Quality standards for the management of non-alcoholic fatty liver disease (NAFLD): consensus recommendations from the British Association for the Study of the Liver and British Society of Gastroenterology NAFLD Special Interest Group

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Non-alcoholic fatty liver disease (NAFLD) is common, affecting approximately 25% of the general population. The evidence base for the investigation and management of NAFLD is large and growing, but there is currently little practical guidance to support development of services and delivery of care. To address this, we produced a series of evidence-based quality standard recommendations for the management of NAFLD, with the aim of improving patient care. A multidisciplinary group of experts from the British Association for the Study of the Liver and British Society of Gastroenterology NAFLD Special Interest Group produced the recommendations, which cover: management of people with, or at risk of, NAFLD before the gastroenterology or liver clinic; assessment and investigations in secondary care; and management in secondary care. The quality of evidence for each recommendation was evaluated by the Grading of Recommendation Assessment, Development and Evaluation tool. An anonymous modified Delphi voting process was conducted individually by each member of the group to assess the level of agreement with each statement. Statements were included when agreement was 80% or greater. From the final list of statements, a smaller number of auditable key performance indicators were selected to allow services to benchmark their practice. It is hoped that services will review their practice against our recommendations and key performance indicators and institute service development where needed to improve the care of patients with NAFLD.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is common, affecting approximately 25% of the population in many developed countries.[1] The disease ranges from steatosis to non-alcoholic steatohepatitis (NASH; fat with hepatocyte injury and hepatic inflammation) and can progress to cirrhosis and liver-related complications including hepatocellular carcinoma and liver failure.[2] Individuals with NAFLD have an increased risk of overall mortality compared with the general population, and common causes of death include cardiovascular disease, malignancy, and liver-related complications.[3–5] Most of the estimated 14·1 million individuals with NAFLD in the UK remain undiagnosed and, worryingly, the prevalence of advanced fibrosis and cirrhosis is projected to double to 1 million individuals by 2030.[6] Despite the high prevalence of NAFLD in the population, recognition and management of the condition is variable across the UK. One multicentre study from England found large variability in the primary and secondary care management of NAFLD, with clear deficiencies identified in primary care investigations, fibrosis staging, provision of lifestyle treatments, and assessment and management of cardiovascular risk factors.[7] There is therefore a clear need to improve the holistic management of patients with NAFLD to achieve better outcomes.

The purpose of this work was to develop a series of quality standard recommendations from a multidisciplinary panel of experts for the management of patients with NAFLD to provide a standardised management approach, with the ultimate objective of reducing variability in care nationally. In addition, we have developed a series of auditable key performance indicators to measure practice against to help drive service improvement.

Methods

A group of experts from the British Association for the Study of the Liver and British Society of Gastroenterology NAFLD Special Interest Group developed the recommendations. SM and WA chaired the group. All members of the NAFLD Special Interest Group were invited to participate via email and those expressing an interest were included in the working group. Ultimately, the working group included a multidisciplinary team of 29 individuals from hepatology, diabetes, dietetics, hepatology specialist nursing, pathology, primary care, psychology, pharmacy, and physiotherapy. The group also included a representative from the British Liver Trust (VH). The group was subdivided into three working groups that led the writing of draft recommendations for one of three parts of the document: management of people with, or at risk of, NAFLD before the gastroenterology or liver clinic (lead LC); assessment and investigations in secondary care (lead MJA); and management in secondary care (lead JFC).

Each group produced a list of key topics in the NAFLD diagnosis and management pathway to address within

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the standards document. A literature search was conducted using PubMed/MEDLINE to identify relevant original research papers and existing guidelines published from database inception to June 30, 2021. Specific statements were then made by each group, informed by the quality of the evidence evaluated in line with the Grading of Recommendation Assessment, Development and Evaluation (GRADE) tool. SM and WA amalgamated the draft statements from the three working parties and removed any duplication. An anonymous modified Delphi voting process was conducted individually by each member of the working group using an online survey tool to assess the level of agreement with each statement on a five-point scale (strongly disagree, disagree, neutral, agree, or strongly agree). Given the working group was multidisciplinary, members could abstain from questions that related to areas outside their usual clinical practice (eg, a dietitian may not feel qualified to make clinical decisions regarding when to perform a liver biopsy). After each round of voting, statements were redrafted if necessary through a combination of discussions via teleconference meetings and email. Agreement was defined when statements received a score of strongly agree or agree. Statements were included where agreement was 80% or greater, after exclusion of any abstentions. The result of this process produced a series of recommendations, with a corresponding level of expert agreement and grading of the relevant evidence.

From this final list of statements, a smaller number of auditable key performance indicators were selected to allow services to benchmark their practice. These indicators were chosen on the basis of their potential to influence patient outcomes as well as being easily measurable.

Quality standards

Following the Delphi voting process and the review of evidence, 34 quality standard recommendations (table 1) were made covering the management of NAFLD in the community and in secondary care. A review of the supporting evidence is shown below. In addition, 11 auditable key performance indicators were developed (table 2).

Management of people with, or at risk of, NAFLD before the gastroenterology or liver clinic

Identification of people with NAFLD

Use of defined pathways for the investigation of suspected liver disease has been shown to increase the diagnosis of clinically significant liver disease and reduce unnecessary referrals.[8,9] Therefore, services should have an agreed local clinical pathway for the investigation of suspected liver disease that includes an assessment for liver fibrosis using available non-invasive liver fibrosis tests (recommendation 1, table 1). Key aspects to consider when developing pathways are described below.

NAFLD is considered to be the hepatic manifestation of metabolic syndrome (defined as any three of the following: impaired fasting glucose or type 2 diabetes; hypertriglyceridaemia; low HDL; increased waist circumference or high blood pressure).[10] As well as NAFLD being highly prevalent in people with type 2 diabetes or metabolic syndrome, the presence of these risk factors is associated with more progressive liver disease in NAFLD.[11] Therefore, one should consider the possibility of liver fibrosis due to NAFLD in individuals with type 2 diabetes or the metabolic syndrome (recommendation 2, table 1).

Proactive assessment for the presence of liver fibrosis in patients at risk can permit earlier identification of significant liver disease.[12–14] The Scarred Liver Project,[15] which offered community fibrosis testing to people with diabetes or obesity alongside those with hazardous alcohol consumption, identified 3688 patients at risk from a cohort of 25 018. Overall, 20% of at-risk individuals who attended a follow-up clinic had evidence of significant liver disease. Furthermore, a study including FIB-4 testing in annual diabetes reviews in primary care, followed by transient elastography in patients with an indeterminate or high FIB-4, found that 4·5% of the cohort had previously undiagnosed advanced liver disease, defined as imaging, endoscopic or biopsy evidence of cirrhosis, portal hypertension, or hepatocellular carcinoma.[16]

Evidence to support a case-finding strategy among people with relevant risk factors is currently limited and remains an area of divergence between current European and north American clinical guidelines.[17,18] However, it is likely that a fibrosis risk-based approach in primary care would be more successful—and cost-effective—for the early identification of liver disease than reliance on abnormal liver function or incidental finding of steatosis on imaging.[19] However, it is also important to acknowledge that greater efforts to investigate and identify advanced liver disease in this group might result in a substantial increase in primary and secondary care workload, and local service development considerations should be planned accordingly.

