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British Society of Gastroenterology guidelines on the investigation of suspected liver disease in adults

Stuart McPherson ,[1] Jeremy F Cobbold,[2] Ashwin D Dhanda,[3] John F Dillon ,[4] Wenhao Li ,[5] Alastair O'Brien,[5,6] Quentin Mark Anstee,[7] Hazel Borthwick,[8] David Blane,[9] Erica Fairbairn,[10] James Franklin,[11] Girish Gupte,[12] Edmund M Godfrey,[13] Vanessa Hebditch,[14] Helen Jarvis,[15] Teesha Joshy,[16] Laura Kent,[17] Neil McDougall,[18] Nick Murch,[19] Thomas Pembroke,[20] Latif Rahman,[21] James Richards,[22] Jeremy W Tomlinson,[2,23] Palak Trivedi ,[24,25] Peter Walsh,[14] Kim Yun,[26] Ahmed Elsharkawy[25]

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For numbered affiliations see end of article.

Correspondence to
Professor Stuart McPherson; stuart.mcpherson2@nhs.net

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ABSTRACT

Chronic liver disease is increasingly prevalent yet often undiagnosed. The British Society of Gastroenterology (BSG) published guidance on the investigation of abnormal liver blood tests in 2000, and this was comprehensively updated in 2018. Since then, significant developments including the adoption of new nomenclature for steatotic liver disease (SLD), advances in non-invasive fibrosis assessment and expanding strategies for early detection in primary care have necessitated further revision. This update was commissioned by the BSG Clinical Services Committee. The guideline scope was defined a priori and focused on the investigation of adults with suspected liver disease. A multidisciplinary guideline development group generated key clinical questions and conducted a systematic literature review. Recommendations were formulated using Appraisal of Guidelines for Research and Evaluation II (AGREE II) and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology. Major updates include integration of the revised SLD terminology, updated pathways for fibrosis risk stratification, and recommendations on targeted case finding in groups at highest risk, including people with type 2 diabetes mellitus and those with harmful alcohol consumption. Clear, evidence-based recommendations are presented for the investigation of abnormal liver blood tests, evaluation of imaging findings suggestive of liver disease, case finding among people with recognised risk factors, use of non-invasive fibrosis assessment tools and indications for referral to secondary care. The guidelines aim to standardise diagnostic pathways, facilitate earlier detection of clinically significant liver disease, reduce unwarranted variation and support scalable models of care across primary and secondary healthcare settings.

EXECUTIVE SUMMARY

Investigation of abnormal liver blood tests

Recommendation 1. Initial investigation for potential liver disease should include bilirubin, albumin, alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and a full blood count. (Recommendation Strong, Certainty Moderate)

Recommendation 2. Laboratories should use methodologies that incorporate pyridoxal 5′-phosphate (PLP) supplementation to ensure that accurate results for ALT and aspartate aminotransferase (AST) are obtained. (Recommendation Strong, Certainty Moderate)

Recommendation 3. Laboratory IT systems should have the ability to add reflex tests to initial samples or develop liver function testing profiles (eg, Fibrosis-4 (FIB-4) score, intelligent Liver Function Testing (iLFT)) to facilitate the diagnosis/exclusion of liver disease without the need for additional phlebotomy sessions. (Recommendation Strong, Certainty High)

Recommendation 4. The following groups should have standard liver blood tests: people with non-specific symptoms; clinical or imaging features suggestive of chronic liver disease; risk factors for liver disease or viral hepatitis; people taking hepatotoxic drugs; and people with suspicion of, or confirmed family history of, genetic liver disease. (Recommendation Strong, Certainty High)

Recommendation 5. With reference to liver blood tests, 'abnormal' refers to an analyte that is outside the laboratory reference range. (Not Graded)

Recommendation 6. All people with abnormal liver blood tests, regardless of the degree or duration of elevation, should undergo an aetiology screen and fibrosis assessment, unless a self-limiting cause is clinically apparent. (Recommendation Strong, Certainty High)

Liver aetiology screen

Recommendation 7. A standard first-line liver aetiology screen should include alcohol and medication history, body mass index, blood pressure and blood tests to include: hepatitis B surface antigen (including reflex hepatitis B serology, hepatitis B virus (HBV) DNA and hepatitis D antibody when positive); hepatitis C antibody (with reflex RNA for people who are antibody-positive); antimitochondrial antibody; anti-smooth muscle antibody; antinuclear antibody; serum immunoglobulins; serum ferritin and transferrin saturation; glycated haemoglobin (HbA1c) and lipid profile. (Recommendation Strong, Certainty High)

Recommendation 8. An extended liver aetiology screen may be considered by hepatology specialist services in those with a hepatitic blood profile, including alpha-1-antitrypsin levels, coeliac serology, caeruloplasmin in those under the age of 40 years, extended autoimmune profile and sexually transmitted infection screen. (Recommendation Strong, Certainty High)

Recommendation 9. In people with severely elevated aminotransferase values (>350 IU/L or >10× the upper limit of normal (ULN)), the liver aetiology screen should comprise: hepatitis A immunoglobulin M (IgM), hepatitis B surface antigen (including reflex hepatitis B serology, HBV DNA and hepatitis D antibody when positive), hepatitis C antibody (with reflex RNA for people who are antibody-positive), hepatitis E IgM, acute Epstein–Barr virus (EBV) serology, cytomegalovirus (CMV) IgM, anti-mitochondrial antibody; anti-smooth muscle antibody; antinuclear antibody and serum immunoglobulins. (Recommendation Strong, Certainty Moderate)

Imaging

Recommendation 10. Abdominal ultrasound (US) is recommended as the first-line imaging test for people with raised liver blood tests, suspected liver-associated symptoms and/or fibrosis staging blood tests that indicate possible advanced chronic liver disease. (Recommendation Strong, Certainty Moderate)

Recommendation 11. People with cholestatic liver blood tests in whom hepato-pancreato-biliary (HPB) malignancy is suspected should be referred for pancreatic protocol CT. (Recommendation Strong, Certainty Moderate)

Recommendation 12. Magnetic resonance cholangiopancreatography (MRCP)±MRI pancreas (or pancreatic protocol CT) is recommended following US in people with cholestatic liver blood tests when:

- The US demonstrates biliary thickening or dilatation. (Recommendation Strong, Certainty High)
- Following a normal US scan and a negative liver aetiology screen. (Recommendation Conditional, Certainty Low)

Recommendation 13. MRCP is specifically recommended in people with inflammatory bowel disease and abnormal liver blood tests. (Recommendation Strong, Certainty Moderate)

Incidental findings of suspected liver disease on imaging

Recommendation 14. People with hepatic steatosis identified incidentally on imaging should be clinically assessed to establish the cause, followed by risk stratification for advanced chronic liver disease. (Recommendation Strong, Certainty Low)

Recommendation 15. People with suspected liver disease identified incidentally on imaging should be assessed for liver disease risk factors including alcohol use, cardiometabolic risk factors and bloodborne virus risks, and have a liver aetiology screen and liver fibrosis testing as per Recommendations 7 and 16. (Recommendation Strong, Certainty Moderate)

Fibrosis assessment

Recommendation 16. The liver fibrosis staging pathway in primary care should comprise two-step sequential testing starting with Fibrosis-4 (FIB-4) score, with second-line testing depending on local availability. Second-line fibrosis testing may include Enhanced Liver Fibrosis (ELF) test, vibration-controlled transient elastography (VCTE) or other validated non-invasive tests (NITs). (Recommendation Strong, Certainty High)

Recommendation 17. The aetiology of liver disease should not influence the choice of fibrosis test or the threshold value for alcohol-related liver disease (ALD), metabolic dysfunction-associated steatotic liver disease (MASLD), MASLD with increased alcohol intake (MetALD) or chronic viral hepatitis. (Recommendation Strong, Certainty Moderate)

Recommendation 18. For patients in whom there is a strong clinical suspicion of advanced liver disease, referral to secondary care should be considered, even if initial risk-stratifying fibrosis tests are normal or low risk. (Recommendation Strong, Certainty Moderate)

