. Methods

The current review follows on from an earlier literature search and review [35] which explored publications between 2005 and 2019. An update was undertaken employing the same methodology and included publications up to October 2020.

In the original literature search, the PubMed, Embase, and DynaMed publication databases were screened for potential publications. For the update described here, PubMed, MEDLINE, Embase, and Cochrane databases were screened. Targeted, iterative literature searches were conducted to identify relevant English-language publications related to key themes in the objectives and the predefined research questions described below. Search terms included at least one of the following: 'non-alcoholic fatty liver disease,' 'non-alcoholic steatohepatitis,' 'fatty liver,' 'liver fibrosis,' and 'cirrhosis.' Additional search terms were included to identify guidelines, consensus statements, and relevant research relating to all stages of the identification, evaluation, and management of NAFLD. Search results included a range of publication types: research papers, systematic literature reviews, narrative reviews, qualitative/quantitative research, clinical guidelines, or consensus statements.

The final publications for inclusion were reviewed and summarized in the context of predefined research questions. Study findings are described qualitatively; quantitative data synthesis was not feasible owing to the high levels of heterogeneity across the study/publication types, patient characteristics, and data presented.

To aid evaluation and synthesis of the narrative from this literature review, the authors analyzed the results in the context of the following topics relating to real-world practice in NAFLD.

- *Disease awareness among patients diagnosed with NAFLD.*
- *Discrepancies between routine diagnosis and screening practice and the implementation of recommendations in NAFLD guidelines.*
- *Lifestyle modification and pharmacotherapeutic management of NAFLD in practice.*

Initially identified articles of relevance were supplemented through hand search, including review of 'cited in' articles in PubMed and with additional publications known to the authors or cited in the papers considered.

3. Results

3.1. Guidelines included in this review

Seven sets of national or international society guidelines or consensus statements were identified. Three of these (European Association for the Study of the Liver [EASL] [26], National Institute for Health and Care Excellence [NICE] [31] and Asia-Pacific Working Party [28,29]) were based on systematic literature reviews. Literature review and/or consensus among experts supported recommendations in other guidelines (Table 1) [27,30,32,33]. The American Association for the Study of Liver Diseases (AASLD) guideline was an update to an earlier document published in 2012 [37]. The earliest published guidelines were from Italy (2014) [32], with the rest published in the years 2016 to 2018 [26–31,33]. Only three of the guidelines use an evidence-based approach (the Grading of Recommendations Assessment, Development and Evaluation [GRADE] system) to develop their recommendations: EASL [26], Asia-Pacific Working Party [28,29] and the Chinese National Consensus Workshop [33] (Table 1). The AASLD [37] differentiates its guidance developed from expert consensus from evidence-based recommendations. Quality assessment used and considered ranking of credibility.

3.2. Comparative overview of guidelines and consensus statements for NAFLD

3.2.1. Summary and overview

Seven guidelines and consensus statements published in English were identified for inclusion (Table 1).

All included guidelines provided recommendations for screening of individuals deemed likely to have NAFLD (Table 2), their diagnosis and where there is a risk of advanced disease, an assessment of severity. In patients with NAFLD with or at risk of severe and/or progressive NASH, recommendations for follow-up and monitoring are included (Tables 1 and 3). They also provided recommendations for management through lifestyle changes and where deemed necessary, off-label prescription of pharmacological agents and use of dietary supplements and plant-derived preparations that may protect the liver against damage (hepatoprotectors), as well as surgical interventions (Table 4). Screening patients with NAFLD risk factors in primary care is essential to identify those in need of further evaluation in specialist hepatology services for risk of advanced disease [36,38–41]. However, there was a general lack of detailed guidance on referral to hepatologists and implementation of multidisciplinary models of care in the guidelines. In particular, screening, diagnostic and follow-up pathways, and recommendations for primary care management and referral pathways were not clearly stated.

3.2.2. Risk groups

All seven guidelines define at-risk populations in which the exclusion of other causes, such as viral hepatitis or excessive alcohol consumption has to be considered (Table 1). All guidelines except those from NICE in England and Wales [31] included a lower limit for hepatic fat accumulation of 5%.

Although all guidelines acknowledged multiple risk factors for NAFLD, particularly T2DM, metabolic syndrome and obesity, there was considerable variation in the number and types of other risk factors between sets of guidelines, most of which appeared in three guidelines or fewer (Table 2). All except the Asia-Pacific guidelines, which refer to overnutrition as 'invariable' in this context [29], included T2DM and metabolic syndrome as risk factors (Table 2).

All except guidelines issued by NICE in England and Wales did not include the presence of obesity as a risk factor (Table 2); However, NICE does identify this condition as a target for intervention to reduce overweight via its specific obesity recommendations (CG189) [31,42]. In the context of bodyweight, it should be noted that managing 'lean NAFLD' (i.e. without obesity/elevated body mass index [BMI <30 kg/m^2 [26,33]]) is highlighted as an issue in some populations, in particular, Asian subjects and those with metabolic disturbances [26,29,31,33].

Insulin resistance, which is considered to have a central role in the development of NAFLD, was only mentioned in guidelines issued by the World Gastroenterology Organization (WGO) [32], EASL [26] and the Asia-Pacific region [29]. Other metabolic risk factors mentioned included hypertension [32], dyslipidemia [27,32], weight gain [29,30] and sleep apnea [27,33] (Table 2).

Although the role of genetics, particularly the SNPs *PNPLA3, TM6SF2,* and *MBOAT7*, in NAFLD, NASH and HCC risk are recognized [43], current guidelines do not recommend routine screening for these mutations (Table 1). Although genetic targets for therapeutic interventions offer the possibility of precision medicine, this aspect of NAFLD medicine must be considered in its infancy currently [43].

3.2.3. Modalities used for screening for NAFLD and assessing severity

There was agreement across all guidelines that universal screening of the general population is not recommended. Six of the seven guidelines, but not those issued in the USA [27], included recommendations for screening of high-risk populations defined by the presence of the risk factors, including obesity with or without T2DM [26,29,31,33], metabolic syndrome and abnormal liver enzyme profiles [26], NASH cirrhosis [30], and insulin resistance [32] (Table 1). Subsequently, EASL has issued updated specific clinical practice guidelines on the use of noninvasive tests (NITs) for assessing severity of [44].

Although evaluation of liver biopsy is the reference standard method for the grading and staging of NAFLD it is not practical or affordable for large-scale, routine use [31,38,40,45]. Alternative, noninvasive and cost-effective tests that are easy to implement are therefore necessary to sequentially screen and assess the large number of patients who may have NAFLD, exclude those with low risk of advanced disease from further assessment, and identify those at risk of severe disease [38,40].

For screening of patients who may have NAFLD, all seven of the guidelines we analyzed highlighted use of NITs, including blood-based, imaging and elastography techniques to exclude those at low risk of AF (who can be managed using diet and lifestyle modification in the first instance) and help

Table 1. Current NAFLD guidelines for the screening, diagnosis, and management of NAFLD in adults.