Liver blood tests

Liver blood tests, including alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin, and gamma glutamyl transferase (GGT), are frequently included as part of routine clinical investigation in primary care. While unexplained persistently abnormal liver blood tests should always be investigated, normal liver blood tests do not exclude NAFLD or significant fibrosis.[17,18] In a study of 223 patients with biopsy-proven NAFLD, ALT more than two times the upper limit of normal (>70 IU/L) had a sensitivity of just 50% and specificity of 61% for NASH, and a sensitivity of 40% and specificity of 58% for advanced fibrosis.[20] Moreover, the serum ALT level typically decreases as liver fibrosis progresses and patients with

cirrhosis frequently have a normal range ALT level.[21] Therefore, one should not rely on abnormal liver blood tests to prompt consideration of liver disease. However, persistently unexplained abnormal liver blood tests should always be investigated (recommendation 3, table 1).

Patients with abnormal liver blood tests should be evaluated in line with national recommendations,[22] with a focused history eliciting risk factors for chronic liver disease including unhealthy alcohol consumption, the presence of metabolic risk factors, and a detailed drug history. Automated systems, such as intelligent liver function tests, can streamline the investigation of abnormal liver blood tests, giving a full panel of results, a suggested diagnosis, and advice for further management.[8] This approach increases the diagnosis of liver disease and is cost-effective.

	Quality of evidence	Agreement	Responses
Management of people with, or at risk of, NAFLD before the gastroenterology or liver clinic			
1. Services should have an agreed local clinical pathway for the investigation of suspected liver disease that includes an assessment for liver fibrosis using available non-invasive liver fibrosis tests	Low	100%	100% strongly agree
2. Consider the possibility of liver fibrosis due to NAFLD in people with type 2 diabetes or metabolic syndrome	Low	96%	70% strongly agree, 26% agree, 4% neutral
3. Do not rely on abnormal liver blood tests to prompt consideration of liver disease. However, persistently unexplained abnormal liver blood tests should always be investigated	Low	96%	67% strongly agree, 29% agree, 4% neutral
4. The finding of liver steatosis on ultrasound, or unexplained abnormal liver blood tests, should prompt risk assessment for liver fibrosis	Low	100%	89% strongly agree, 11% agree
5. Use validated widely available non-invasive tests (eg, FIB-4 score or NAFLD fibrosis score) with high negative predictive value to risk assess for clinically significant liver fibrosis in the community	Moderate	100%	85% strongly agree, 15% agree
6. Refer patients stratified as high risk for advanced fibrosis or cirrhosis to a hepatologist. For patients stratified as indeterminate risk, offer further discriminatory tests (eg, transient elastography or Enhanced Liver Fibrosis test) or refer for further evaluation	Low	100%	67% strongly agree, 33% agree
7. Manage people at low risk of significant fibrosis in the community, with focus on lifestyle advice and cardiovascular risk reduction. Reassess fibrosis using non-invasive tests every 3 years	Low	100%	62% strongly agree, 38% agree
8. Secondary care liver services and community services should collaborate on audits, research, and education to share knowledge, strengthen links, and encourage service and quality improvement, and involve patients as part of this as appropriate	Not graded	92%	69% strongly agree, 23% agree, 8% neutral
Assessment and investigations in secondary care			
9. Patients with NAFLD should be assessed for additional causes of steatosis (eg, drugs and alcohol) and undergo investigations for other causes of liver disease (ie, completion of blood aetiology screen) if these were not already done in primary care	Low	100%	85% strongly agree, 15% agree
10. Patients with NAFLD should have a detailed alcohol (eg, AUDIT-C), illicit drug, and smoking history documented	Moderate	100%	67% strongly agree, 33% agree
11. Practitioners should document a treatment history and medicines use review. The rationalisation of medicines that may accelerate disease progression should be considered	Low	100%	65% strongly agree, 35% agree
12. An assessment of dietary habits and physical activity levels should be obtained	Low	93%	67% strongly agree, 26% agree, 7% neutral
13. Patients with NAFLD should undergo sequential use of a simple non-invasive test (eg, FIB-4) and specialist non-invasive tests (eg, Enhanced Liver Fibrosis test, transient elastography, or acoustic radiation force impulse elastography) to assess the severity of fibrosis	Moderate	96%	69% strongly agree, 27% agree, 4% disagree
14. Patients with NAFLD should be considered for a liver biopsy in the following situations: (A) if there is diagnostic uncertainty (other aetiologies or overlap conditions); (B) to evaluate the severity of NASH and be considered for potential drug therapies (including clinical trials); or (C) to determine the stage of liver fibrosis where non-invasive tests are inconclusive to aid with future management (eg, F4 for hepatocellular carcinoma surveillance)	Moderate	92%	50% strongly agree, 42% agree, 8% neutral
15. Liver biopsies should be processed, stained, and examined according to the UK Royal College of Pathologists guidelines and reported by pathologists who participate in the liver External Quality Assurance scheme using a validated score such as the NASH Clinical Research Network criteria (NAS) or steatosis activity fibrosis (SAF) score	Low	96%	56% strongly agree, 40% agree, 4% neutral
16. Patients with NAFLD cirrhosis should be offered surveillance for complications of cirrhosis, including hepatocellular carcinoma and varices, in accordance with national or international recommendations. The Baveno VI exclusion criteria should be considered as a non-invasive tool to rule out the presence of varices requiring treatment	Moderate	100%	79% strongly agree, 21% agree
17. People with NAFLD should undergo systematic assessment of cardiovascular risk factors including use of an objective risk score (eg, QRISK-3)	High	96%	55% strongly agree, 41% agree, 4% neutral
18. Patients with NAFLD should be screened annually for type 2 diabetes (using HbA_{1c}), hypertension, and dyslipidaemia	Low	85%	46% strongly agree, 39% agree, 11% neutral, 4% strongly disagree

(Table 1 continues on next page)