Referral to secondary care

Recommendation 19. People with unexplained jaundice should be referred urgently to secondary care. (Recommendation Strong, Certainty High)

Recommendation 20. Secondary care referral should be considered when:

- The liver aetiology screen indicates a disease such as autoimmune liver disease, viral hepatitis, haemochromatosis or other rare liver diseases. (Recommendation Strong, Certainty High)
- People have unexplained persistent moderate-severely raised ALT or AST (>5× the ULN). (Recommendation Strong, Certainty Moderate)
- Advice and guidance should be sought from hepatology services if ALP values are >1.5 × the ULN for 6 months or more *with* commensurate anomalies in GGT *and* no alternative explanation (eg, normal imaging, negative autoimmune serology and no compatible drug history). (Recommendation Strong, Certainty Low)

Recommendation 21. People with suspected advanced chronic liver disease (advanced fibrosis or cirrhosis) on non-invasive fibrosis testing (eg, fasting liver stiffness measurement (LSM) ≥10 kPa or ELF≥9.8) should be referred to hepatology services. (Recommendation Strong, Certainty Low)

Recommendation 22. People with features of cirrhosis or portal hypertension on imaging should be referred for specialist management. (Recommendation Strong, Certainty Moderate)

Recommendation 23. In asymptomatic people with mildly raised liver blood tests, a negative liver aetiology screen, low-risk fibrosis markers, normal imaging and without an identified drug or lifestyle aetiology, referral to secondary care is unlikely to change management and guidance may be sought. (Recommendation Conditional, Certainty Low)

Follow-up and monitoring

Recommendation 24. In those without advanced disease, but with ongoing risk factors for progressive liver disease, repeat testing for fibrosis is recommended 3-yearly. (Recommendation Conditional, Certainty Low)

Liver biopsy

Recommendation 25. Liver biopsy may be considered to investigate suspected liver disease in the following situations: unexplained persistently raised liver blood tests, diagnosis of autoimmune hepatitis, staging of liver disease when NITs are indeterminate or discordant and a precise diagnosis may alter management, or as part of a clinical trial/research study. (Recommendation Strong, Certainty Moderate)

Case finding

Recommendation 26. Routine population-wide screening for chronic liver disease in asymptomatic adults is not recommended. (Recommendation Strong, Certainty Moderate)

Recommendation 27. People with type 2 diabetes mellitus (T2DM) should be assessed for the presence of advanced chronic liver disease at diagnosis of T2DM, where appropriate for age (eg, <75 years), comorbidity and performance status (0–1). (Recommendation Strong, Certainty Moderate)

Recommendation 28. When case finding in people with T2DM, a two-step non-invasive fibrosis testing pathway (as per Recommendation 16) should be used to identify those at risk of advanced chronic liver disease. (Recommendation Strong, Certainty Moderate)

Recommendation 29. People with T2DM without evidence of advanced liver fibrosis (eg, FIB-4<1.3, LSM<10 kPa or ELF<9.8 (or age-adjusted thresholds)) should undergo repeat assessment at 5-yearly intervals up to the age of 75 years. (Recommendation Conditional, Certainty Low)

Recommendation 30. Case finding for people with obesity but without T2DM or harmful alcohol intake is not recommended. (Recommendation Conditional, Certainty Low)

Recommendation 31. In people with harmful alcohol consumption (eg, >50 units/week in men, >35 units/week in women), offer non-invasive fibrosis assessment to identify significant/advanced liver disease using two-step sequential fibrosis testing as per Recommendation 16. (Recommendation Strong, Certainty Low)

Recommendation 32. Case finding for advanced chronic liver disease with VCTE should be considered in individuals attending inpatient and outpatient services for alcohol use disorder. (Recommendation Conditional, Certainty Low)

Special circumstances

Recommendation 33. Elevated ferritin values should be investigated according to the British Society of Gastroenterology (BSG)-endorsed British Society of Haematology guidelines. (Not Graded)

Research recommendations

Research Recommendation 1. Further research is required to define the upper limit of normal (ULN) for ALT and AST assays based on sex, age, ethnicity and body weight.

Research Recommendation 2. Research is required to determine whether US aids diagnosis or alters clinical management in asymptomatic individuals with isolated, mildly elevated aminotransferase values.

Research Recommendation 3. Assess the performance characteristics of non-invasive fibrosis test thresholds in case finding versus known disease populations to determine optimal thresholds for use.

Research Recommendation 4. Assessment of the cost-effectiveness of case finding for advanced liver disease in at-risk populations including people with T2DM; people with obesity, but without T2DM; and people with harmful alcohol intake.

Research Recommendation 5. Determine the optimum fibrosis screening strategy for people at risk of advanced liver disease due to alcohol.

Research Recommendation 6. Determine whether case finding for individuals with alcohol use disorder to test for advanced chronic liver disease is clinically and cost effective.

INTRODUCTION

Chronic liver disease is a major public health problem in the UK and worldwide. Globally, liver disease accounts for approximately 2 million deaths per year, largely due to cirrhosis and its complications, and remains a leading cause of premature mortality.[1] In the UK, liver disease accounts for more than 18 000 deaths annually and has shown a marked increase in premature mortality over recent decades, reflecting both greater disease prevalence and late diagnosis in many cases.[2] Common causes of chronic liver disease, including excessive alcohol consumption, metabolic dysfunction-associated steatotic liver disease (MASLD; formerly known as non-alcoholic fatty liver disease (NAFLD)) and viral hepatitis account for more than 90% of chronic liver disease worldwide and, importantly, are potentially preventable.[3] If untreated, these cause hepatocellular injury, which leads to hepatic inflammation and fibrosis, that can progress to cirrhosis and complications such as hepatocellular carcinoma (HCC) or portal hypertension (eg, varices, ascites, hepatic encephalopathy) (figure 1). In addition, there are multiple other less frequent but treatable liver diseases such as hereditary haemochromatosis, alongside rare liver conditions that have a large and disproportionate impact on morbidity and mortality, such as autoimmune liver disease. These entities require prompt diagnosis and treatment to prevent disease progression to cirrhosis and improve health-related quality of life for patients.[4]

Importantly, liver disease is often asymptomatic until advanced stages, with abnormal liver blood tests or signs of liver disease detected incidentally on imaging (eg, steatosis or cirrhosis), representing the only indication of underlying pathology.[5] Timely and appropriate investigation of suspected liver disease therefore remains critical to improving outcomes through early diagnosis, risk stratification and intervention.[6] The previous British Society of Gastroenterology (BSG) guidelines on the investigation of abnormal liver blood tests published in 2018 provided clinicians with evidence-based recommendations for the initial investigation of abnormal liver blood tests, including laboratory assessment and risk stratification for common causes such as alcohol-related liver disease (ALD) and MASLD.[4] Since this publication there have been several developments that necessitate a revision of these guidelines and expansion beyond the investigation of liver blood tests to the investigation of suspected liver disease. These include the reclassification of steatotic (fatty) liver disease (SLD), refinement of diagnostic and staging approaches for liver disease, and studies evaluating case finding for liver disease. A major development was the consensus-based nomenclature change from NAFLD to MASLD in 2023 by an international multisociety group (including the BSG).[7] These changes reflect advances in pathophysiological understanding, emphasising metabolic risk factors rather than exclusion of alcohol intake, and aim to reduce stigma while improving diagnostic clarity. MASLD is now the most common cause of chronic liver disease globally and is a rapidly increasing cause of cirrhosis and HCC.[8] Moreover, a new subtype of SLD, MASLD with increased alcohol intake (MetALD), has been defined to recognise the large cohort of people who have both metabolic risk factors and consume moderately excessive amounts of alcohol. A summary of the diagnostic criteria for SLD is shown in figure 2.

The aim of these guidelines is to provide evidence-based recommendations for the investigation of adults with suspected liver disease across primary and secondary care, incorporating advances since the 2018 guidelines. This update integrates the MASLD nomenclature, evolving non-invasive fibrosis assessment strategies and a risk-based approach to investigation, case finding and referral. The guidelines also seek to promote earlier identification of clinically significant liver disease, reduce unwarranted variation in practice and support efficient use of healthcare resources, while remaining pragmatic and applicable to routine clinical settings.