	EASL [26]	NICE [31]	Asia-Pacific [28,29]	AISF [30]	AASLD [27]	CSH [33]	WGO [32]
Year of publication	2016	2016	2018	2017	2018	2019	2014
Region/country	Europe	England and Wales	Asia-Pacific	Italy	USA	China	Global
Evidence base/origin	Systematic literature review	Systematic literature review	Systematic literature review and author consensus	Literature review	Literature review and author consensus	Author consensus	Author consensus
GRADE-based evidence assessment	Yes	No	Yes	No	No	Yes	No
Screening							
• Systematic	No	No	No	No	No	No	No
• High risk (subgroups)	Yes (Ob, met syn, abnormal liver enzymes)	Yes (Ob, T2DM)	Yes (Ob, T2DM)	Not stated	No	Yes (risk factors)	Yes (risk factors)
• Recommended methods	Liver enzymes	US	US, TE	-	-	US or liver enzymes	US, liver enzymes
• Genetic screening	Selected patients and in clinical trials (PNPLA3 I148M; TM6SF2 E167K)	No	No	No	No	No	No
Diagnosis							
• Criteria	Hepatic steatosis >5%*, insulin resistance, no other causes of steatosis	Excessive fat in liver, no other causes of steatosis	Hepatic steatosis*, no other causes of steatosis	Hepatic steatosis*, no other causes of steatosis	Hepatic steatosis*, no other causes of steatosis	Hepatic steatosis*, no other causes of steatosis	NASH: Hepatic steatosis >5%*, insulin resistance, no other causes of steatosis
• Alcohol limit (men)	30 g/d	30 g/d	140 g/wk (2 standard drink/d)	30 g/d	294 g/wk** (21 standard drinks/wk)	210 g/wk	30 g/d
• Alcohol limit (women)	20 g/d	20 g/d	70 g/wk (1 standard drink/d)	20 g/d	196 g/wk*** (14 standard drinks/wk)	140 g/wk	20 g/d

*Identified using either imaging or histology
**Equivalent to an average of 42 g/d
***Equivalent to an average of 28 g/d
AASLD: American Association for the Study of Liver Diseases; AISF: Italian Association for the study of the Liver; CSH: Chinese Society of Hepatology; d: day; EASL: European Association for the Study of the Liver; GRADE: Grading of Recommendations Assessment, Development and Evaluation; met syn: metabolic syndrome; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; NICE: National Institute for Health and Care Excellence; Ob: obesity; T2DM: type 2 diabetes mellitus; TE: transient elastography; wk: week; WGO: World Gastroenterology Organization

Table 2. Comparison of NAFLD risk factors stated in the guidelines under consideration (green: included in at least four of the guidelines; gray: mentioned in three guidelines; red: included in one or two guidelines).

	EASL [26]	NICE [31]	Asia-Pacific [28,29]	AISF [30]	AASLD [27]	CSH [33]	WGO [32]
Region/country	Europe	England and Wales	Asia-Pacific	Italy	USA	China	Global
T2DM	✓	✓		✓	✓	✓	✓
Metabolic syndrome	✓	✓		✓	✓	✓	✓
Obesity	✓		✓	✓	✓	✓	✓
Insulin resistance	✓		✓				✓
Overnutrition			✓				
Sleep Apnea					✓	✓	
Dyslipidemia					✓		✓
Polycystic Ovary Syndrome					✓	✓	
Hypopituitarism					✓	✓	
Hypertension							✓
Ethnicity				✓			✓
Age	✓			✓			
Weight gain			✓	✓			

AASLD: American Association for the Study of Liver Diseases; AISF: Italian Association for the study of the Liver; CSH: Chinese Society of Hepatology; EASL: European Association for the Study of the Liver; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; NICE: National Institute for Health and Care Excellence; T2DM: type 2 diabetes mellitus; WGO: World Gastroenterology Organization

identify those in need of further assessment for liver fibrosis. There is ongoing evaluation of NIT selection in routine clinical practice and choice of methodology may be influenced by a range of factors, including proven diagnostic ability, operator competence, ease of access, clinical setting (primary versus specialist care), patient preference and cost [38–42,45]. A detailed evaluation of these factors is beyond the scope of this review, and the recent review by Campos-Murguía *et al* [45] is recommended for test-specific technical details, together with the latest practice guidance from EASL for the use of NITs in liver disease assessment [44].

Beyond individual measures of liver status/performance and patient characteristics that are known risk factors (Table 2), composite scores based on risk factors assessment (T2DM, obesity, etc.) and serological measurements are recommended. In particular, the Enhanced Liver Fibrosis (ELF) test, the Fatty Liver Index [33], Fibrosis-4 (FIB-4) Index, Hepatic Steatosis Index, and NAFLD Fibrosis Score (NFS) can be used for assessment of disease severity (including fibrosis) and risk of progression [38,40,45].

Guidelines from NICE in England and Wales [31], the Asia-Pacific region [29], China [33], Italy [30] and the WGO [32] recommend ultrasound, supported by measurement of liver enzyme levels in the Chinese National Consensus Workshop and WGO guidelines [32,33] and transient elastography (TE) according to those for the Asia-Pacific region [29] (Table 1).

For patients with suspected NAFLD requiring an assessment of severity, including the presence and extent of fibrosis (see below), the WGO recommends measuring blood markers, anthropometric features (weight, BMI, waist circumference, height), blood pressure and imaging, including ultrasound and abdominal computed tomography scan where required [32]. TE using FibroScan is recommended in the EASL and Italian guidelines as confirmation where other tests are inclusive [26,30]. TE is also recommended for assessment of NAFLD in the guidelines from China along with NFS [33], and may also be used in accordance with AASLD recommendations [27].

Liver fibrosis plays a major role in the progression to severe liver disease and associated mortality [38,45], so its assessment is vital in patients with NAFLD deemed to be at risk of, or suspected to have, fibrosis. Liver fibrosis assessment is recommended using FIB-4 and/or NFS in guidelines from AASLD [27], China [33], EASL [26], and Italy [30]. However, the NFS may not be suitable for use in assessing patients with NAFLD and T2DM [38]. In England and Wales, ELF is recommended test for AF [31].

Liver biopsy is the acknowledged reference standard, but all guidelines agree that it is not suitable for routine screening and assessment. Where specified, liver biopsy is to be reserved for cases of diagnostic uncertainty after NITs [32] and in cases where patients are considered at risk of having or likely to have NASH or AF [26,27,32,33].

3.2.4. Follow-up recommendations

Guidance on follow-up to monitor risk and progression of disease varies between guidelines, with no recommendations included in those from the Asia-Pacific region [28], the AASLD [27], and the WGO [32]. EASL recommends monitoring in specialist care, including NITs and repeat liver biopsy after at least 5 years in patients at high risk of liver disease progression [26]. Repeat assessment of disease severity every 3 years are recommended by NICE [31] and every 2 years in Italy [30], rising to every 6 months when cirrhosis is present. In China, regular follow-up of 'lean' patients with NAFLD is advised [33]. No generally accepted model of care has yet been published, although NICE in England/Wales has issued a pathway (available at http://pathways.nice.org.uk/pathways/nonalcoholic-fatty-liver-disease; see discussion).

Recommendations for HCC screening are not universal. Guidelines from Asia-Pacific [29], China [33] and the USA [27] recommend screening when cirrhosis is present, whereas those from Italy recommend screening specifically in proven cases of NAFLD with AF [30] (Table 3). European guidelines acknowledge the risk of HCC in NAFLD, they do not make any specific recommendation about timing of surveillance [26]. Although outside of the scope of this literature search, it is worth noting that some national guidelines include pre-cirrhotic NASH as a condition for HCC screening, and the American Gastroenterology Association has recently published an evidence-based review and best practice advice for HCC screening in people with NAFLD [23].

Table 3. Screening guidance and use of markers and measurements of liver fibrosis in current NAFLD guidelines.