	Quality of evidence	Agreement	Responses
(Continued from previous page)			
Management in secondary care			
19. People with NAFLD should be asked about smoking and, if they smoke, should be advised to stop and offered referral to smoking cessation services	High	100%	67% strongly agree, 33% agree
20. People with NAFLD should be advised on the benefits of regular exercise; a baseline assessment of physical activity should be made and individualised advice given to increase physical activity	Moderate	92%	78% strongly agree, 14% agree, 4% neutral, 4% strongly disagree
21. Patients with NAFLD should have a regular reassessment of their alcohol consumption	Low	100%	50% strongly agree, 50% agree
22. Abstinence from alcohol should be strongly recommended to patients with NAFLD and cirrhosis. Patients with pre-cirrhotic NAFLD should be advised that alcohol consumption may accelerate disease progression and so should minimise or abstain from alcohol to reduce the risk of disease progression	Low	100%	69% strongly agree, 31% agree
23. Tailored dietary advice should be given with the aim of 5–10% bodyweight loss through a calorie deficit including, but not limited to, reduction of refined carbohydrates and processed foods, and increased consumption of vegetables, lean protein sources, and fish. Referral to weight management services should be considered, especially if weight loss goals have not been achieved	Low	100%	54% strongly agree, 46% agree
24. Referral for consideration of bariatric surgery should be considered in patients with NAFLD with obesity who meet the eligibility criteria for bariatric surgery according to national recommendations	Moderate	96%	50% strongly agree, 46% agree, 4% disagree
25. People with NAFLD who are at significantly increased risk of disease progression and potential risk of liver-related complications should continue to be managed in the secondary care setting. Such patients include those with cirrhosis or clinically significant or advanced fibrosis whose liver disease is not outweighed by comorbidities or performance status	Low	100%	42% strongly agree, 58% agree
26. Patients with decompensated liver disease caused by NAFLD should be considered for transplant assessment	Moderate	96%	78% strongly agree, 18% agree, 4% neutral
27. Patients with hypertension should be managed in accordance with NICE guidelines	High	100%	76% strongly agree, 24% agree
28. Patients who are at increased cardiovascular risk (type 2 diabetes, QRISK-3 >10%, or both) should be offered HMG-CoA reductase inhibitor (statin) treatment in accordance with NICE guidelines	High	100%	76% strongly agree, 44% agree
29. Statins should not be withheld from patients with NAFLD, including those with compensated cirrhosis, because hepatotoxicity is very rare and the benefits are likely to significantly outweigh the risks	Moderate	100%	64% strongly agree, 36% agree
30. In people with NAFLD and type 2 diabetes, treatment with glucose-lowering agents that promote weight loss and reduce cardiovascular risk should be considered	Moderate	96%	77% strongly agree, 19% agree, 4% neutral
31. Patients with NAFLD should be considered for research studies and offered the opportunity to participate in clinical trials where available	Not graded	100%	85% strongly agree, 15% agree
32. Management of patients with advanced NAFLD in secondary care should be by multidisciplinary teams with expertise in clinical hepatology, management of diabetes and cardiovascular risk factors, lifestyle intervention, and health promotion (diet, exercise, and physical activity)	Low	92%	58% strongly agree, 34% agree, 4% neutral, 4% disagree
33. In patients discharged to primary care, recommendations should be made about triggers for re-referral back to secondary care liver services	Low	100%	65% strongly agree, 35% agree
34. Patients should be provided with written information about NAFLD and weight management in a format appropriate to their needs and signposted to other credible sources of information such as the National Health Service and the British Liver Trust	Not graded	100%	65% strongly agree, 35% agree

NAFLD=non-alcoholic fatty liver disease. NASH=non-alcoholic steatohepatitis. NICE=UK National Institute for Health and Care Excellence.

Table 1: **Summary of the NAFLD quality standard recommendations**

Liver fibrosis assessment

An increasing body of evidence has demonstrated that advancing liver fibrosis is the key predictor of liver-related events and mortality in patients with NAFLD.[4] Patients with advanced fibrosis and cirrhosis (equivalent to Brunt fibrosis stage 3 or 4) are at increased risk of complications of chronic liver disease, decompensation, liver transplantation, and death in the short to medium term.[5,23–25]

Since liver blood tests and ultrasound poorly discriminate fibrosis stage, primary care pathways for patients with NAFLD should assess for the presence of advanced fibrosis and cirrhosis using validated non-invasive fibrosis tests.[22] Accordingly, we suggest the finding of liver steatosis on ultrasound, or unexplained abnormal liver blood tests, should prompt risk assessment for liver fibrosis (recommendation 4, table 1). Validated widely available non-invasive tests with high negative predictive value should be used to risk assess for significant liver fibrosis in the community (recommendation 5, table 1). Patients stratified as high risk for advanced fibrosis or cirrhosis should be referred to a hepatologist. For patients stratified as indeterminate risk, offer further discriminatory tests (eg, transient

elastography or Enhanced Liver Fibrosis [ELF] test) or refer for further evaluation (recommendation 6, table 1).

Indirect biomarkers of liver fibrosis, such as FIB-4 and NAFLD fibrosis score (NFS), have been shown to have prognostic value for long-term outcomes and are validated against liver biopsy with good negative predictive value to rule out advanced liver fibrosis in NAFLD.[21,26,27] They combine routinely applied laboratory tests with clinical parameters and are easily applicable. Patients with a FIB-4 index of less than 1·3 (or <2·0 if >65 years) or NFS of less than –1·455 (or <0·12 if >65 years) have a low probability of having advanced fibrosis and can be reassured.[28–30] Of note, neither the FIB-4 nor the NFS have been validated in patients under 35 years of age.[29] Evidence for the performance of other biomarkers such as ELF or transient elastography in young patient cohorts is also lacking, so non-invasive tests should be interpreted with caution in this age group.

Exemplar pathways exist, as recently reviewed.[31] The Camden and Islington NAFLD pathway stratified fibrosis in over 1450 patients with NAFLD over 2 years using FIB-4 in all patients and ELF test in FIB-4 indeterminate cases.[9] Patients identified as high risk for advanced fibrosis and cirrhosis were re-assessed in secondary care; the odds of detecting advanced fibrosis were five times higher and the odds of detecting cirrhosis three times higher in the Camden and Islington pathway versus in the normal pathway. There was an 81% reduction in referrals of patients with mild disease in comparison to the absence of any defined care pathway.

A number of cost-effectiveness studies have demonstrated the benefit of such risk stratification strategies. The use of serum markers and elastography, either alone or in combination, has been shown to be clinically effective and cost saving compared to standard care.[32–34]

Patients stratified as high risk for advanced fibrosis or cirrhosis whose liver disease is not outweighed by comorbidities or performance status should be referred to a hepatologist or gastroenterologist with an interest in liver disease for further evaluation of their condition.

For patients stratified as indeterminate risk for advanced fibrosis or cirrhosis using simple non-invasive tests, the result is neither sensitive nor specific enough to confidently rule in or rule out advanced fibrosis or cirrhosis. A second tier liver fibrosis test such as a direct collagen biomarker (eg, ELF) or elastography (eg, transient elastography) should be offered.[22] Although the optimum pathway has not yet been determined, liver stiffness measurement (LSM) by transient elastography of more than 8 kPa or an ELF of more than 9·5 has been used to prompt referral to secondary care liver services among existing pathways.[32]

Ideally, second-stage non-invasive testing should be delivered in the community to reduce the unnecessary referral to secondary care for some individuals with a false-positive simple non-invasive test result. However, when these services are not available in the community, patients should be referred to secondary services for further workup.[32]

Most liver-related complications in patients with NAFLD occur in those with cirrhosis.[4] Non-invasive tests have high negative predictive values for advanced fibrosis, so they can reliably exclude the presence of cirrhosis. Moreover, long-term follow-up studies have shown that patients with low-risk non-invasive test results have a low risk of liver-related events in the short to medium term, and their main morbidity is cardiovascular disease and non-hepatic malignancy.[26,35] One long-term follow-up study of 1057 patients showed that individuals with NAFLD and a FIB-4 score of less than 1·3 had a low incidence rate for liver-related events of 2·6 per 1000 patient years.[36] Therefore, for these patients the focus should be on lifestyle advice and cardiovascular risk reduction with the aim of improving their overall quality and length of life (figure). NAFLD can progress to advanced fibrosis in a substantial proportion of patients in the medium term, particularly those with, or who develop, type 2 diabetes and those who gain weight.[37] Therefore, individuals with these risk factors should be targeted for more proactive lifestyle modification, optimisation of treatment for type 2 diabetes, and cardiovascular risk reduction. Accordingly, those at low risk of significant fibrosis should be managed in the community, with a