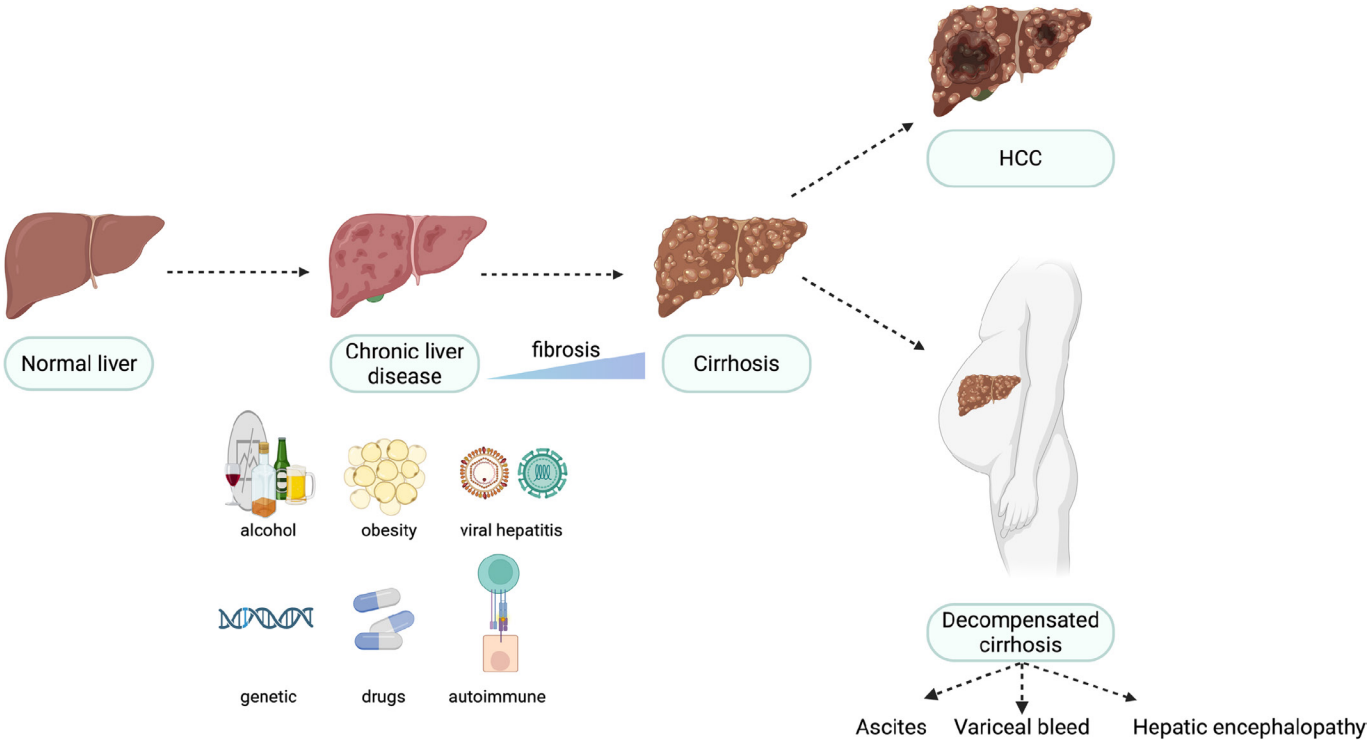


Figure 1 Natural history of liver disease. HCC, hepatocellular carcinoma.

GUIDELINE DEVELOPMENT

Guideline development group and stakeholder involvement

The guidelines were commissioned by the BSG and followed their processes for the development, writing and review of guidelines (2025).[9] A multidisciplinary guideline development group (GDG) was convened, comprising hepatologists, gastroenterologists, radiologists, primary care representatives, acute medicine physicians, liver specialist nurses, a clinical biochemist, a liver surgeon, a pharmacist, a metabolic physician and patient representatives. The following specialist societies and organisations were represented in the GDG to ensure applicability across key stakeholders: Liver UK (formerly British Liver Trust), British Association for the Study of the Liver, Royal College of General Practice, British Society of Gastrointestinal and Abdominal Radiologists, Society for Acute Medicine, Scottish Society of Gastroenterology, Association for Laboratory Medicine, British Liver Nurse Association, British Hepatology Pharmacists Group, Ulster Society of Gastroenterology and the Welsh Association of Gastroenterology and Endoscopy.

Following disclosure of potential conflicts of interest, GDG membership was approved by the BSG. There was full editorial independence from the BSG.

Scope

The scope of the guidelines was agreed a priori and focused on the investigation of adults with suspected liver disease, including those with abnormal liver blood tests or clinical features or incidental imaging suggestive of liver pathology. The guidelines are intended to be of use for all healthcare professionals, with a major focus on the asymptomatic patient with abnormal liver blood tests or suspected liver disease.

Literature search and evidence review

A series of clinical questions were written by the GDG to be addressed by the guidelines. The GDG was divided into four subgroups to address specific questions on common themes. The subgroups reviewed the evidence, developed draft recommendations and wrote supporting text for the recommendations.

A systematic approach to identify evidence published since the previous guidelines was undertaken. Electronic databases including MEDLINE, Embase and the Cochrane Library were searched, supplemented by manual review of reference lists from key articles and relevant international guidelines. Search strategies incorporated terms relating to liver disease aetiologies, diagnostic investigations, non-invasive fibrosis assessment, imaging modalities and evolving disease classifications, including MASLD. Searches were conducted up to 31 December 2025. Data from relevant studies reporting after this date were also included.

Identified studies were screened for relevance by members of the GDG, with priority given to systematic reviews, meta-analyses, randomised controlled trials (RCTs) and high-quality observational studies.

Assessment of evidence and formulation of recommendations

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology was used to assess the certainty of evidence and strength of recommendations.[10] Certainty of evidence was graded as high (high confidence; further research is unlikely to change confidence estimate), moderate (moderate confidence; further research might influence confidence in (or change) the effect estimate), low (low confidence and the true value of the estimate may deviate from the target of the certainty rating) or very low (very low confidence and the true value of the estimate may deviate significantly