	EASL [26]	NICE [31]	Asia-Pacific [28,29]	AISF [30]	AASLD [27]	CSH [33]	WGO [32]
Region/ country	Europe	England and Wales	Asia-Pacific	Italy	USA	China	Global
Algorithm	Yes*	Yes**	No	No	No	No	Yes
Noninvasive tests	NFS, FIB-4. TE where other tests are inconclusive	ELF for all patients with NAFLD	Serum test and imaging (specific tests not specified)	NFS plus FIB-4. TE where other tests are inconclusive	NFS or FIB-4 to identify patients at high risk of AF. VCTE™ or MRE may also be used.	NFS, TE	Serum tests (specific tests not specified)
Follow-up	Progression followed in specialist care	No evidence of fibrosis repeat testing every 3 years Evidence of fibrosis: liver biopsy	Not stated	Negative test: repeat every 2 years; fibrosis or abnormal liver enzymes: erases every year; cirrhosis: reassess every 6 months		Diagnosis of NASH: liver biopsy	Not stated
HCC screening	No recommendation made per timing	Not stated	NASH with cirrhosis	NAFLD with AF and/or cirrhosis	NAFLD with cirrhosis	NASH with cirrhosis	Not stated

*For assessing severity and risk of fibrosis
**Available at http://pathways.nice.org.uk/pathways/non-alcoholic-fatty-liver-disease (last accessed 16 July 2021)
AASLD: American Association for the Study of Liver Diseases; AF: advanced fibrosis; AISF: Italian Association for the study of the Liver; CSH: Chinese Society of Hepatology; EASL: European Association for the Study of the Liver; ELF: Enhanced Liver Fibrosis; FIB-4: Fibrosis-4 Index; HCC: hepatocellular carcinoma; MRE: magnetic resonance elastrography; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; NFS: NAFLD Fibrosis Score; NICE: National Institute for Health and Care Excellence; TE: transient elastography; VCTE: Vibration Controlled Transient Elastography; WGO: World Gastroenterology Organization

3.2.5. Algorithms in guidelines

Algorithms for diagnosis and/or follow-up were absent in four of the seven guidelines (Table 3) [27,29,30,33]. The guidelines did not include information to support decisions on patient referral from primary care to specialist hepatology care, although the EASL guidelines did include an algorithm for fibrosis assessment [26]. It is also noteworthy that differentiation and integration of care across primary and secondary care, relating to screening and referral, as well as long-term monitoring, is currently lacking in the guidelines reviewed here. This is reflected in clinical practice, where care pathways are often lacking or, where they do exist, are not standardized based on best-practice principles [46]. The paucity of easy-to-follow care pathways developed from evidence-based best practice therefore remains a major hurdle to translating the knowledge base for NAFLD and NASH into improved outcomes for patients.

3.2.6. Treatment using lifestyle modification

All guidelines recommend the use of lifestyle modification to manage NAFLD. Interventions feature structured programs incorporating diet and regular physical activity, often with personalization and expert nutritional support, to facilitate long-term adherence [26–28,31–33]. However, no clear and consistent guidance was provided regarding the care pathway through which lifestyle modification should be delivered.

All seven guidelines reviewed included recommendations for weight loss, with only those from NICE not quantifying therapeutic weight loss [31]. Five of the seven propose a standard target weight loss 5%–10% [26,29,30,32,33], whereas the AASLD recommends weight loss stratified by NAFLD severity: 3%–5% for steatosis and 7%–10% for NASH [27]. To achieve recommended weight loss, guidelines from Asia-Pacific, Europe, China and the USA recommend a target daily energy *intake deficit* of between 500 and 1000 kcal [26–28,33], whereas in Italy a target daily *intake limit* of 1200 to 1600 kcal is stated [30]. WGO guidelines indicate reducing by 25% the normally recommended daily calorie intake to achieve weight loss [32].

3.2.7. Treatment using pharmacological agents and supplements

Despite the universally acknowledged absence of an approved pharmacological therapy in the explored countries, all of the guidelines identified in this review included consideration of the use of pharmacological agents and nutritional supplements. However, their use was restricted to patients with NASH [26–28,30,33], and/or fibrosis [26,28,31,33] or at high risk of disease progression [26,30] (Table 4). No guidelines made strong, evidence-based recommendations for the use of any pharmacological agent, with three stating that specific agents 'may be used' [27,28,33]. EASL states that 'no firm recommendation' can be made [26], and the WGO states that any use is to be 'considered experimental' [32] (Table 4).

Several of the recommended agents described in Table 4 target, and are appropriately indicated for, NAFLD risk factors and comorbidities. Specifically, in the context of NAFLD and NASH, they have been evaluated for their effects on blood markers and histology (reviewed in the development of the European guidelines) [26]. However, other than in India no drugs have yet been approved specifically for the treatment of NAFLD or NASH. A systematic review undertaken in the development of the EASL guidelines of randomized controlled trials in NAFLD that included histological outcomes showed poor, inconsistent efficacy across drug types in small or

medium-sized trials [26]. It is also noteworthy that most of the trials of antidiabetic drugs that are considered potentially beneficial in managing NAFLD, in particular glucagon-like peptide I receptor antagonists (GLP-1 RAs) and sodium-glucose cotransporter 2 (SGLT-2) inhibitors, were ongoing and unpublished when the guidelines under consideration were being developed [47]. Although not suitably indicated, GLP-1 RAs are favorably viewed for evaluation as pharmacotherapy in NAFLD, due to their combined effects on markers of steatosis, weight, and cardiometabolic parameters [16,47,48]. SGLT-2 inhibitors also show promise, although the risk of urinary tract infections may limit their use [16]. Both classes of antidiabetic appear to have better benefit–risk profiles than pioglitazone, which features in NAFLD guidelines from EASL [26], NICE [31] and the AASLD [16,27]. Other, novel agents with mechanisms of action that target metabolic, inflammatory, or fibrotic processes have also been studied, some in late-phase trials, but development has stalled due to benefit–risk profiles perceived as inadequately favorable [49,50]. For patients with multiple cardiovascular risk factors, statins have been viewed favorably due to their proven safety profile and their strong efficacy for the reduction of the cardiovascular risk, but not for benefits in NAFLD *per se* [34].

Many studies of dietary supplements (e.g. vitamin E and omega-3 fatty acids) and plant-derived hepatoprotectors (e.g. silymarin, phosphatidylcholine, and ursodeoxycholic acid [UDCA]) have been performed, with summaries of evidence and outcomes provided in guidelines from EASL [26], the USA [27] and the Asia-Pacific region [28]. In the Chinese guidelines, silymarin, bicyclol, polyene, and phosphatidylcholine, along with vitamin E, are noted as having broad utility as add-on treatments for liver injury in patients with chronic liver diseases [33]. However, a lack of evidence, the overall low quality of source data where assessments have been made, and the need for data from clinical trials were noted.