	Minimum standard	Aspirational standard
Management of people with, or at risk of, NAFLD before the gastroenterology or liver clinic		
1. Services should have an agreed local clinical pathway for the investigation of suspected liver disease that includes an assessment for liver fibrosis using available non-invasive liver fibrosis tests	100%	Not applicable
2. Individuals referred to secondary care with suspected NAFLD should have their non-invasive fibrosis staging (eg, FIB-4 score or NAFLD fibrosis score) documented in the referral letter	90%	100%
Investigations and management in secondary care		
3. People with NAFLD should have their weight and body-mass index documented	90%	100%
4. People with NAFLD should have an alcohol history documented and advice given, when appropriate	90%	100%
5. People with NAFLD should have a smoking history documented and advice given, when appropriate	90%	100%
6. People with NAFLD should undergo liver fibrosis staging using available non-invasive tests or liver biopsy	90%	100%
7. People with NAFLD should be screened for type 2 diabetes	90%	100%
8. People with NAFLD should be screened for hypertension	90%	100%
9. Patients with NAFLD should have weight loss advice documented, including objective goals for weight change and physical activity	90%	100%
10. Patients who are at increased cardiovascular risk (type 2 diabetes, QRISK-3 >10%, or both) should be offered statin treatment in accordance with UK National Institute for Health and Care Excellence guidelines	90%	100%
11. Patients should be provided with written information about NAFLD and weight management, or signposted to credible information sources	90%	100%

NAFLD=non-alcoholic fatty liver disease.

Table 2: **Auditable key performance indicators for the management of patients with suspected NAFLD**

focus on lifestyle advice and cardiovascular risk reduction. Risk should be reassessed using non-invasive tests after 3 years (recommendation 7, table 1).

Given fibrosis progresses in a substantial proportion of individuals with NAFLD, repeated fibrosis assessment is required in individuals who remain at risk. The interval for a repeat fibrosis assessment is proposed to be 1–3 years in a recent clinical practice guideline on non-invasive fibrosis assessment.[38] Taking into account that the time to progression by one stage of liver fibrosis is estimated to be between 7 and 14 years,[39] a 3-year interval is a realistic timeframe to reassess fibrosis. In individuals with NAFLD and no evidence of significant liver fibrosis who have no risk factors for fibrosis progression and achieve weight loss goals, it might be appropriate to extend this interval for fibrosis reassessment to 5 years. An automatic recall will need to be built in the patients' electronic records.[32,34]

Service development

Secondary care liver services and community services should collaborate on audits, research, and education to share knowledge, strengthen links, and encourage service and quality improvement, and involve patients as part of this as appropriate (recommendation 8, table 1). Health-care partnerships between primary and secondary care can be helpful to strengthen collaboration and improve outcomes for patients with chronic liver disease. A multidisciplinary liver working group comprising local hepatology or gastroenterology leads, primary care leads for liver disease, strategy leads for commissioners, public health doctors, and public and patient involvement representatives can lead on local service improvement initiatives for patients with chronic liver disease. This approach enables development of strategies tailored to local resources and allows collaboration for development of education programmes for health-care professionals, audit of interventions, and research.

Assessment and investigations in secondary care

Assessment for additional causes for steatosis

Patients with NAFLD should be assessed for additional causes of steatosis (eg, drugs and alcohol) and undergo investigations for other causes of liver disease (ie, completion of blood aetiology screen) if these were not already done in primary care (recommendation 9, table 1). Consumption of alcohol at unhealthy levels is associated with high rates of hepatic steatosis, with half of heavy drinkers of normal body-mass index and more than 90% of obese heavy drinkers affected.[40] In addition, alcohol use among non-heavy drinkers is also associated with an increased risk of steatosis, particularly among those who binge drink.[41] An accurate alcohol history is therefore required, both to identify unsuspected

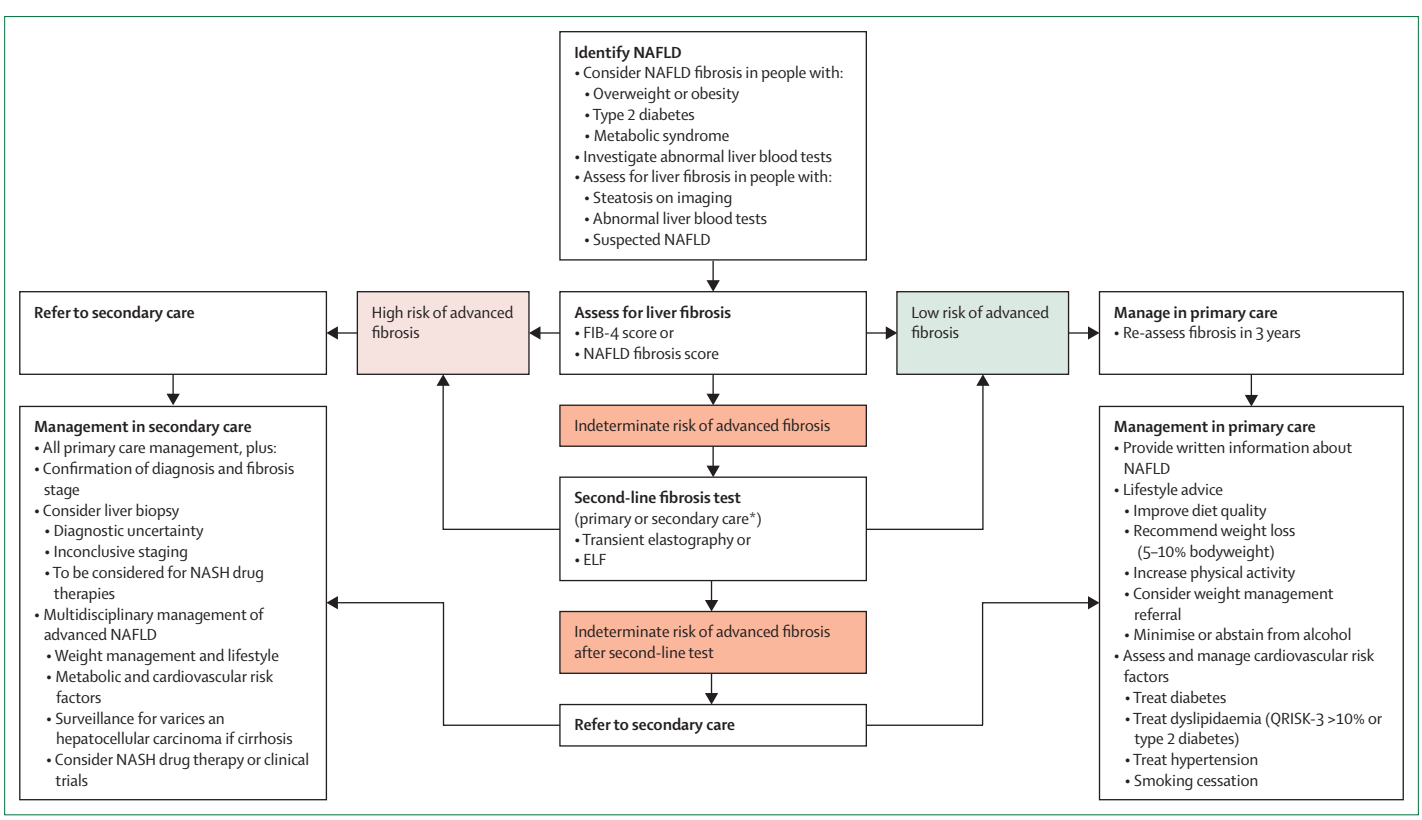

Figure: **An overview of the clinical management of individuals with NAFLD in primary and secondary care**

ELF=Enhanced Liver Fibrosis test. NAFLD=non-alcoholic fatty liver disease. NASH=non-alcoholic steatohepatitis. *Dependent on local clinical pathway.

alcohol-related liver disease, and to facilitate tailored alcohol advice to those who drink within recommended limits. Screening for alcohol misuse, including identification of binge drinking, may be standardised by incorporating a tool such as the AUDIT-C questionnaire[42] into assessment of patients with suspected NAFLD. Therefore, patients with NAFLD should have a detailed alcohol (eg, AUDIT-C), illicit drug, and smoking history documented (recommendation 10, table 1).