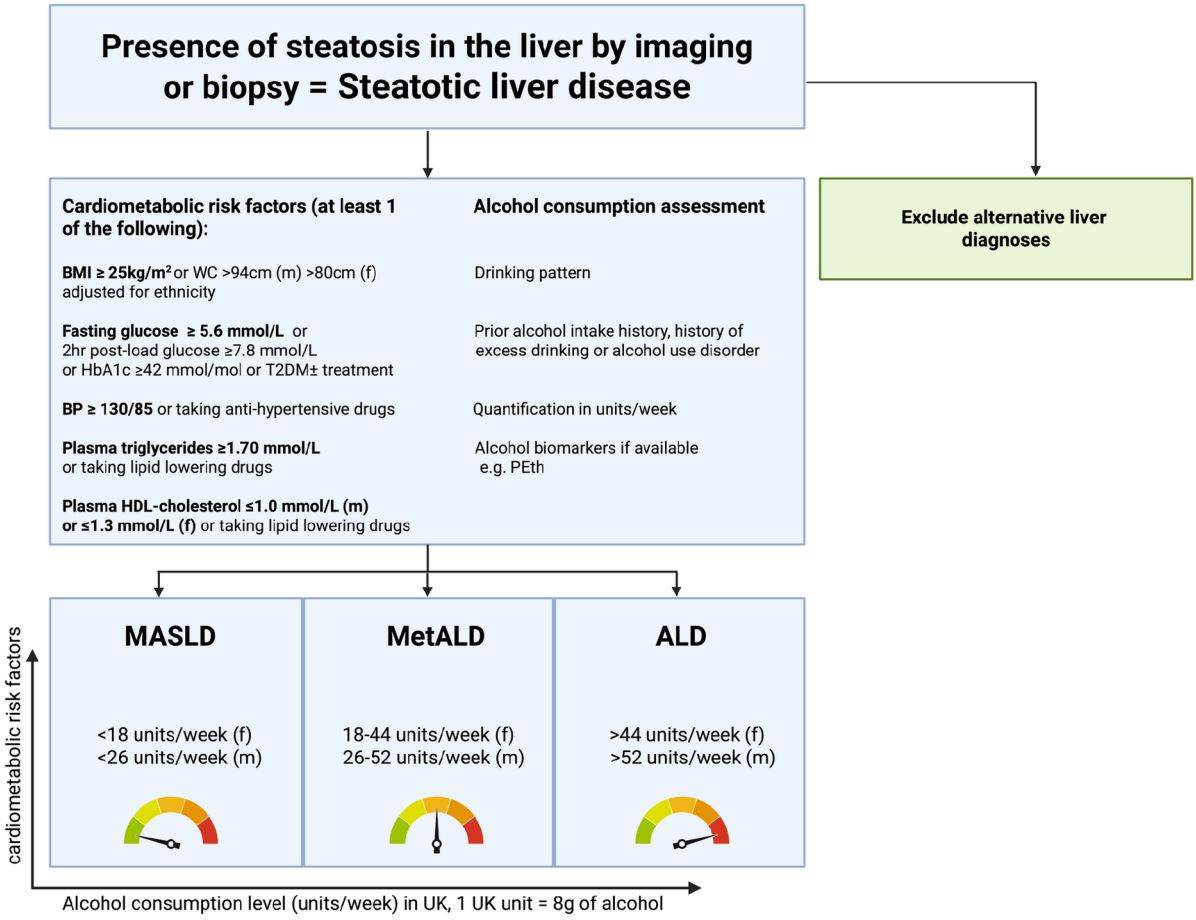


Figure 2 Diagnostic criteria for steatotic liver disease. ALD, alcohol-related liver disease; BMI, body mass index; BP, blood pressure; f, female; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; m, male; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, MASLD with increased alcohol intake; PEth, phosphatidylethanol; T2DM, type 2 diabetes mellitus; WC, waist circumference.

from the target of the certainty rating) based on study design, risk of bias, consistency, directness and precision initially by the subgroups. Recommendations were categorised initially by the subgroups as strong or conditional, considering the balance of benefits and harms, quality of evidence, patient values and preferences and resource implications. Where high-quality evidence was lacking, recommendations were based on expert consensus following structured discussion within the GDG. Where gaps in evidence were identified, recommendations for future research were made.

Table 1 Overview of liver blood tests

Test/component	What it measures	Key causes of elevation/reduction	Clinical interpretation/notes
Bilirubin (total, conjugated, unconjugated)	Breakdown product of haem; liver uptake and conjugation	Unconjugated ↑: haemolysis, impaired conjugation (Gilbert's) Conjugated ↑: parenchymal liver disease, biliary obstruction	Laboratories measure total bilirubin. Isolated high bilirubin usually Gilbert's
Albumin	Liver-produced protein; reflects synthetic function	Reduced in liver disease, sepsis, inflammation, nephrotic syndrome, malabsorption, GI protein loss	Not specific for liver disease; many non-hepatic causes of low albumin
PT/INR	Clotting factor synthesis (II, V, VII, IX, X)	Prolonged in liver dysfunction, vitamin K deficiency, malabsorption, cholestasis	Sensitive marker of synthetic failure; prolonged PT/INR requires differentiation between liver disease vs vitamin K deficiency
Platelets	Indirect marker of fibrosis and portal hypertension	Reduced due to decreased production, splenic sequestration, increased destruction	Most common haematologic abnormality in chronic liver disease; indicates advanced fibrosis
ALP	Cholestasis marker; produced in liver and bone	Raised in PBC, PSC, biliary obstruction, drug-induced cholestasis, bone disease, metastases, pregnancy	GGT helps determine hepatic vs bone origin. Isoenzymes if uncertain
AST and ALT	Hepatocellular injury markers	Raised in hepatitis, alcohol-related disease, AIH, MI, myositis	ALT more liver-specific; AST may rise earlier in alcohol-related or autoimmune disease
GGT	Helps confirm hepatic origin of ALP; cholestasis marker	Raised from alcohol, hepatic steatosis, drugs	Low specificity but strong predictor of liver mortality; confirms hepatic ALP

AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; GI, gastrointestinal; INR, International Normalised Ratio; MI, myocardial infarction; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; PT, prothrombin time.

Draft recommendations and evidence from each subgroup were presented to the whole GDG and statements revised iteratively until consensus was achieved. Final wording of statements and the quality of evidence and grading of provisional recommendations were discussed in a face-to-face meeting (21 January 2026) by the group. For several recommendations, the certainty of evidence was low, but the estimated patient benefit versus risk was high, leading to strong recommendations being made. Recommendations with insufficient evidence to support them were discarded or modified to become research recommendations, where appropriate.

All authors approved of the final recommendations and the submitted manuscript.

Guideline quality assurance

The development and reporting of these guidelines followed the Appraisal of Guidelines for Research and Evaluation II (AGREE II) framework to ensure methodological rigour, transparency and applicability.[11]

Patient and public involvement

Patient representatives (EF and PW) contributed to the guideline development process, including refinement of the scope, consideration of patient-centred outcomes, and review of draft recommendations to ensure clarity and relevance to clinical practice.

Key performance indicators and audit standards

From the final list of recommendations, a smaller number of auditable key performance indicators (KPIs) were selected to allow services to benchmark their practice. These indicators were selected based on their potential to influence patient outcomes as well as being measurable.

Peer review

The draft guidelines were submitted for review by the BSG Liver Section and Clinical Services Committee. Finally, full peer review was undertaken by reviewers selected by the editor of *Gut*.

Scheduled review of the guidelines

The proposed time for review of the guidelines is 5 years to consider new developments. The BSG will be the forum for collecting feedback on these guidelines.

HOW ARE PEOPLE WITH LIVER DISEASE IDENTIFIED?

Most people with liver disease are asymptomatic at presentation and identified incidentally with raised liver blood tests or imaging performed for another reason that identifies features of liver disease during routine care, or through case finding in at-risk groups, such as those with metabolic risk factors, harmful alcohol use, inflammatory bowel disease or at risk for viral hepatitis. An approach to the investigation of suspected liver disease via these routes is presented below.

If symptoms are present, they may include right upper quadrant pain, fatigue and cognitive impairment, nausea or pruritus; or in advanced stages, jaundice, weight loss or sarcopenia, easy bruising, ascites, oedema, confusion (hepatic encephalopathy) or gastrointestinal bleeding.[12 13] Examination findings may be normal but in advanced liver disease may include jaundice, ascites, spider naevi, bruising, oedema, splenomegaly and asterixis.

Table 2 Patterns of abnormal liver blood test abnormalities and common causes

Pattern of liver injury	Characteristic findings	Common causes
Hepatocellular injury (hepatitis)	↑ ALT and AST, normal or mild ↑ ALP	Viral hepatitis (A–E) MASLD/MASH Drug-induced liver injury (eg, paracetamol overdose, rifampicin) Autoimmune hepatitis Ischaemic hepatitis Haemochromatosis Wilson's disease Post heavy exercise
Cholestatic pattern	↑ ALP and GGT predominantly, mild ↑ ALT/AST	Gallstones/choledocholithiasis Primary biliary cholangitis (PBC) Primary sclerosing cholangitis (PSC) Biliary obstruction (malignancy: cholangiocarcinoma, pancreatic cancer) Drug-induced cholestasis (eg, anabolic steroids, co-amoxiclav) Sepsis Sarcoidosis Hepatic congestion
Mixed hepatocellular–cholestatic	Simultaneous ↑ ALT/AST and ↑ ALP	Drug-induced liver injury (mixed pattern: many antibiotics, NSAIDs) Alcohol-related hepatitis Viral hepatitis (some cases, eg, EBV hepatitis) Autoimmune hepatitis/overlap syndromes Hepatic congestion Budd–Chiari syndrome
Isolated bilirubin	↑ Bilirubin (unconjugated)	Gilbert syndrome Haemolysis
AST>ALT pattern	AST>ALT	Alcohol-related hepatitis Cirrhosis of any cause (AST often >ALT) Muscle disease (AST from muscle)/heavy exercise
Isolated ALP elevation	↑ ALP but normal ALT/AST/GGT	Bone disease (Paget's, metastases) Pregnancy Cholestasis – mild or genetic cause
Isolated GGT elevation	↑ GGT alone	Chronic excess alcohol consumption Hepatic steatosis Enzyme induction: phenytoin, carbamazepine

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EBV, Epstein–Barr virus; GGT, gamma-glutamyl transferase; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NSAID, nonsteroidal anti-inflammatory drug.