3.2.8. Bariatric interventions

Bariatric surgery is recommended to be considered in the absence of cirrhosis to reduce obesity (for example, where dietary interventions, lifestyle modifications and/or supplements are unsuccessful) [26–28,32,33] or as an adjunct to liver transplant [26]. No BMI cutoffs for bariatric interventions were specified in guidelines from EASL [26], AASLD [27] or WGO [32]. Those for the Asia-Pacific region [28] define a qualifying BMI greater than 30 kg/m^2 as eligible for bariatric surgery, whereas guidelines for China [33] differentiate obesity by BMI level (severe obesity: at least 40 kg/m^2; moderate obesity: 35 to 39.9 kg/m^2, stipulating a 2.5 kg/m^2 reduction in threshold for Asian populations). Patients with NAFLD having a BMI between 30 and 34.0 kg/m^2 (adjusted accordingly for Asian populations) might also be considered for bariatric surgery when cardiometabolic risk factors are present [33]. Evidence is accumulating in support of bariatric surgery for patients with NASH in need of rapid weight loss, leading to reduction in hepatic steatosis and even resolution of NAFLD in some cases [51–53]. There were no recommendations for endoscopic bariatric devices such as gastric balloons.

3.2.9. Liver transplantation

Liver transplantation is a recognized option for patients with end-stage liver disease due to decompensated cirrhosis or the onset of HCC (Table 4) according to regional standards. However, thorough assessment of patient status, in particular, age and cardiovascular and renal disease risk factors, is necessary [26–28,33,54]. High BMI (>40 kg/m^2) may also present challenges in performing liver transplant [27,28,32]. Risks associated with post-transplant infections should also be borne in mind [26,28,54].

3.3. Clinical practice, awareness, and application of NAFLD guidelines in the real world

3.3.1. Disease awareness among patients diagnosed with NAFLD

Patients with significant risk factors for NAFLD repeatedly report low levels of awareness of potential liver disease [55–59]. A recent study of awareness around NAFLD among 30 patients with T2DM revealed that just half were familiar with the concept of 'fatty liver' [58]. Although disease awareness among patients with NAFLD was found to be low, it has increased slightly over the past two decades [57]. It is worth noting that just 16 of 667 (2.4%) with imaging-confirmed NAFLD had been made aware of their diagnosis through physician and/or nurse communication [56]. Regarding high-risk comorbidities, NAFLD awareness rates of between 19% and 38% have been reported among those with risk factors, such as obesity or T2DM [55]. There was also a poor level of understanding of the therapeutic nature of lifestyle modification and the interplay between NAFLD and T2DM (including insulin resistance), as well as the possible consequences of NAFLD, including risk of progression. Experience of post-diagnosis follow-up examinations, including monitoring of disease progression, was reported by just half of the subjects [58].

Further details on disease awareness among patients and practitioners are provided in the Appendix.

3.3.2. Discrepancies between routine diagnosis and screening practice and the implementation of recommendations in NAFLD guidelines

National healthcare policy and support is essential to facilitate necessary changes in clinical practice to implement clinical guidelines as they become available. Lazarus *et al.* identified very low levels of health policy support and awareness programs for the implementation of NAFLD guidelines across Europe [36]. Surveying experts across Europe and reviewing official documents relating to policies, clinical guidelines, awareness, and monitoring showed that necessary guidance and information is missing on a country level. In the 29 countries studied, there were no written strategies or action plans for NAFLD despite over 40% having policies on obesity, cardiovascular disease, T2DM, and/or healthy living and nutrition. Two countries incorporated NAFLD/NASH into obesity and alcohol strategies. Subsequent analysis of these data and evaluation of a 'European Preparedness Index' for meeting the NAFLD challenge shows that none of the countries involved in the study have a

Table 4. Patient groups and strength of recommendations for pharmacotherapy, and surgery recommendations included in clinical guidelines for the management of NAFLD/NASH (recommended drugs are not approved by regulatory bodies specifically for the treatment of NAFLD as of December 2020; shading: green, recommended in guidelines (off-label use form prescription-only medicines)); gray, may be considered; red, not recommended; white, not stated).

	EASL [26]	NICE [31]	Asia-Pacific [28,29]	AISF [30]	AASLD [27]	CSH [33]	WGO [32]
Patient groups considered suitable for pharmacotherapy	NASH, particularly with significant fibrosis (≥F2); high risk of progression	AF	NASH and/or fibrosis	NASH at maximal risk of progression	Biopsy-proven NASH	Suspected of NASH; AF in the absence of biopsy	Not stated
Strength of recommendation for pharmacotherapy	'No firm recommendation can be made'	Not stated	Specific agents 'may be used'	Not stated	Specific agents 'may be considered'	'May be considered'	Any use 'should be considered experimental'
Drugs approved for risk factors							
Metformin	✕	✕	✕	-	✕	✓*	✕
PPAR-gamma agonists (glitazones)	✓	✓	✕	✕*	✓	✓*	✕
Statins	✓*	✓*	✓*	✓*	✓*	✓*	✓
GLP-1 analogues	✕*	✕	✕	✕*	✕		
Supplements and hepatoprotective agents							
Vitamin E	✕	✓	✕	✕	✓	✕*	✕*
PUFA	✕	✕	✕	-	✕	-	-
Pentoxifylline	✕	-	✕	-	-	✕*	✕*
UDCA	✕	✕	-	-	✕	-	-
Phosphatidylcholine	-	-	-	-	-	✕*	
Obeticholic acid	✕	-	✕**	✕**	✕	-	-
Silymarin	-	-	✕*	-	-	✕*	-
Omega-3 fatty acid supplements	-	✕	✕	-	✕	✓*	✕
Bariatric surgery	Acceptable for improving obesity and T2DM No BMI limit stated	Not mentioned	Acceptable in patients with obesity BMI >30 kg/m^2	Not mentioned	As adjunct to liver transplant No BMI limit stated	To improve liver histology in obesity, metabolic syndrome and T2DM Stratified: ≥40/≥35 and ≤39.9/≤34.9 kg/m^2 Adjustment for Asian patients: reduce BMI score by 2.5 kg/m^2	To reduce obesity No BMI limit stated
Liver transplant	Acceptable in NASH with end-stage liver disease	Not mentioned	Acceptable in NASH with end-stage liver disease	Not mentioned	Acceptable in NASH with end-stage liver disease	NASH-related decompensated cirrhosis, HCC	In patients meeting criteria for liver transplantation

Drugs/classes considered for use indicated by ✓. Where use is restricted to specific groups, these are stated in parentheses. Those where evidence is considered insufficient, or where the agent is not beneficial are indicated by ✕. ✓*: acceptable safety but not considered beneficial; ✕*: insufficient evidence, potentially useful; ✕**: no trial results

AASLD: American Association for the Study of Liver Diseases; AF: advanced fibrosis; AISF: Italian Association for the study of the Liver; BMI: body mass index; CSH: Chinese Society of Hepatology; EASL: European Association for the Study of the Liver; GLP-1: glucagon-like peptide 1; HCC: hepatocellular carcinoma; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; NICE: National Institute for Health and Care Excellence; PPAR: peroxisome proliferator-activated receptor; PUFA: polyunsaturated fatty acids; T2DM: type 2 diabetes mellitus; UDCA: ursodeoxycholic acid; WGO: World Gastroenterology Organisation.

high level of preparedness [60]. Only the UK could be considered to have above a low level of preparedness in this scenario.

A third of countries had issued national guidelines, all of which recommended screening of risk factors and liver cirrhosis. Specifically, in the UK, only one-fifth of 84 specialist gastroenterology/hepatology centers reported having access to local NAFLD guidelines [61]. Specialist care (gastroenterology and hepatology) was responsible for NAFLD management in over 80% of countries, and around half involved primary care [36]. However, in keeping with the observations on the published guidelines, just five countries (17%) had developed algorithms for primary follow-up and referral to specialist care [36].