Less commonly, other drugs may precipitate hepatic steatosis, with around 2% of cases of NAFLD attributable to prescribed medication.[43] Drugs implicated in steatosis span many classes including anti-arrhythmics (amiodarone), anticonvulsants (carbamazepine, sodium valproate), analgesics (non-steroidal anti-inflammatory drugs), glucocorticoids, anti-metabolites (fluorouracil, methotrexate), oestrogen receptor modulators (tamoxifen), and antiretrovirals (efavirenz).[44,45] Initial assessment of patients with suspected NAFLD should therefore include a drug history, with consideration given to whether medication might be either the precipitant or a cofactor for steatosis. In addition, documenting a smoking history is important, especially given that cigarette smoking is associated with progressive fibrosis and cardiovascular disease.[46,47]

A comprehensive metabolic and serological screen should be undertaken (autoimmune, viral, iron and copper studies, alpha-1 antitrypsin) to consolidate the diagnosis of NAFLD and exclude co-existent liver disease.[22] Genotype 3 strains of hepatitis C virus are associated with increased rates of steatosis,[48] reinforcing the need for viral serology as part of a liver screen for all patients undergoing evaluation for suspected NAFLD.

Treatment history and medicines use review

Individuals with NAFLD frequently have comorbidities and as a result, polypharmacy is common.[49] Therefore, a review of prescribed medications, over-the-counter medications, and alternative or complementary medicines should be undertaken. As discussed above, commonly prescribed agents used to treat other conditions could contribute to hepatic fat accumulation (eg, amiodarone, tamoxifen) or accelerate progression (eg, methotrexate). Although the published literature is at times conflicting, capturing the use of methotrexate (including duration of exposure and cumulative dose) is particularly relevant as it is a potential cofactor promoting presence of a persistent transaminitis or an increased risk of advanced fibrosis or cirrhosis in patients who are overweight or have diabetes.[50,51] Consider recommending the discontinuation of relevant hepatotoxic medications after risk assessment, involving other relevant specialists as necessary. Moreover, it is important to conduct a medicines use review because discrepancies between patient-reported and medical record documented medications exist in more than 50% of patients with liver disease, particularly those taking more than five medications.[52] Accordingly, we suggest that practitioners document a treatment history and medicines use review. The rationalisation of medicines that might accelerate disease progression should be considered (recommendation 11, table 1).

Assessment of dietary habits and physical activity

Poor diet and limited physical activity are common in people diagnosed with NAFLD.[53–55] Nutrition surveys are difficult to interpret, but poor dietary choices are associated with an increased risk of NAFLD, for example consumption of fructose-rich soft drinks[53,56,57] and animal protein.[58–60] Understanding patients' diets can allow for dietary advice to improve health. Changes to diet, including calorie restriction, carbohydrate restriction, or fat reduction, can improve NAFLD;[61,62] encouraging a Mediterranean diet might be more acceptable to patients than these options.[63,64] Increasing physical activity can improve NAFLD;[61,65,66] this could be aerobic exercise or resistance training (or both) in patients with limited mobility.[67] Therefore, an assessment of dietary habits and physical activity levels should be obtained (recommendation 12, table 1).

Non-invasive liver fibrosis assessment

Patients with NAFLD should undergo sequential use of a simple non-invasive test (eg, FIB-4) and specialist non-invasive tests (eg, ELF, transient elastography, or acoustic radiation force impulse [ARFI] elastography) to assess the severity of fibrosis (recommendation 13, table 1). Ideally, an initial fibrosis assessment should have been undertaken in primary care and patients with suspected advanced fibrosis referred to secondary care as they have the greatest risk of hepatic morbidity.[4] In secondary care, fibrosis stage should be confirmed, or second-line testing conducted with more specialist tests in individuals in whom simple non-invasive tests are indeterminate. The performance of biomarkers might be influenced by the prevalence of the target condition in the population being assessed, so clinicians should consider the likely disease prevalence in their practice setting and adopt suitable test thresholds to achieve the desired performance.[68] In general, use of simple non-invasive tests excludes most cases of mild fibrosis.[9,21,29] Addition of a second-line test (eg, ELF, transient elastography, or ARFI) further reduces the number of cases with an indeterminate score, allowing liver biopsy to be reserved for use in a minority of patients for whom it adds additional useful information.[26,69,70] Such two-stage care pathways are currently considered to provide the most robust means for the risk stratification of patients with NAFLD.[31,71] Ongoing regular non-invasive fibrosis reassessment should be considered every 1–3 years to monitor response to treatment or for fibrosis progression.[38]

Liver biopsy

Given the high prevalence of NAFLD in the general population, fatty liver frequently co-exists with other liver diseases (especially viral hepatitis, autoimmune,

and haemochromatosis), thereby necessitating a biopsy to understand their relative contributions to the patient's condition.[72] Furthermore, the diseases may be synergistic—eg, iron overload and NAFLD.[73]

Liver biopsy remains the standard for diagnosing NASH and assessing disease activity (inflammation, ballooning) as there are no approved non-invasive radiological or serological markers specific for NASH. International drug authorities (US Food and Drug Administration and European Medicines Agency) therefore continue to recommend that phase 2/3 clinical trials use liver biopsy to confirm the diagnosis and assess the grade and stage of the disease, to determine trial entry, as well as act as a primary trial endpoint. There has been a recent debate about the role and reliability of histology in this setting.[74,75]

If there is discordance between non-invasive fibrosis markers, a biopsy may be required to stage fibrosis and, most importantly, rule in or rule out cirrhosis.

Patients with NAFLD should therefore be considered for a liver biopsy in the following circumstances: (A) if there is diagnostic uncertainty (other aetiologies or overlap conditions); (B) to evaluate the severity of NASH and be considered for potential drug therapies (including clinical trials); or (C) to determine the stage of liver fibrosis where non-invasive tests are inconclusive to aid with future management (eg, F4 for hepatocellular carcinoma surveillance; recommendation 14, table 1).

The UK Royal College of Pathologists has developed guidelines for the processing, staining, and reporting of liver biopsies[76] and these should be followed. Pathologists who report these biopsies should be active participants in the External Quality Assurance scheme run by the UK Liver Pathology Group. It is recommended that the biopsy reporting include the individual components of either the NASH Clinical Research Network criteria (NAS) or steatosis activity fibrosis (SAF) score with the choice of score being made by agreement with clinicians (recommendation 15, table 1).[77,78]

Surveillance for liver-related complications

Individuals with NAFLD cirrhosis are at risk of complications of cirrhosis, similar to other liver diseases. Therefore, patients should be screened for gastro-oesophageal varices and hepatocellular carcinoma, in accordance with national or international recommendations.[79–81] The Baveno VI exclusion criteria to guide screening for varices (LSM <20 kPa and platelet count >150×10⁹/L) or the expanded Baveno VI criteria (LSM <25 kPa and platelet count >110×10⁹/L) have been validated in NAFLD,[82–84] allowing endoscopy to be safely avoided in these selected patients. At present there is no prospective evidence to support screening for hepatocellular carcinoma in patients with NAFLD without cirrhosis. Accordingly, we suggest patients with NAFLD cirrhosis should be offered surveillance for complications of cirrhosis, including hepatocellular carcinoma and varices, in accordance with national or international recommendations. The Baveno VI exclusion criteria should be considered as a non-invasive tool to rule out the presence of varices requiring treatment (recommendation 16, table 1).