INVESTIGATION OF ABNORMAL LIVER BLOOD TESTS

Liver blood tests are widely used in primary and secondary care to screen for liver disease, monitor drug-related liver effects and investigate non-specific symptoms. An overview of routinely measured liver blood tests and their clinical significance is shown in table 1. Liver blood tests are commonly abnormal, with one large UK study finding that nearly one-third of more than 130 000 samples from primary care in a year showed at least one abnormal result.[4] A primary care cohort study of almost 3 million people found that approximately 25% of the population had an alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) or bilirubin test performed each year, of which between 8% and 27% were abnormal.[14] Moreover, the ALFIE study in Scotland found that a quarter of adults had liver blood tests over a 10-year period, and one-third of them had at least one abnormal result.[15] Liver blood tests are non-specific and can be raised for a multitude of reasons, including acute self-limiting illnesses, effect of hepatotoxic medications, chronic liver diseases or extrahepatic diseases such as cancer.

Typically, abnormalities in liver enzymes follow characteristic patterns, such as hepatocellular, cholestatic or mixed, which may help determine the underlying cause (table 2). However, while

it should be noted that abnormal liver blood tests can signify underlying liver disease, the ALFIE study found that only 3.9% of people with raised transaminases were diagnosed with significant liver disease by 5 years.[15] Moreover, normal liver blood tests do not exclude liver disease; one study found that 37% of people with cirrhosis had normal liver blood tests.[16] Therefore, liver blood tests alone are neither sufficiently sensitive nor specific for diagnosing or excluding liver disease and additional investigations may be required.

What constitutes a standard liver blood test panel?

Few studies have evaluated the optimal standard liver blood test panel. The 2018 guidelines recommended "initial investigation for potential liver disease includes bilirubin, albumin, ALT, ALP, GGT and a full blood count".[4] This recommendation remains unchanged. The main data supporting this recommendation came from the BALLETS study, which showed that ALT and ALP identified most adults with necro-inflammatory liver disease in a large primary care cohort, while adding GGT increased the sensitivity for detecting MASLD and ALD.[17] In contrast, the routine addition of AST may not improve detection of specific diseases, though it remains clinically useful for calculating non-invasive fibrosis tests such as FIB-4, which can be 'reflex' tested on the same sample in those with raised ALT if needed.

Recommendation 1. Initial investigation for potential liver disease should include bilirubin, albumin, ALT, ALP, GGT and a full blood count. (Recommendation Strong, Certainty Moderate)

Laboratory testing for liver blood tests

Assays that do not incorporate pyridoxal 5′-phosphate (PLP) supplementation generate lower results for ALT and AST than those that do, with a 12%–13% and 18% average difference in ALT and AST, respectively.[18 19] Specific manufacturers' performance demonstrated that the difference between method principles is greater for AST than ALT and is also more noticeable for ALT with the Abbott and Roche Cobas methods than the Beckman AU and Siemens Atellica methods.[20]

The International Federation of Clinical Chemistry (IFCC) recommends that PLP is added to the reaction.[21] The lower ALT and AST levels observed in tests from laboratories not including PLP supplementation may lead to lower FIB-4 scores, potentially leading to reduced sensitivity for advanced fibrosis.

Recommendation 2. Laboratories should use methodologies that incorporate PLP supplementation to ensure that accurate results for ALT and AST are obtained. (Recommendation Strong, Certainty Moderate)

Reflex and automated laboratory testing

When raised liver blood tests are identified, this should trigger two questions:

1. What is the cause of the abnormality?
2. What is the stage of liver fibrosis?

Previous studies have shown that abnormal liver blood tests are frequently not investigated, leading to delays in diagnosis and missed opportunities for treatment.[15] One of the factors that may contribute to people not undergoing further investigations is the need to have further phlebotomy. Reflex testing for second-line tests using the original blood sample can overcome this problem, reducing the need for a further attendance at a healthcare facility. This has been performed for many years in virology, with second-line tests such as hepatitis C virus (HCV) RNA conducted on the original sample to determine whether people with anti-HCV antibody positivity have active HCV infection, and is both clinically and cost effective.[22] Therefore, if there is clear indication of a specific clinical risk—for example, in high-risk groups such as injecting drug users, migrants from high-prevalence areas or prisoners—then some aspects of second-line testing can be undertaken simultaneously.

In many patients with liver injury, an assessment of liver fibrosis is critical in making decisions about referral and management. Clues to the level of liver fibrosis can be gleaned from the use of non-invasive algorithms that include ALT and AST such as the AST/ALT ratio (AAR)[23] or FIB-4 score.[24] An AAR>1 indicates high likelihood of advanced fibrosis/cirrhosis, hence inclusion of this ratio in algorithms has the potential to assess the risk of significant fibrosis in adults with abnormal liver blood tests.[25] While the routine analysis of both AST and ALT on every liver blood test is not justifiable, the introduction of reflex AST testing for people with elevated ALT was introduced in Wales, alongside advice to the general practitioner (GP) to consider referral for fibrosis assessment with vibration-controlled transient elastography (VCTE) for people with an AAR>1, and this significantly increased the diagnosis of cirrhosis.[26]

FIB-4, another simple non-invasive fibrosis test that can exclude advanced fibrosis/cirrhosis with reasonable accuracy,[27] is recommended first line to stage fibrosis in primary care in many guidelines.[28–30] This test requires testing from biochemistry (AST and ALT) and haematology (platelets) and can be automatically calculated within laboratory systems to provide the requestor with the result and relevant clinical advice.[31]

The intelligent Liver Function Testing (iLFT) pathway is a comprehensive, automated system with integrated reflex testing for a blood aetiology screen and fibrosis tests that was developed and validated in Tayside, Scotland.[32 33] The algorithm provides a comprehensive diagnostic and staging platform with an accurate decision-making support tool that provides interpretation of abnormal liver blood tests and fibrosis staging, and clinical advice to the requestor. iLFT underwent an RCT and its use was associated with increased diagnosis of liver disease and improved quality of care by providing appropriate investigation to all people, while remaining cost-effective and reducing GP workload.[33]

Reflex laboratory testing for ELF for people with a raised FIB-4 also significantly increases the proportion of people undergoing complete fibrosis assessment. This was shown in a prospective evaluation of the National Health Service (NHS) England primary care Liver Health Checks pilots, where of the 11 908 people who had FIB-4 testing, people from sites that had reflex Enhanced Liver Fibrosis (ELF) testing were significantly more likely to have complete investigations as per the protocol with ELF and VCTE (65% vs 19%).[34]

Recommendation 3. Laboratory IT systems should have the ability to add reflex tests to initial samples or develop liver function testing profiles (eg, FIB-4, iLFT) to facilitate the diagnosis/exclusion of liver disease without the need for additional phlebotomy sessions. (Recommendation Strong, Certainty High)

Who should have standard liver blood tests?

Liver blood tests are important for detecting and monitoring liver disease in various clinical scenarios. Certain conditions also increase the likelihood of liver disease, warranting proactive testing. Liver blood testing can be considered in the following scenarios.

Non-specific symptoms

Liver disease often progresses asymptomatically, with many cases of advanced liver disease remaining undiagnosed until late stages.[30] Inflammatory liver conditions, such as viral hepatitis or autoimmune hepatitis (AIH), may present with non-specific symptoms like fatigue, nausea or loss of appetite.[35 36] Many individuals who present with chronic cholestatic diseases are also asymptomatic. However, approximately 50% with autoimmune biliary diseases, such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), develop pruritus to some degree, with fatigue, cognitive impairment and 'brain fog' being other well-recognised symptoms. These conditions are treatable, but delayed diagnosis is common. Therefore, non-specific symptoms should prompt routine liver blood tests, acknowledging that these symptoms may have other causes.