Given the underdiagnosis of NAFLD and NASH, implementing guidelines should help to identify cases in need of monitoring and/or referral. However, there is concern that attempts to optimize diagnosis could result in a rapid increase in the number of patients being referred to specialized care [62–64]. Over-referral from primary to specialist care has been identified as a potential problem, particularly among patients with T2DM [63]. On the other hand, referral rates may often be higher among specialists than physicians in primary care [65–68]. Moreover, if appropriately applied, adhering to current guidelines could avoid unnecessary rates of invasive liver biopsy [69]. For example, patients in specialist care for HIV mono-infection suspected of having NAFLD are not subjected to unnecessarily high rates of referral to hepatologists when EASL guidelines are applied [70], further supporting the application of current clinical guidance. Developments in nurse-led screening could further help redirect patients from specialist back to primary care, thereby avoiding or limiting the impact and increased workload due to higher numbers of referrals [71].

Development of clear algorithms and training for primary care physicians would also facilitate selection of patient types for screening, including a recognition of fibrosis and its implications for advanced disease [41,71,72]. For example, applying local processes such as the UK's Camden and Islington NAFLD Pathway can reduce unnecessary referrals to specialist care by 80%, offering both clinical and economic efficiencies [73,74]. However, there are currently widespread deficiencies in the number and standardization of care pathways for NAFLD [46].

Specifically, regarding fibrosis evaluation, the available data indicated that assessment of fibrosis using noninvasive techniques is not consistently conducted according to guideline-defined recommendations, and many physicians are unsure of the assessments and interpretations required or do not apply them rigorously [65,67,75]. Limited use of noninvasive scoring systems and infrequent referral of high-risk patients to specialists as described above likely result in underdiagnosis and missed opportunities to identify patients at risk of progression to severe, advanced NASH [68,76].

3.3.3. Lifestyle modification and pharmacotherapeutic management of NAFLD in practice

Adherence to lifestyle modifications has repeatedly been observed to be suboptimal [77,78]. In a study of patients with NAFLD in Russia, 86% of those assigned to strict diets were not adherent to strict dietary recommendations on more than a few occasions per month [77]. Among patients with T2DM, levels of disease awareness and understanding of the therapeutic importance of lifestyle modification were found to be low [58]. Moreover, a qualitative study revealed low levels of patient education, support, and follow-up related to their diagnosis and implementation of lifestyle modification [59]. Poor understanding and inadequate support have been associated with low adherence to lifestyle modification programs among patients with NAFLD across Europe [78–80].

Improved patient education about NAFLD and the therapeutic role of lifestyle modification to reduce future risk of clinically burdensome disease could help to bridge this gap in awareness [79,81]. However, an evaluation of online material developed for patients with liver cirrhosis highlighted that the available information from health platforms and specialist hepatology centers in the USA is often overly lengthy and complex, hindering broad understanding [82].

Per guidelines, analysis of real-world practice reveals that most physicians recognize and adhere to recommendations for lifestyle modification through physical activity and diet to manage NAFLD. These studies also show that pharmacotherapy is commonly used despite the lack of approved drugs and minimal, generally low-quality, evidence base for agents cautiously mentioned in guidelines. The number of individual drugs and rates of use vary across studies, which may be partly driven by local practices. Overall, use of drugs otherwise indicated for the management of risk factors and that may improve liver pathology (e.g. metformin, glitazones, and statins), or other agent, including vitamin E, silymarin, phosphatidylcholine, and UDCA, was reported repeatedly: Asia [83], France [84], Germany [80], Poland [67], Romania [85], Russia [77] and the USA [86].

Current guidelines emphasize that supportive evidence for some treatments is lacking or inadequate (e.g. metformin and UDCA). However, usage of products such as vitamin E, UDCA, phosphatidylcholine, and silymarin) and drugs classes, such as antidiabetics (glitazones, GLP-1 antagonists) and statins is observed in real-life practice. Clinical evidence from multiple sources reviewed in guidelines from EASL [26], the Asia-Pacific region [28], and the USA [27] does not indicate a clear benefit in terms of reducing fibrosis, but does suggest that tolerability is generally acceptable. On the other hand, a number of small but promising clinical trials, the results of which were not available when the guidelines were being developed, suggest that GLP-1 RAs and SGLT-2 inhibitors offer promise in the management of NAFLD across NASH and cardiometabolic endpoints [16,47]. Further investigations in clinical trials are needed to better understand the therapeutic effects of these treatments on steatohepatitis and fibrosis in NAFLD [33].

4. Discussion and conclusion

This literature review identified the availability of current clinical guidelines that offer recommendations for the identification, evaluation, and management of the growing number of patients with NAFLD or at risk of NASH in the absence of approved pharmacological interventions. However, despite broad consistencies in their approach, inconsistencies across guidelines and gaps in recommendations that support their application risk suboptimal clinical practice, including the

identification of those individuals most at risk of severe disease who require referral to specialist care. This is supported by observational data from routine clinical practice.

Although extensive clinical guidelines on the screening, diagnosis, and management of NAFLD have been published, the real-world evidence that we have discussed reveals substantial shortfalls in disease awareness and management, patient education, and adherence to therapeutic programs, as well as physician practice, referral, and the off-label use of pharmacological agents. Rates of awareness were lowest among primary care physician and non-gastroenterology /hepatology specialists [55,65,75]. The risk of under-recognition due to low awareness of patients with or at risk of NASH/cirrhosis is compounded by low rates of referral from primary care and 'other' specialists to gastroenterologists or hepatologists [65–68]. This is a particular clinical concern in cases where patients with normal liver enzymes who are, nevertheless, at high risk of NAFLD are overlooked in primary care [65,84]. Consequently, rates of NAFLD and the associated clinical, healthcare system and economic burden continue to increase.

Education about NAFLD and relevant guidelines would help primary care physicians overcome the reported lack of comfort dealing with liver diseases [61,76,87,88]. When asked, general physicians expressed requirements for improved levels of awareness, knowledge and confidence to allow improved identification and management of liver disease [87,88]. As patients may be referred back to primary care for lifestyle modification therapy in some systems [61], there remains an unmet need for development of skills and the use of multidisciplinary care to optimize early management of NAFLD in community and primary health services, and streamline specialist hepatology care accordingly [39,73,74,76].

Although the majority of clinicians recognize and adhere to recommendations for lifestyle modification through physical activity and diet, as we describe here, patients often appear not to understand the therapeutic intent of such interventions and have poor adherence to them. Consequently, the potential benefits of dietary control and physical activity may be limited.

Dietary supplements and hepatoprotective agents are commonly used, despite variable evaluations in clinical guidelines. Guidelines allow for some off-label use of drugs to aid management of NAFLD, specifically reducing impact of risk factors, and based on limited evidence, improving disease pathology. However, pharmacotherapy usage is commonly reported in observational studies. Despite substantial investment in clinical development, pharmacological treatment has yet been approved for advanced disease, despite the existence of evidence that interventions can reduce steatosis and dysmetabolism. The absence of clear, evidence-based recommendations for pharmacotherapy of NAFLD is partly due to the practical challenges of designing and implementing trials of new drugs in NAFLD impeding progress [49] and partly due to the timing of data availability versus guideline development [47].

In advanced disease, including end-stage liver disease, surgical interventions involving highly specialized, targeted care can offer major clinical benefits. We did not examine data relating to bariatric surgery in the publications we reviewed. Likewise, there were no evaluations of the outcomes of liver transplantation, although there is growing evidence that it can be beneficial in suitably selected patients [51–54]. However, the cost-effectiveness and long-term effectiveness of bariatric surgery for weight loss and liver transplantation to correct liver failure require more evidence in the context of the increasing burden of NAFLD and its consequences.