While a higher prevalence of advanced colorectal neoplasms has been reported in patients with NAFLD,[85] there is currently no evidence to recommend surveillance in these individuals over and above the National Health Service (NHS) bowel cancer screening programme.

Cardiometabolic risk assessment

Patients with NAFLD have increased cardiovascular-related morbidity and mortality, largely as a result of the association between NAFLD and metabolic syndrome.[5,86] Cardiovascular disease is the leading cause of death among patients with NAFLD, accounting for more than a third of deaths.[5] The risk of cardiovascular mortality increases with disease severity, with higher rates in patients with biopsy-confirmed NASH and advanced fibrosis.[87] Even though debate remains over the true causal relationship between NAFLD and cardiovascular disease,[86,88] the overall consensus is that traditional cardiovascular risk factors should be actively assessed and modified (when possible) to improve clinical outcomes in patients with NAFLD. Modifiable risk factors of cardiovascular disease include smoking, hypertension, high non-HDL cholesterol, lack of physical activity, unhealthy diet, alcohol intake above recommended levels, and overweight and obesity. In addition, there should be an increased awareness of non-modifiable risk factors including older age, male sex, family history of cardiovascular disease, and ethnic background (especially South Asian origin) when evaluating cardiovascular risk in patients with NAFLD.[89]

Several risk scores (eg, Framingham, QRISK) have been suggested over the years to estimate 10-year risk of cardiovascular disease in the general population. UK guidelines[89] currently recommend the QRISK-3 assessment tool (which includes ethnicity) in all individuals older than 40 years who have no history of cardiovascular disease. Although these guidelines are for asymptomatic individuals and are yet to be validated in patients with NAFLD, there is no reason to suggest that QRISK-3 would not be applicable in NAFLD clinics to guide primary prevention with pharmacological therapy (eg, lipid lowering therapy).[89,90] Therefore, people with NAFLD should undergo systematic assessment of cardiovascular risk factors including use of an objective risk score (eg, QRISK-3; recommendation 17, table 1). Individuals with 10% or greater 10-year risk of developing cardiovascular disease should be offered statin therapy for primary prevention in line with existing guidelines for people at risk of cardiovascular disease.[89,91]

NAFLD has a strong relationship with multi-organ insulin resistance, most notably the liver, muscle, and adipose tissue. NAFLD is associated with a two to five times greater risk of developing type 2 diabetes after adjustment

for several metabolic and lifestyle confounders.[92] We therefore suggest that patients with NAFLD should be screened annually for type 2 diabetes (using HbA_{1c}), hypertension, and dyslipidaemia (recommendation 18, table 1). The American Diabetes Association recommends annual screening for type 2 diabetes in individuals considered to be at high risk of diabetes (ie, those with obesity, older age, first-degree relative with diabetes).[93] The UK National Institute for Health and Care Excellence (NICE) guidelines recommend annual screening for type 2 diabetes among individuals with risk factors and evidence of an elevated plasma fasting glucose and pre-diabetes (defined as an HbA_{1c} 42–47 mmol/mol [6·0–6·4%]).[94] For people with an HbA_{1c} of less than 42 mmol/mol they recommend a reassessment in 3 years.[94] Given NAFLD is recognised as a high-risk group for type 2 diabetes,[34] and for simplicity, we advocate annual screening for diabetes in patients with NAFLD. A HbA_{1c} of 48 mmol/mol (6·5%) or above is diagnostic for type 2 diabetes.[95] The utility and convenience of blood testing for HbA_{1c} in the out-patient setting favours its use over that of fasting glucose sampling or 75 g oral glucose tolerance test.

Patients with NAFLD are at risk of proatherogenic dyslipidaemia characterised by high triglycerides, increased VLDL, and a higher concentration of small dense LDL coupled with low HDL concentrations.[96] In addition, many prospective studies have shown that NAFLD is an independent risk factor for systemic hypertension (a three times greater risk *vs* non-NAFLD),[97] which, when left uncontrolled (clinic blood pressure >130/85 mm Hg), is a major risk of all-cause and cardiovascular-related mortality.[98] Not only are these metabolic conditions treatable (eg, statin, anti-hypertensives), but they can be used as clinical markers to predict patients with NAFLD who are at risk of underlying NASH and progressive fibrosis.[99]

Management of NAFLD in secondary care

Lifestyle management

Tobacco smoking markedly increases the risk of cardiovascular, neoplastic, and respiratory diseases, leading to increased all-cause morbidity and mortality; conversely, smoking cessation reduces age-specific mortality rates.[100] People with NAFLD should be asked about their current and past cigarette smoking history. People who currently smoke should be advised to stop, offered assistance in stopping, and referred to smoking cessation services (recommendation 19, table 1).[101]

People with NAFLD should be advised about the benefits of regular exercise; a baseline assessment of physical activity should be made and individualised advice given to increase physical activity (recommendation 20, table 1). Both aerobic and resistance training are effective in reducing liver fat independently of weight loss.[67] The two types of exercise have different characteristics that make them suitable for different patients: resistance exercise has a lower cardiorespiratory demand so may be preferential for patients with poor baseline fitness or those with comorbidities that prevent participation in aerobic exercise. Recommendations for exercise in NAFLD include 150–300 min per week of moderate intensity aerobic exercise performed over a minimum 3 days a week and resistance exercise on at least 2 days.[102] Most importantly, advice should be individualised to promote adoption and long-term adherence to the physical activity or exercise intervention, which may be facilitated by behaviour change strategies.[103]

The widely accepted European definition of NAFLD emphasises the absence of excessive alcohol consumption (≥30 g per day for men and ≥20 g per day for women) and a quantitative alcohol history is essential for diagnosis.[17] There are additive and synergistic interactions between alcohol and cardiometabolic risk factors in the progression of fatty liver disease.[104] Much of the evidence linking alcohol to health outcomes relies on cohort studies in which alcohol consumption was measured only once at baseline, but it is recognised that alcohol consumption fluctuates widely over the life course.[105] In view of this, we recommend that patients with NAFLD should have a quantitative alcohol history taken at regular intervals (recommendation 21, table 1).

The transition from compensated to decompensated disease is associated with greatly increased morbidity and mortality. In people with alcohol-related liver disease, continued drinking is a stronger risk factor for decompensation than any histological or laboratory parameters.[106] As cofactors, both alcohol use and obesity have been shown to correlate with progression of portal hypertension in chronic liver disease.[107,108]

In patients with NAFLD who do not have cirrhosis, the 2016 NICE clinical guideline reported insufficient evidence to restrict alcohol consumption beyond the national recommended advisory limits.[34] However, alcohol can be a source of additional dietary calories[109] and minimising use may avoid further weight gain with worsening of metabolic risk factors. Accordingly, abstinence from alcohol should be strongly recommended to patients with NAFLD and cirrhosis. Patients with pre-cirrhotic NAFLD should be advised that alcohol consumption may accelerate disease progression and so should minimise or abstain from alcohol to reduce the risk of disease progression (recommendation 22, table 1).