Clinical features of chronic liver disease

Patients with clinical signs or symptoms of advanced liver disease, such as cirrhosis, portal hypertension or liver failure, including ascites, peripheral oedema, spider naevi or hepatosplenomegaly, require liver blood tests to assess and monitor function.[13 37]

Imaging features of chronic liver disease

Steatosis, cirrhosis and portal hypertension may all be diagnosed incidentally on imaging tests performed for other reasons. These findings can provide an opportunity for further assessment and intervention.

Risk factors for viral hepatitis

Although chronic viral hepatitis may be associated with non-specific symptoms such as fatigue, most affected individuals are asymptomatic and are diagnosed via risk factor-based testing. Screening for hepatitis B virus (HBV) and HCV is recommended in people with risk factors including blood transfusion prior to 1996, injecting drug use, migration from high-prevalence regions, or incarceration, and close contacts of people with HBV and HCV including household members, children or sexual partners.[38] Screening with serology (table 3) rather than liver blood tests is recommended because liver blood tests are often normal. Universal opt-out testing for bloodborne viruses, including HBV and HCV, is now commonly performed in emergency departments across the UK.[39]

Harmful alcohol consumption

People who consume potentially harmful levels of alcohol are at high risk of developing chronic liver disease.[40] Although liver blood tests may be abnormal in people who consume excess alcohol, ALT, AST and ALP are poor markers for detecting advanced fibrosis or cirrhosis, though their elevation may assist in motivating lifestyle change.[41] The National Institute for Health and Care Excellence (NICE) recommends screening for advanced disease using VCTE, rather than liver blood tests, in individuals drinking at harmful levels (men: >50 units/week, women: >35 units/week for several months) or anyone with known ALD.[37] Case finding for liver disease among those who consume excess alcohol is discussed below.

Risk factors for MASLD

MASLD is closely associated with cardiometabolic risk factors, including obesity and type 2 diabetes mellitus (T2DM), so screening or case finding has been suggested in people with metabolic risk factors.[8] The more metabolic risk factors an individual exhibits, the greater the risk of steatohepatitis and progressive fibrosis. A standard liver blood test panel has low sensitivity for MASLD and advanced fibrosis/cirrhosis, and is not recommended by NICE.[42] However, raised liver blood tests in people with risk factors for MASLD should prompt liver fibrosis assessment. Risk-based approaches are more effective for detecting clinically significant MASLD and are discussed below (Recommendations 26–29).

Risk factors for autoimmune liver disease

People with autoimmune conditions, such as inflammatory bowel disease (IBD), rheumatoid arthritis or systemic lupus erythematosus, have a higher likelihood of developing autoimmune liver diseases, including AIH, PBC and PSC.[36] Symptoms such as pruritus (particularly common in PBC), tiredness or jaundice should prompt liver blood testing.[43]

PSC occurs in up to 4.3% of people with IBD, with higher rates reported in people with extensive pancolitis (5%–7%) or pancolitis with colorectal dysplasia (14%–21%).[44–46] PSC-IBD carries increased risks of liver-related complications compared with individuals with IBD alone (recurrent cholangitis, cirrhosis, cholangiocarcinoma and colorectal cancer).[47] Routine liver blood tests are advised for all IBD patients, and even mild cholestatic abnormalities (eg, raised ALP or GGT) should be further evaluated with magnetic resonance cholangiopancreatography (MRCP).[48] MRCP is also recommended to screen for PSC in people with right-sided predominant colitis or right-sided colorectal cancer.[46 49]

Use of hepatotoxic medications

Many medications are associated with drug-induced liver injury (DILI), some with predictable patterns of injury and others idiosyncratic.[50] Commonly implicated drugs include paracetamol, carbamazepine, co-amoxiclav, flucloxacillin, methyldopa, minocycline, macrolide antibiotics, rifampicin, nitrofurantoin, sulfonamides, terbinafine, fibric acid derivatives (fibrates), chlorpromazine and methotrexate.[51] Monitoring of liver biochemistry is recommended with some of these drugs. For drugs that may potentiate liver fibrosis, guidelines recommend additional regular assessment using non-invasive markers of fibrosis, such as serum biomarkers or VCTE.[52] Historically, prolonged methotrexate use was considered a risk factor for the development of liver fibrosis. However, more recent studies demonstrate no association between cumulative methotrexate dose or treatment duration and liver fibrosis. Instead, metabolic risk factors, including T2DM and elevated body mass index (BMI), are associated with fibrosis, suggesting that clinical management should prioritise optimisation of these risk factors in patients treated with methotrexate.[53 54]

Statins are rarely associated with DILI and generally considered safe, even in patients with pre-existing liver enzyme abnormalities.[55] Routine liver blood test monitoring for statins is no longer universally required.[56]

Determining the contribution of a specific drug to liver injury can be challenging, especially in the presence of concurrent liver conditions. Clinical judgement is critical to assess the primary cause and decide whether to discontinue a medication. This evaluation should consider the pattern of liver blood test abnormalities, the timing of medication initiation relative to the onset of liver issues, and the overall clinical context. Roussel Uclaf Causality Assessment Methods (RUCAM) can be used to help determine the likelihood of causality of suspected drug-induced liver injury.[57]

Table 3 Overview of liver aetiology screen

Standard liver aetiology screen		
Test/assessment	**What it is testing for**	**Clinical notes**
Alcohol history	Alcohol-related liver disease	Assess quantity, pattern, binge drinking; look for signs of dependence and withdrawal risk Consider screening tools such as AUDIT
Medication history	Drug-induced liver injury (DILI)	Include OTC, herbal, supplements; consider latency periods for DILI
Body mass index (BMI)	Risk of MASLD	Higher BMI increases risk of steatosis and MASH; assess alongside waist circumference
Blood pressure	Risk MASLD/metabolic syndrome	Hypertension often coexists with MASLD; can be raised with excessive alcohol consumption
Hepatitis B surface antigen	HBV infection	Positive test requires hepatitis B e-antigen (HBeAg), HBV DNA and anti-HDV antibody
Hepatitis C antibody	Exposure to HCV	If positive, reflex RNA needed to confirm active infection
Anti-mitochondrial antibody (AMA)	Primary biliary cholangitis	High specificity for PBC with raised ALP
Anti-smooth muscle antibody (ASMA)	Autoimmune hepatitis	Associated with raised IgG and hepatitic liver blood test pattern Isolated raised ASMA with normal IgG can be seen in people with MASLD
Antinuclear antibody (ANA)	Autoimmune liver disease	Associated with hepatitic blood test pattern and raised IgG often indicates AIH Isolated raised ANA with normal IgG can be seen in people with MASLD
Serum immunoglobulins	Patterns, eg, IgG↑ AIH, IgM↑ PBC, IgA↑ alcohol or MASLD	Helpful in refining autoimmune vs SLD causes
Serum ferritin and transferrin saturation	Haemochromatosis/iron overload	Ferritin alone unreliable; TS>40% (female) or >50% (male) suggests biochemical iron overload and HFE genotype is recommended
HbA1c	Diabetes mellitus	T2DM associated with MASLD progression
Lipid profile	Dyslipidaemia/metabolic syndrome	High triglycerides often accompany hepatic steatosis
Extended liver aetiology screen (may be considered mainly in secondary care liver services)		
Alpha-1-antitrypsin level	A1AT deficiency	Low levels warrant phenotype/genotype testing
Coeliac serology	Coeliac disease	Consider in unexplained mild transaminitis; improves on gluten-free diet
Caeruloplasmin (<40 years)	Wilson's disease	Low levels may require 24 hours urinary copper and slit lamp examination
Extended liver autoimmune profile	Autoimmune liver disease	Useful for overlap syndromes (eg, PBC-AIH) Anti-gp210 and anti-sp-100 antibodies by immunoblot useful in people with cholestatic liver enzymes and suspected AMA-negative PBC
Sexually transmitted infection screen	Infectious causes	Syphilis and HIV may cause raised liver blood tests
Additional tests for severely elevated ALT levels (>350 IU/L or 10x ULN)		
Hepatitis A IgM	Acute hepatitis A	Important in acute hepatitis with very high ALT. Can be confirmed by hepatitis A RNA (preferred test in the severely immunocompromised)
Hepatitis E IgM	Acute hepatitis E	Important in acute hepatitis with very high ALT. Can be confirmed by hepatitis E RNA (preferred test in the severely immunocompromised)
Acute EBV serology	EBV hepatitis	Common in young adults; often presents with lymphocytosis. EBV DNA used in severely immunocompromised patients
CMV IgM	CMV hepatitis	CMV DNA used in severely immunocompromised patients
Imaging tests		
Ultrasound scan (US)	First-line imaging in raised liver blood tests, suspected liver-related symptoms or fibrosis tests indicating possible ACLD	Assesses for steatosis, features of cirrhosis or portal hypertension, biliary dilatation, gallstones, gallbladder pathology; widely available and non-invasive
Pancreatic protocol CT	Suspected hepato-pancreatobiliary malignancy	A sensitive imaging test for pancreaticobiliary malignancy Late arterial phase of the upper abdomen, portal phase of the abdomen and pelvis. Does not include all phases to image for HCC
MRCP	Suspected biliary disorders. Recommended for people with IBD and abnormal liver blood tests	A sensitive imaging test for the biliary tree. Used if US is normal or equivocal and there is clinical concern Does not involve intravenous contrast medium
Pancreatic protocol MRI	Suspected hepato-pancreatobiliary malignancy.	A sensitive imaging test for pancreaticobiliary malignancy using intravenous contrast medium. Can be combined with MRCP to assess the biliary tree and pancreas at the same sitting. Can also be used instead of pancreatic protocol CT in patients with CT contrast medium allergy
Endoscopic ultrasound (EUS)	Suspected biliary disorders	Most sensitive test for detecting cholelithiasis and useful for evaluation of biliary obstruction, biliary stricturing or pancreatic masses. Useful when planning biliary intervention. EUS-guided liver biopsy is an alternative to percutaneous biopsy and can be undertaken during endosonographic evaluation of the biliary tree