In conclusion, despite the availability of clinical recommendations and guidelines for the diagnosis and management of NAFLD, real-world practice reveals substantial disparities in levels of application and outcomes. The evidence indicates a need for education, training, and development of algorithms to close the gap between current and optimal screening, diagnosis, and management of NAFLD. This needs to be supplemented by healthcare policy and associated structural developments to turn recommendations into actionable patient care.

5. Expert opinion

Since the mid-2010s, multiple national clinical guidelines for the diagnosis, assessment, and management of NAFLD and NASH has been published (in English). The need for such clinical guidance reflects the growing prevalence of NAFLD and its increasing health, humanistic, and economic burden, particularly among those who have or are at risk of developing NASH and/or fibrosis. However, challenges persist in the optimal identification of these patients and their direction into appropriate specialist care must be prioritized to reduce the impact of NAFLD on individual and public health.

Application of guideline recommendations for promotion of lifestyle changes is often suboptimal. To date, no drugs have received regulatory approval for the treatment of NAFLD or NASH. All guidelines included weak recommendations for pharmacological support, restricted to patients diagnosed with NASH with or at risk of fibrosis or disease progression. Investigational drugs have reached late phases of development, but none to date have demonstrated benefit–risk profiles likely to be acceptable to health regulators. Overall, NAFLD clinicals are therefore limited in terms of recommendations for the management of progressive, advanced disease.

In practice, awareness of NAFLD, its diagnosis, and management remain poor outside of specialist hepatology. We suggest that poor guidance and education may result in suboptimal rates of diagnosis, and potentially leading to cases of serious, potentially life-threatening NASH being overlooked. There is a clear need for education and for integration across healthcare disciplines to improve identification of at-risk individuals and to optimize referral pathways. Development and adoption of algorithms for sequential screening and diagnosis of NAFLD and risk assessment based on these guidelines could help address this need.

Although early intervention may help to minimize the health impact of NAFLD, patients frequently appear not to understand the therapeutic intent of such interventions and rates of adherence to such recommendations are low. In this context, the recent recommendations from the international Liver Forum's Standard of Care Working Group proposing

standardized core features of lifestyle modification assessment and implementation in the management of NAFLD, principally to refine measurement of outcomes in clinical trials, are important to highlight [89].

We believe that harmonizing clinical guidelines and developing clear, easily applied screening and assessment algorithms will help establish optimum pathways of care for patients with NAFLD. In the first instance, this will help to streamline referral and monitoring of individuals according to disease status and severity as well as risk of progression, making the most of current options for clinical care. It would also aid efficient allocation of health resources and budgets. By optimizing current resources, the true extent of unmet needs in NAFLD and NASH management can be fully understood, which will help the development of new pharmacological interventions on a background of best practice in both primary care and specialist hepatology services. Identification of clinical trial populations, definitions of care in the control arms of randomized clinical trials, and selection of endpoints and appropriate size effects for assessment of efficacy will be central to improving drug development and assessment of agents approved for other, physiologically relevant conditions. Additionally, the development and routine implementation of precision medicine based on genetic screening will help to direct efficient and optimal management using available resources and agents as they evolve.

There is encouraging evidence that this optimization of care and identification of trial-ready patient populations is beginning to be realized. Published models of care, although limited in number, demonstrating impacts on outcomes and cost efficiencies are becoming available. Likewise, testable, algorithms for sequential assessment of patients at risk of advanced NASH fibrosis are in the literature. To fully assess standards of care, there is a need for large, long-term, international observational studies to fully understand the state of current practice such as the European NAFLD Registry [90] and the TARGET-NASH study [91]. The results of these investigations can help identify and support the development of new paradigms to inform updated, refined guidelines in the light of current challenges. Improved standards of care will help to define patient cohorts and clinical outcomes for the investigation and development of new interventions aimed at alleviating the growing burden of NAFLD and NASH.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Lindenmeyer CC, McCullough AJ. The natural history of nonalcoholic fatty liver disease-an evolving view. Clin Liver Dis. 2018;22(1):11–21.
2. Huber Y, Boyle M, Hallsworth K, et al. Health-related quality of life in nonalcoholic fatty liver disease associates with hepatic inflammation. Clin Gastroenterol Hepatol. 2019;17(10): 2085–2092. e1.

•• **Highlights substantial burden of symptoms experienced by patients with NAFLD.**

3. Younossi ZM, Stepanova M, Anstee QM, et al. Reduced patient-reported outcome scores associate with level of fibrosis in patients with nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol. 2019;17(12): 2552–2560. e10.

•• **Data from 1667 patients show impact on patient-reported outcomes of NASH with AF.**

4. O'Hara J, Finnegan A, Dhillon H, et al. Cost of non-alcoholic steatohepatitis in Europe and the USA: the GAIN study. JHEP Rep. 2020;2(5):100142.
5. Alexander M, Loomis AK, Fairburn-Beech J, et al. Real-world data reveal a diagnostic gap in non-alcoholic fatty liver disease. BMC Med. 2018;16(1):130.