Tailored dietary advice should be given with the aim of 5–10% bodyweight loss through a calorie deficit including, but not limited to, reduction of refined carbohydrates and processed foods, and increased consumption of vegetables, lean protein sources, and fish. Referral to weight management services should be considered, especially when weight loss goals have not been achieved (recommendation 23, table 1). Weight reduction through caloric restriction is fundamental to improving disease severity. Although 5% bodyweight loss improves steatosis,[110] 7–10% is required to positively affect NAFLD activity score and fibrosis.[111,112] Histological

changes achieved by weight loss show a dose–response relationship, with 10% or greater bodyweight reduction associated with NASH resolution and improvement of fibrosis by one stage.[113]

Dietary composition can affect hepatic fat accumulation, particularly if high in saturated fats, processed foods, and refined sugars. However, histological improvement is dependent on the degree of weight loss rather than the method used to achieve it. To date, studies assessing specific diets in NAFLD have been small and limited in their outcomes assessment, so the optimal diet for NAFLD is not known. Given its documented potential to reduce hepatic fat content and have positive effects on cardiovascular risk, the Mediterranean diet is the most widely recommended diet for NAFLD.[114] Taking an individualised approach to promote weight loss and improve diet quality is likely to be the most effective approach. Therefore, referral to weight management services should be considered for specialist dietetic support, pharmacological, or surgical intervention, particularly when dietary goals have not been achieved.

Referral for consideration of bariatric surgery should be considered in patients with NAFLD with obesity and who meet the eligibility criteria for bariatric surgery according to national recommendations (recommendation 24, table 1). NAFLD, across the entire spectrum of severity (including cirrhosis) is highly prevalent in patients with severe obesity.[115] In addition to the established benefits of bariatric surgery (sleeve gastrectomy or roux-en-Y gastric bypass) on morbidity and mortality, there is robust evidence to demonstrate improvements in NAFLD liver histology.[116] Bariatric surgery in patients with NASH can result in NASH resolution; a prospective study of 109 individuals with NASH found 85% (95% CI 75·8–92·2) had resolution on biopsy a year after bariatric surgery.[117] A meta-analysis showed that obesity surgery improves steatosis and steatohepatitis in 88% (95% CI 80–94) and 59% (38–75) of patients respectively, and fibrosis in 30% (21–41).[118] Furthermore, bariatric surgery also improves overall mortality from cardiovascular and malignant causes.

The decision to undertake bariatric surgery needs to be carefully considered in an appropriate multidisciplinary setting. Patients with cirrhosis can undergo bariatric surgery safely[119] and in small case series, bariatric surgery combined with liver transplantation has been performed.[120]

Management of chronic liver disease

Patients with NAFLD who are at risk for development of liver-related complications include those with cirrhosis and clinically significant or advanced fibrosis. These patients need to be managed in a secondary care setting, akin to those with other aetiologies. Regular surveillance of patients with cirrhosis with 6-monthly ultrasound is one of the quality standards laid down by NICE[79] and allows early diagnosis of hepatocellular carcinoma and prompt treatment, which can improve the individual's survival.[121] Regular monitoring also allows early detection and treatment of liver-related complications such as ascites, varices, and hepatic encephalopathy and appropriate referral for liver transplantation once clinical thresholds are met.[122] The process should be individualised wherein patients with significant comorbidities and poor performance status are counselled against active monitoring.[123]

Individuals with NASH who have significant fibrosis (F2), advanced fibrosis (F3), or cirrhosis (F4) are at risk of progression to end-stage liver disease and potential complications in the medium to long term.[4,5,37] Therefore, secondary care follow-up may be appropriate for these individuals to consider specific treatment for NASH or investigational drugs.[17,34] Accordingly, we suggest that people with NAFLD who are at significantly increased risk of disease progression and potential risk of liver-related complications should continue to be managed in the secondary care setting. Such patients include those with cirrhosis or clinically significant or advanced fibrosis whose liver disease is not outweighed by comorbidities or performance status (recommendation 25, table 1).

Patients with decompensated liver disease caused by NAFLD should be considered for transplant assessment (recommendation 26, table 1). This includes patients with jaundice, ascites, hepatic encephalopathy, variceal bleeding, or hepatocellular carcinoma within the accepted UK liver transplant criteria.[124] Factors that can influence the decision to refer for assessment include the presence of life-limiting comorbidities or recent (within 5 years) extrahepatic malignancy (except skin) that would be contraindications to transplantation.

Management of cardiometabolic risk factors

NAFLD is strongly associated with an increased risk of hypertension.[97] Approximately 50% of patients with hypertension have NAFLD and correspondingly the prevalence of hypertension is significantly higher in patients with NAFLD, independently of other cardiometabolic risk factors.[125] In addition to lifestyle advice, pharmacological therapy should be offered to all patients, with the aim of optimising blood pressure and thereby reducing cardiovascular risk.[126] We recommend that patients with hypertension should be managed in accordance with NICE guidelines (recommendation 27, table 1).

Despite the risk of progressive liver disease, the leading cause of death in patients with NAFLD is cardiovascular disease.[127] This increase in mortality from cardiovascular disease in patients with NAFLD is related to shared cardiometabolic risk factors. Patients with more advanced degrees of fibrosis and type 2 diabetes demonstrate a higher propensity to cardiovascular disease.[128,129]

While statins confer a survival benefit in both primary and secondary prophylaxis of cardiovascular events,[130] their use in NAFLD is sometimes limited by concerns

about hepatotoxicity. A pairwise meta-analysis of more than 120 000 people in whom the presence of NAFLD was not recorded reported a small increase in liver dysfunction (odds ratio 1·33, 95% CI 1·12–1·58]) in those receiving statins, but these and other adverse effects did not outweigh the reduction in risk of major cardiovascular events.[131] Conversely, there is evidence of benefit in the context of liver disease: in patients undergoing biopsy for suspected NASH, statin use conferred dose-dependent protection against liver-related histological endpoints, including steatohepatitis and fibrosis.[132] A cross-sectional study of individuals with biopsy-proven NAFLD and type 2 diabetes demonstrated that statins were negatively associated with steatohepatitis and significant fibrosis in multivariate analyses.[133] A recent meta-analysis of eight studies including patients with mixed aetiologies of cirrhosis (n=3195) concluded that statin use was associated with an improvement in portal pressure gradients and a reduced risk of variceal haemorrhage.[134]

Therefore, we recommend that patients who are at increased cardiovascular risk (type 2 diabetes, QRISK-3 >10%, or both) should be offered statin treatment in accordance with NICE guidelines (recommendation 28, table 1). Statins should not be withheld from patients with NAFLD, including patients with compensated cirrhosis, because hepatotoxicity is very rare and the benefits are likely to significantly outweigh the risks (recommendation 29, table 1).

Weight loss and cardiovascular risk reduction are crucial components of the management of patients with both NAFLD and type 2 diabetes. There is robust evidence to demonstrate the cardiovascular benefit of specific classes of glucose-lowering agents, including glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter 2 inhibitors.[135] In addition, both classes of agent promote weight loss and may have a beneficial effect on the liver.[136,137] In line with published guidance,[138] we advocate a low threshold for the preferential use of agents that lower weight and reduce cardiovascular risk in patients with NAFLD to treat their diabetes. Accordingly, in people with NAFLD and type 2 diabetes, treatment with glucose-lowering agents that promote weight loss and reduce cardiovascular risk should be considered (recommendation 30, table 1).