A1AT, alpha-1 antitrypsin; ACLD, advanced chronic liver disease; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; AMA, anti-mitochondrial antibody; ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; AUDIT, Alcohol Use Disorders Identification Test; BMI, body mass index; CMV, cytomegalovirus; DILI, drug-induced liver injury; EBV, Epstein–Barr virus; EUS, endoscopic ultrasound; HbA1c, glycated haemoglobin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HFE, homeostatic iron regulator (haemochromatosis gene); IBD, inflammatory bowel disease; Ig, immunoglobulin; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MRCP, magnetic resonance cholangiopancreatography; OTC, over-the-counter; PBC, primary biliary cholangitis; SLD, steatotic liver disease; T2DM, type 2 diabetes mellitus; TS, transferrin saturation; ULN, upper limit of normal; US, ultrasound.

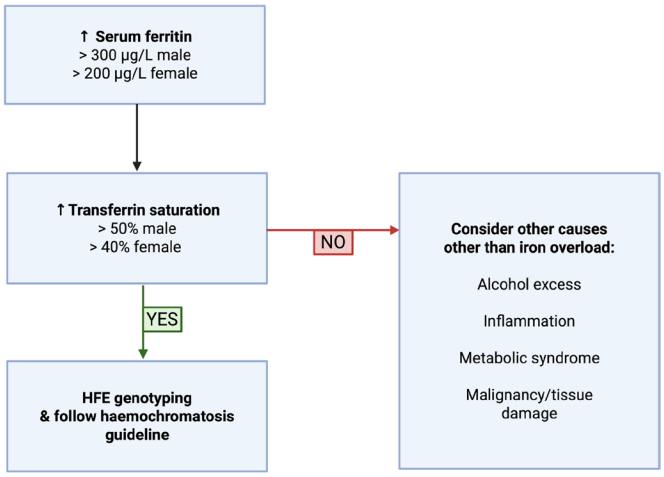


Figure 3 Investigation of elevated ferritin. HFE, homeostatic iron regulator.

Family history of liver disease

When congenital or hereditary liver conditions such as haemochromatosis, alpha-1 antitrypsin (A1AT) deficiency or Wilson's disease are suspected, screening of first-degree relatives is important to enable early diagnosis and prevent progression. However, standard liver blood tests lack the sensitivity or specificity for these conditions. For haemochromatosis, serum ferritin and transferrin saturation are recommended and, if abnormal, homeostatic iron regulator (HFE) genotyping should be carried out (see later; figure 3).[58 59] For Wilson's disease, serum ceruloplasmin, 24-hour urinary copper excretion and slit lamp examination for Kayser–Fleischer rings or genetic testing is recommended.[60] A1AT deficiency can be assessed through testing A1AT levels, A1AT phenotyping or genotyping.[61]

Among individuals with a personal or family history indicative of a genetic cholestatic disease (early cholestasis in pregnancy, atypical gallstone disease (intrahepatic choledocholithiasis, gallstones age <40 years), drug-induced liver injury), testing for familial intrahepatic cholestatic conditions is recommended.

Recommendation 4. The following groups should have standard liver blood tests: people with non-specific symptoms; clinical or imaging features suggestive of chronic liver disease; risk factors for liver disease or viral hepatitis; people taking hepatotoxic drugs; and people with suspicion of, or confirmed family history of, genetic liver disease. (Recommendation Strong, Certainty High)

What constitutes abnormal liver blood tests?

It is assumed that the magnitude of derangement of a liver blood test panel correlates with prognosis, and for this reason threshold values above the upper limit of the reference interval are commonly used when directing the need for further investigation. However, current evidence does not support this assumption in non-cholestatic diseases; prognosis is more reliably determined by the underlying diagnosis and the clinical context in which the tests are undertaken. For example, patients presenting with an acute viral hepatitis frequently have ALT levels greater than 1000 IU/L that can return to normal in a few weeks with no long-term sequelae. In contrast, many patients with cirrhosis have normal or mildly raised ALT levels and as such can go undetected.[62] It is now well recognised that the current upper limits of normal for enzymes, such as ALT, may be set too high because historic reference populations included individuals with unrecognised MASLD.[63] There have been attempts to redefine the normal range for liver blood tests. In a large community-based cohort of more than 400 000 people, the upper limit of normal (ULN) for ALT was suggested to be 36 IU/mL and 28 IU/mL in healthy men and women without metabolic risk factors, respectively.[64] Overall, further research is required to define the ULN for ALT and AST assays based on sex, ethnicity, body weight and local populations. Until further evidence is available, with reference to liver blood tests 'abnormal' refers to an analyte that is outside the reference range as per the previous guideline.[4]

Recommendation 5. With reference to liver blood tests, 'abnormal' refers to an analyte that is outside the laboratory reference range. (Not Graded)

Research Recommendation 1. Further research is required to define the ULN for ALT and AST assays based on sex, age, ethnicity and body weight.

Further investigation of abnormal liver blood tests

The assumption that the duration of liver blood test abnormalities reflects clinical significance, necessitating routine repeat testing for mildly abnormal results, persists in clinical practice. This is based on the belief that many abnormalities are transient and incidental, resolving without indicating significant liver disease. This is not the case for chronic liver diseases such as hepatitis C or MASLD, where normalised liver blood tests do not necessarily confirm the absence or resolution of disease. Up to 80% of patients with chronic liver conditions, including MASLD, may have intermittently normal liver blood tests despite ongoing disease progression.[65]

The cost of routine repeat testing must also be considered, including patient recall, sample collection, transport and laboratory analysis. NHS England's 2024 diagnostic cost analysis estimates that each liver blood test panel costs approximately £15–£20 per patient, excluding indirect costs like appointment time. The BALLETS study showed that 84% of adults with abnormal liver blood tests still had deranged results when retested after 1 month.[17] More recent primary care data from the 2024 ALFIE-2 study, an extension of the Health Technology Assessment-commissioned ALFIE study, confirmed this, with 78% of patients having persistent abnormalities on repeat testing within 6 weeks, underscoring the need for timely investigation rather than expectant management.[66 67] Therefore, a strategy of repeating abnormal tests is only justified when there is high certainty of resolution following an identified acute insult, such as alcohol-related elevation in transaminases.