6. Allen AM, Therneau TM, Larson JJ, et al. Nonalcoholic fatty liver disease incidence and impact on metabolic burden and death: a 20 year-community study. Hepatology. 2018;67(5):1726–1736.
7. Mahfood Haddad T, Hamdeh S, Kanmanthareddy A, et al. Nonalcoholic fatty liver disease and the risk of clinical cardiovascular events: a systematic review and meta-analysis. Diabetes Metab Syndr. 2017;11(Suppl 1):S209–S216.
8. Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 2018;15(1):11–20.
9. 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(1): 73–84.
   - **Evidence suggests that NAFLD burden will greatly increase in the future as obesity becomes more prevalent.**
10. Ofosu A, Ramai D, Reddy M, et al. Non-alcoholic fatty liver disease: controlling an emerging epidemic, challenges, and future directions. Ann Gastroenterol. 2018;31(3):288–295.
11. Sahota AK, Shapiro WL, Newton KP, et al. Incidence of nonalcoholic fatty liver disease in children: 2009-2018. Pediatrics. 2020;146(6): e20200771.
12. Castillo-Leon E, Cioffi CE, Vos MB, et al. Perspectives on youth-onset nonalcoholic fatty liver disease. Endocrinol Diabetes Metab. 2020;3 (4):e00184.
13. Loomba R, Wong R, Fraysse J, et al. Nonalcoholic fatty liver disease progression rates to cirrhosis and progression of cirrhosis to decompensation and mortality: a real world analysis of medicare data. Aliment Pharmacol Ther. 2020;51(11): 1149–1159.
   - **NAFLD is often overlooked despite being associated with significant mortality.**
14. Tanase DM, Gosav EM, Costea CF, et al. The intricate relationship between type 2 diabetes mellitus (T2DM), insulin resistance (IR), and nonalcoholic fatty liver disease (NAFLD). J Diabetes Res. 2020;2020:3920196.
15. Labenz C, Prochaska JH, Huber Y, et al. Cardiovascular risk categories in patients with nonalcoholic fatty liver disease and the role of low-density lipoprotein cholesterol. Hepatol Commun. 2019;3 (11):1472–1481.
16. Niederseer D, Wernly B, Aigner E, et al. NAFLD and cardiovascular diseases: epidemiological, mechanistic and therapeutic considerations. J Clin Med. 2021;10(3):467.
17. American Diabetes Association. 4. Comprehensive medical evaluation and assessment of comorbidities: standards of medical care in diabetes-2020. Diabetes Care. 2020;43(Suppl 1):S37–S47.
18. 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(3):505–515.
19. Liu YL, Patman GL, Leathart JBS, et al. Carriage of the PNPLA3 rs738409 C>G polymorphism confers an increased risk of non-alcoholic fatty liver disease associated hepatocellular carcinoma. J Hepatol. 2014;61(1):75–81.
20. Eslam M, Valenti L, Romeo S, et al. Genetics and epigenetics of NAFLD and NASH: clinical impact. J Hepatol. 2018;68(2):268–279.
21. Weinmann A, Alt Y, Koch S, et al. Treatment and survival of non-alcoholic steatohepatitis associated hepatocellular carcinoma. BMC Cancer. 2015;15(1):210.
22. Global Burden of Disease (GBD) 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: a systematic analysis for the global burden of disease study 2017. Lancet Gastroenterol Hepatol. 2020;5(3):245–266.
23. Loomba R, Lim JK, Patton H, et al. AGA clinical practice update on screening and surveillance for hepatocellular carcinoma in patients with nonalcoholic fatty liver disease: expert review. Gastroenterology. 2020;158(6):1822–1830.
24. Huang DQ, El-Serag HB, Loomba R, et al. Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 2021;18(4):223–238.
25. JM S, Jv L, PN N, 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. Feb 15;Online ahead of print.
26. EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64 (6):1388–1402.
27. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American association for the study of liver diseases. Hepatology. 2018;67(1):328–357.
28. Chitturi S, Wong VW, Chan WK, et al. The Asia-Pacific working party on non-alcoholic fatty liver disease guidelines 2017-part 2: management and special groups. J Gastroenterol Hepatol. 2018;33 (1):86–98.
29. Wong VW, Chan WK, Chitturi S, et al. Asia-Pacific working party on non-alcoholic fatty liver disease guidelines 2017-part 1: definition, risk factors and assessment. J Gastroenterol Hepatol. 2018;33 (1):70–85.
30. Lonardo A, Nascimbeni F, Targher G, et al. AISF position paper on nonalcoholic fatty liver disease (NAFLD): updates and future directions. Dig Liver Dis. 2017;49(5):471–483.
31. National Institute for Health and Care Excellence. Non-alcoholic fatty liver disease: assessment and management (NG49). 2016. Available from: https://www.nice.org.uk/guidance/ng49
32. 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 (6):467–473.
33. Fan JG, Wei L, Zhuang H, et al. Guidelines of prevention and treatment of nonalcoholic fatty liver disease (2018, China). J Dig Dis. 2019;20(4):163–173.
34. Leoni S, Tovoli F, Napoli L, et al. Current guidelines for the management of non-alcoholic fatty liver disease: a systematic review with comparative analysis. World J Gastroenterol. 2018;24 (30):3361–3373.
35. Schattenberg JM, Anstee QM, Caussy C, et al. Focused literature review of studies on non-alcoholic fatty liver disease (NAFLD) management in clinical practice: consistency of and adherence to clinical guidelines. Hepatology. 2020;72(1 (Suppl):917A. abstract 1514.
36. Lazarus JV, Ekstedt M, Marchesini G, et al. A cross-sectional study of the public health response to non-alcoholic fatty liver disease in Europe. J Hepatol. 2020;72(1): 14–24.
   - **Expert survey findings highlighted the lack of appropriate public health strategies and poor education about NAFLD across Europe.**
37. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American gastroenterological association, American association for the study of liver diseases, and American college of gastroenterology. Gastroenterology. 2012;142(7):1592–1609.
38. Boursier J, Tsochatzis EA. Case-finding strategies in non-alcoholic fatty liver disease. JHEP Rep. 2020;3(2):100219.
39. Caballeria L, Augustin S, Broquetas T, et al. Recommendations for the detection, diagnosis and follow-up of patients with non-alcoholic fatty liver disease in primary and hospital care. Med Clin (Barc). 2019;153(4):169–177.
40. Castera L. Non-invasive tests for liver fibrosis in NAFLD: creating pathways between primary healthcare and liver clinics. Liver Int. 2020;40(Suppl S1):77–81.
41. Pandyarajan V, Gish RG, Alkhouri N, et al. Screening for nonalcoholic fatty liver disease in the primary care clinic. Gastroenterol Hepatol. 2019;15(7):357–365.
42. National Institute for Health and Care Excellence. Obesity: identification, assessment and management (CG189). 2014. Available from: https://www.nice.org.uk/guidance/cg189
43. Carlsson B, Lindén D, Brolén G, et al. Review article: the emerging role of genetics in precision medicine for patients with non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2020;51 (12):1305–1320.