Service considerations

Patients with NAFLD should be considered for research studies and offered the opportunity to participate in clinical trials where available (recommendation 31, table 1). It is recognised in other disease areas that increased participation in research is associated with improved clinical outcomes for patients.[139] NAFLD is a relatively recently described entity with substantial unmet need in terms of understanding of its natural history, diagnostic tests, and treatment to prevent disease progression. These needs can only be addressed through the engagement of people with NAFLD with research. Where research studies are available, these should be offered to appropriate patients to consider participation.

Given the strong relationship between NAFLD and metabolic syndrome, patients with fatty liver frequently have associated metabolic and cardiovascular comorbidity and a holistic approach to their management is advised. Comprehensive management of NAFLD requires expertise in clinical hepatology for diagnosis and staging of NAFLD and management of hepatic comorbidity. Diabetes is often present in advanced NAFLD and this, with optimisation of cardiometabolic risk factors, requires relevant expertise. Lifestyle intervention and health promotion are required to assist sustainable health improvement. International guidelines highlight the multidisciplinary nature of interventions in NAFLD[17,140] and the feasibility and utility of a multidisciplinary clinic has been demonstrated.[141] Therefore, management of patients with advanced NAFLD in secondary care should be by multidisciplinary teams with expertise in clinical hepatology, management of diabetes and cardiovascular risk factors, lifestyle intervention, and health promotion (eg, diet, exercise, and physical activity; recommendation 32, table 1).

In individuals discharged to primary care, recommendations should be made on triggers for re-referral back to secondary care liver services (recommendation 33, table 1). A baseline assessment cannot adequately exclude the future possibility of fibrosis progression and liver-related outcomes, particularly as patients might accumulate, with time, further risk factors and metabolic comorbidities. There is also the possibility of a false negative baseline fibrosis assessment that could lead to an inappropriate patient discharge to primary care. Therefore, there should also be systems in place for the re-evaluation of fibrosis in patients with NAFLD discharged to primary care. The method of fibrosis assessment should be based on local availability and expertise and some patients may require specific follow-up recommendations: for example, it would be inappropriate to use the FIB-4 score to follow up a patient with non-liver related thrombocytopenia because this could lead to a false positive result. Moreover, it may be appropriate to suggest no further fibrosis assessments in patients who have significant comorbidities or frailty for whom management of liver disease would not alter their long-term outcomes.

Other potential triggers for re-referral might include a significant increase in serum liver enzyme values or laboratory indicators of advanced chronic liver disease, such as decreasing albumin, increased prothrombin time, and increased bilirubin. Moreover, the development of type 2 diabetes should prompt a fibrosis reassessment because this has been associated with progression of NAFLD.[37]

Patients should be provided with written information about NAFLD and weight management in a format appropriate to their needs and signposted to other credible

sources of information such as the NHS and the British Liver Trust (recommendation 34, table 1). It is important that high quality information is provided that is based on reliable and up-to-date evidence. This should be provided in a way that patients understand and is easy to use and navigate. Patients should be asked if they have understood the information and prompted to ask further questions. People often feel overwhelmed with information and patients report that they need it to be provided on multiple occasions and in different ways. A 2020 British Liver Trust survey of more than 2000 patients with liver disease[142] found that nine out of ten people tried to find out more about their condition after leaving their clinic appointment, with more than 90% of them looking on the internet, so it is important to provide information that can be taken away and to signpost patients to credible information.[143,144]

Useful web resources include **the British Liver Trust** www.britishlivertrust.org.uk and **the NHS website** www.nhs.uk

Conclusion

The evidence base for investigation and management of NAFLD is large and growing, but there is currently little practical guidance to support development of services and delivery of care. To address this, we have produced a series of evidence-based quality standard recommendations for the management of NAFLD, with the aim of driving improvement of the care of patients with this common condition. Currently there is no high-quality evidence for liver specific management in NAFLD, so the recommendations are likely to evolve as evidence accumulates. It is hoped that services will review their practice against the key performance indicators and institute service development where needed. The NAFLD Special Interest Group will aim to conduct a national audit of the management of NAFLD using the key performance indicators as a benchmark to promote service development.

Contributors

SM and WA were project co-leads and both took part in conceptualisation, data curation and formal analysis, writing of the original draft and reviewing and editing. SM also took part in the methodology. MJA, JFC, and JC were working group leads. MJA, JFC, LC, QMA, RJA, STB, PNB, TMC, RDG, KH, VB, KJ, HJ, JJ, WL, DM, MM, AM, RP, VR, IAR, AS, PT, AIT, JT, EAT, and AY took part in writing of original draft and reviewing and editing.

Declaration of interests

SM personal fees outside the submitted work from Gilead, Intercept, and Novo Nordisk. MJA has received fees for consultancy, advisory boards, and speaking from Novo Nordisk and Norgine. JFC has received fees for consultancy, advisory boards, and speaking from Intercept, Novo Nordisk, canNASH, and AstraZeneca. EAT has received fees for advisory boards and speaking from Falk Pharma, Intercept, Gilead, and Pfizer. AS has received fees for consultancy and speaking from Siemens. STB has received payment for advisory boards and speaking from AbbVie, Gilead, and Intercept. RJA has received honoraria for speaking and advisory board membership from Falk Pharma, Gilead, Intercept, Novartis, and Norgine. DM has received fees for consultancy from Intercept. PNB has received speaking and educational fees from Takeda. RP has received speaking fees and advisory board fees from Siemens, Norgine, Novo Nordisk, and Shionogi. AY has taken part in advisory boards and consultancy for Intercept and Novo Nordisk. HJ has received speaker fees from Intercept. WA has received fees for consultancy and lecturing from AstraZeneca, Janssen, Novo Nordisk, Gilead Science, Intercept, and Coherus and has received competitive grant funding from GSK and Gilead Science. LC has received personal fees outside the submitted work from Norgine, Intercept, and Novo Nordisk. JT has received personal fees outside the submitted work from Novartis and Poxel. QMA is coordinator of the IMI2 LITMUS consortium, which is funded by the EU Horizon 2020 programme and EFPIA. He reports research grant funding from Allergan/Tobira, AstraZeneca, GlaxoSmithKline, Glympse Bio, Novartis Pharma AG, Pfizer Ltd, and Vertex, consultancy on behalf of Newcastle University for 89Bio, Allergan/Tobira, Altimmune, AstraZeneca, Axcella, Blade, BMS, BNN Cardio, Cirius, CymaBay, EcoR1, E3Bio, Eli Lilly & Company, Galmed, Genentech, Genfit, Gilead, Grunthal, HistoIndex, Indalo, Intercept, Inventiva, IQVIA, Janssen, Madrigal, MedImmune, Medpace, Metacrine, NGMBio, North Sea Therapeutics, Novartis, Novo Nordisk A/S, PathAI, Pfizer Ltd, Poxel, ProSciento, Raptor Pharma, Roche, Servier, Terns, The Medicines Company, and Viking Therapeutics, and speaker fees from Abbott Laboratories, Allergan/Tobira, BMS, Clinical Care Options, Falk, Fishawack, Genfit SA, Gilead, Integritas Communications, Kenes, and MedScape. All other authors declared no competing interests.

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