44. Berzigotti A, Boursier J, Castera L, et al. EASL clinical practice guidelines (CPGS) on non-invasive tests for evaluation of liver disease severity and prognosis - 2020 update. J Hepatol. 2021:S0168-8278-(21)00398–6. (Epub ahead of print).
45. Campos-Murguía A, Ruiz-Margáin A, González-Regueiro JA, et al. Clinical assessment and management of liver fibrosis in non-alcoholic fatty liver disease. World J Gastroenterol. 2020;26 (39):5919–5943.
46. Lazarus JV, Anstee QM, Hagström H, et al. Defining comprehensive models of care for NAFLD. Nat Rev Gastroenterol Hepatol. 2021a; ePub ahead of print. DOI:10.1038/s41575-021-00477-7.
47. Dougherty JA, Guirguis E, Thornby KA, et al. A systematic review of newer antidiabetic agents in the treatment of nonalcoholic fatty liver disease. Ann Pharmacother. 2021;55(1):65–79.
48. Jph W, RL B, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med. 2021;384(11):989.
49. Drenth JPH, Schattenberg JM. The nonalcoholic steatohepatitis (NASH) drug development graveyard: established hurdles and planning for future success. Expert Opin Investig Drugs. 2020;29 (12):1365–1375.
50. Xanthakos SA. Pharmacological, endoscopic, metabolic, and surgical procedures for nonalcoholic fatty liver disease. Clin Liver Dis. 2021;17(3):209–214.
51. Laursen TL, Hagemann CA, Wei C, et al. Bariatric surgery in patients with non-alcoholic fatty liver disease - from pathophysiology to clinical effects. World J Hepatol. 2019;11(2):138–149.
52. Chaim FDM, Pascoal LB, Chaim FHM, et al. Histological grading evaluation of non-alcoholic fatty liver disease after bariatric surgery: a retrospective and longitudinal observational cohort study. Sci Rep. 2020;10:8496.
53. Lee Y, Doumouras AG, Yu J, et al. Complete resolution of nonalcoholic fatty liver disease after bariatric surgery: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2019;17(6):1040–1060.e11.
54. Jayakumar S. Liver transplantation for non-alcoholic fatty liver disease—a review. AME Med J. 2018;3(2):29.
55. Roden M, Popovic B. Drivers of diagnosis and referral decisions in non-alcoholic fatty liver disease in patients. J Hepatol. 2020;73: S426. (Abstract FRI053).
56. Cleveland ER, Ning H, Vos MB, et al. Low awareness of nonalcoholic fatty liver disease in a population-based cohort sample: the CARDIA study. J Gen Intern Med. 2019;34(12):2772–2778.
57. Singh A, Dhaliwal AS, Singh S, et al. Awareness of nonalcoholic fatty liver disease is increasing but remains very low in a representative US cohort. Dig Dis Sci. 2020;65(4):978–986.
58. Alemany-Pagès M, Moura-Ramos M, Araújo S, et al. Insights from qualitative research on NAFLD awareness with a cohort of T2DM patients: time to go public with insulin resistance?. BMC Public Health. 2020;20(1):1142.
59. Avery L, Exley C, McPherson S, et al. Lifestyle behavior change in patients with nonalcoholic fatty liver disease: a qualitative study of clinical practice. Clin Gastroenterol Hepatol. 2017;15(12):1968–1971.
60. 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. 2021b;3(2):100234.
61. Sheridan DA, Aithal G, Alazawi W, et al. Care standards for non-alcoholic fatty liver disease in the United Kingdom 2016: a cross-sectional survey. Frontline Gastroenterol. 2017;8(4):252–259.
62. Blond E, Disse E, Cuerq C, et al. EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease in severely obese people: do they lead to over-referral?. Diabetologia. 2017;60(7):1218–1222.
63. Sberna AL, Bouillet B, Rouland A, et al. European association for the study of the liver (EASL), European association for the study of diabetes (EASD) and European association for the study of obesity (EASO) clinical practice recommendations for the management of non-alcoholic fatty liver disease: evaluation of their application in people with type 2 diabetes. Diabet Med. 2018;35(3):368–375.
64. Rowe IA. Too much medicine: overdiagnosis and overtreatment of non-alcoholic fatty liver disease. Lancet Gastroenterol Hepatol. 2018;3(1):66–72.
65. Patel PJ, Banh X, Horsfall LU, et al. Underappreciation of non-alcoholic fatty liver disease by primary care clinicians: limited awareness of surrogate markers of fibrosis. Intern Med J. 2018;48(2):144–151.
66. Wieland AC, Quallick M, Truesdale A, et al. Identifying practice gaps to optimize medical care for patients with nonalcoholic fatty liver disease. Dig Dis Sci. 2013;58(10):2809–2816.
67. Ciećko-Michalska I, Szczepanek M, Tobiasz-Adamczyk B, et al. Non-alcoholic fatty liver disease in Poland: how and at what stage is diagnosed, and how is treated. A survey study. Przegl Gastroenterol. 2019;14(3): 173–177.
68. Marjot T, Sbardella E, Moolla A, et al. Prevalence and severity of non-alcoholic fatty liver disease are underestimated in clinical practice: impact of a dedicated screening approach at a large university teaching hospital. Diabet Med. 2018;35(1):89–98.
69. Byrne CD, Targher G. EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease: is universal screening appropriate?. Diabetologia. 2016;59 (6):1141–1144.
70. Sebastiani G, Cocciolillo S, Mazzola G, et al. Application of guidelines for the management of nonalcoholic fatty liver disease in three prospective cohorts of HIV-monoinfected patients. HIV Med. 2020;21(2):96–108.
71. Fowell AJ, Fancey K, Gamble K, et al. Evaluation of a primary to secondary care referral pathway and novel nurse-led one-stop clinic for patients with suspected non-alcoholic fatty liver disease. Frontline Gastroenterol. 2020;12(2):102–107.
72. Patel P, Hossain F, Horsfall LU, et al. A pragmatic approach identifies a high rate of nonalcoholic fatty liver disease with advanced fibrosis in diabetes clinics and at-risk populations in primary care. Hepatol Commun. 2018;2(8):893–905.
73. 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(2):371–378.
74. Srivastava A, Jong S, Gola A, et al. Cost-comparison analysis of FIB-4, ELF and fibroscan in community pathways for non-alcoholic fatty liver disease. BMC Gastroenterol. 2019;19 (1):122.
75. Polanco-Briceno S, Glass D, Stuntz M, et al. Awareness of non-alcoholic steatohepatitis and associated practice patterns of primary care physicians and specialists. BMC Res Notes. 2016;9 (1):157.
76. Serfaty L. Management of patients with non-alcoholic steatohepatitis (NASH) in real life. Liver Int. 2018;38(Suppl 1):52–55.
77. Maev IV, Samsonov AA, Palgova LK, et al. Real-world comorbidities and treatment patterns among patients with non-alcoholic fatty liver disease receiving phosphatidylcholine as adjunctive therapy in Russia. BMJ Open Gastroenterol. 2019;6(1):e000307.
78. Haigh L, Bremner S, Houghton D, et al. Barriers and facilitators to Mediterranean diet adoption by patients with nonalcoholic fatty liver disease in Northern Europe. Clin Gastroenterol Hepatol. 2019;17(7):1364–1371. e3.
79. Hallsworth K, Avery L, Trenell MI, et al. Targeting lifestyle behavior change in adults with NAFLD during a 20-min consultation: summary of the dietary and exercise literature. Curr Gastroenterol Rep. 2016;18(3):11.
80. Hofmann WP, Buggisch P, Schubert L, et al. The fatty liver assessment in Germany (FLAG) cohort study identifies large heterogeneity in NAFLD care. JHEP Rep. 2020;2(6):100168.
81. Hallsworth K, Dombrowski SU, McPherson S, et al. Using the theoretical domains framework to identify barriers and enabling factors to implementation of guidance for the diagnosis and management of nonalcoholic fatty liver disease: a qualitative study. Transl Behav Med. 2020;10(4):1016–1030.
82. Kaundinya T, Mazumder N, Atiemo K, et al. Health literacy gaps in online resources for cirrhotic patients. J Curr Surg. 2020;10(1–2):1–6.
83. Chan WK, Treeprasertsuk S, Imajo K, et al. Clinical features and treatment of nonalcoholic fatty liver disease across the Asia Pacific region-the GO ASIA initiative. Alimentary Pharmacol Ther. 2018;47(6):816–825.

84. Ratziu V, Cadranel JF, Serfaty L, et al. A survey of patterns of practice and perception of NAFLD in a large sample of practicing gastroenterologists in France. J Hepatol. 2012;57(2):376–383.
85. Iacob S, Ester C, Lita M, et al. Real-life perception and practice patterns of NAFLD/NASH in Romania: results of a survey completed by 102 board-certified gastroenterologists. J Gastrointestin Liver Dis. 2016;25(2):183–189.
86. Rinella ME, Lominadze Z, Loomba R, et al. Practice patterns in NAFLD and NASH: real life differs from published guidelines. Therap Adv Gastroenterol. 2016;9(1):4–12.
87. HC S, Jarvis H, Orr J, et al. GPs' experiences and perceptions of early detection of liver disease: a qualitative study in primary care. Br J Gen Pract. 2018;68(676):e743–e749.
88. Sanyal AJ. Putting non-alcoholic fatty liver disease on the radar for primary care physicians: how well are we doing?. BMC Med. 2018;16(1):148.
89. Glass O, Filozof C, Noureddin M, et al. Standardisation of diet and exercise in clinical trials of NAFLD-NASH: recommendations from the liver forum. J Hepatol. 2020;73(3):680–693.
90. Hardy T, Wonders K, Younes R, et al. The European NAFLD registry: a real-world longitudinal cohort study of nonalcoholic fatty liver disease. Contemp Clin Trials. 2020;98:106175.
91. Barritt AS 4th, Gitlin N, Klein S, et al. Design and rationale for a real-world observational cohort of patients with nonalcoholic fatty liver disease: the TARGET-NASH study. Contemp Clin Trials. 2017;61:33–38.