In other cases, the first abnormal result should prompt investigation into the aetiology or targeted repeat testing to assess progression or disease severity. Moreover, given that liver fibrosis is the key prognostic factor in chronic liver disease,[68] fibrosis staging should be conducted.[30] The ALFIE-2 study found that only 55% of people with abnormal liver blood tests in primary care were followed up within 12 months, a marginal improvement from the original ALFIE study's 50%.[66 67] This highlights ongoing challenges in early identification of significant liver disease, such as fibrosis or cirrhosis, which NHS England's 2025 liver disease framework identifies as a priority due to rising MASLD prevalence (estimated at 25%–30% of UK adults).

Recommendation 6. All people with abnormal liver blood tests, regardless of the degree or duration of elevation, should undergo an aetiology screen and fibrosis assessment, unless a self-limiting cause is clinically apparent. (Recommendation Strong, Certainty High)

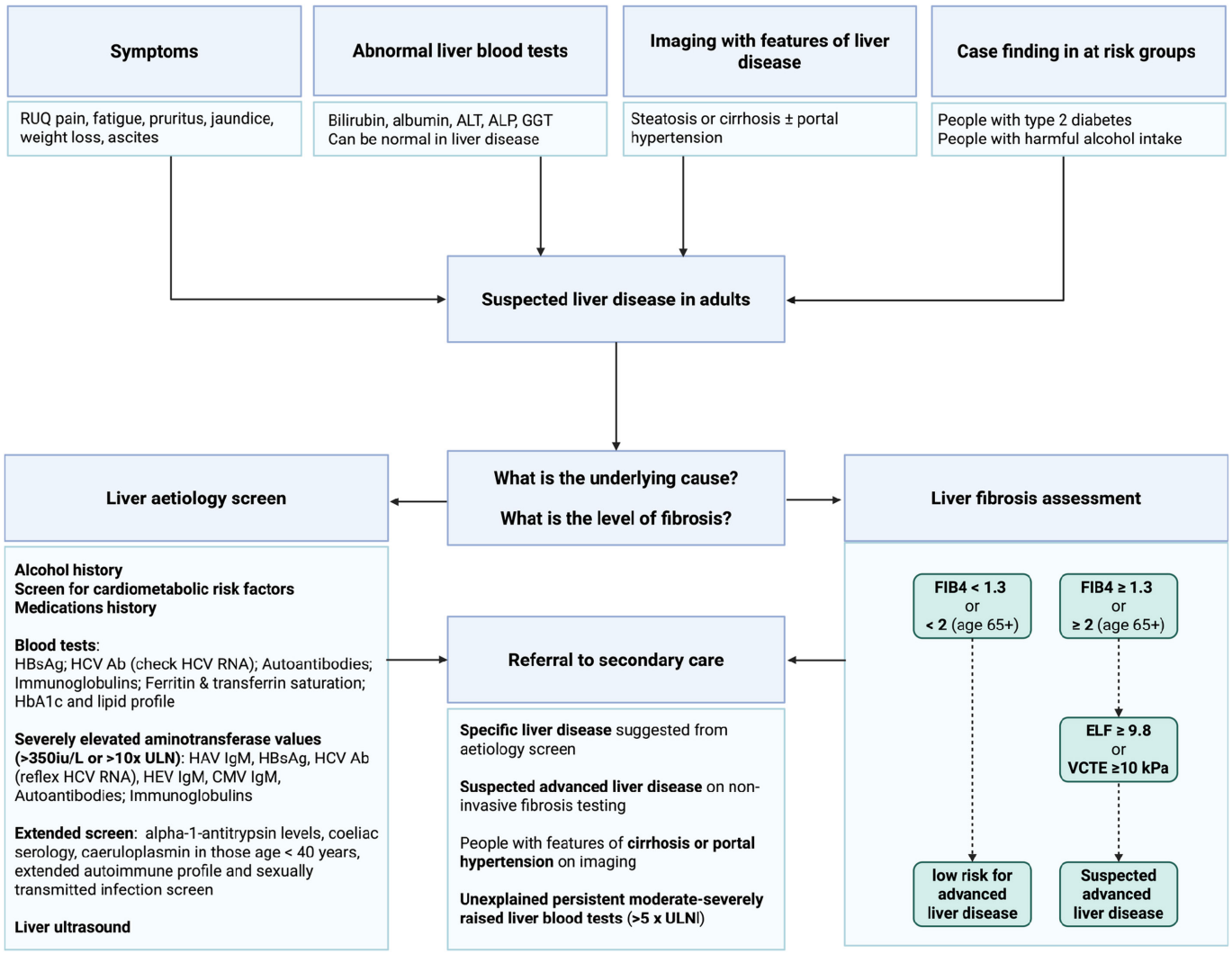


Figure 4 Overview of the investigation of suspected liver disease. ALP, alkaline phosphatase; ALT, alanine aminotransferase; CMV, cytomegalovirus; GGT, gamma-glutamyl transferase; ELF, Enhanced Liver Fibrosis (test); FIB-4, Fibrosis-4, HAV, hepatitis A virus; HbA1c, glycated haemoglobin; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HEV, hepatitis E virus; RUQ, right upper quadrant; ULN, upper limit of normal; VCTE, vibration-controlled transient elastography.

What additional tests should be undertaken in an individual with raised liver blood tests?

Liver aetiology screen

A structured liver aetiology screen is essential for the timely diagnosis of underlying liver disease, as biochemical patterns alone are often insufficient to determine cause or severity. For this reason, a systematic approach that incorporates clinical risk factors (including detailed alcohol history, use of potentially hepatotoxic medications or use of illicit drugs), metabolic assessment and targeted serological testing is fundamental to avoid missed or delayed diagnoses and should be conducted in all people with raised liver blood tests, imaging evidence of liver disease or fibrosis tests that suggest significant liver fibrosis. Table 3 and figure 4 summarise the clinical assessments and investigations that should be included in a standard liver aetiology screen. This strategy will detect prevalent conditions such as MASLD, ALD, viral hepatitis, autoimmune liver disease and haemochromatosis. An extended liver aetiology screen (table 3) may be considered by hepatology services when the cause of liver disease remains unexplained following initial investigations or when uncommon, inherited or complex conditions are suspected.

Severely elevated aminotransferases (>350 IU/ML or >10× ULN), which may indicate a more acute cause, require an urgent and more expansive evaluation, as acute viral hepatitis, drug-induced liver injury, ischaemic injury and other acute hepatitic processes must be rapidly identified and managed. Table 3 outlines the additional tests that should be performed with severely raised transaminases.

The following recommendations outline the essential and extended investigations that should be included in a liver aetiology screen across different clinical scenarios.

Recommendation 7. A standard first-line liver aetiology screen should include alcohol and medication history, body mass index, blood pressure and blood tests to include: hepatitis B surface antigen (including reflex hepatitis B serology, HBV DNA and hepatitis D antibody when positive); hepatitis C antibody (with reflex RNA for people who are antibody-positive); anti-mitochondrial antibody; anti-smooth muscle antibody;

antinuclear antibody; serum immunoglobulins; serum ferritin and transferrin saturation; glycated haemoglobin (HbA1c) and lipid profile. (Recommendation Strong, Certainty High)

Recommendation 8. An extended liver aetiology screen may be considered by hepatology specialist services in those with a hepatitic blood profile, including alpha-1-antitrypsin levels, coeliac serology, caeruloplasmin in those under the age of 40 years, extended autoimmune profile and sexually transmitted infection screen. (Recommendation Strong, Certainty High)

Recommendation 9. In people with severely elevated aminotransferase values (>350 IU/L or >10× ULN), the liver aetiology screen should comprise: hepatitis A IgM, hepatitis B surface antigen (including reflex hepatitis B serology, HBV DNA and hepatitis D antibody when positive), hepatitis C antibody (with reflex RNA for people who are antibody-positive), hepatitis E IgM, acute EBV serology, CMV IgM, anti-mitochondrial antibody; anti-smooth muscle antibody; antinuclear antibody and serum immunoglobulins. (Recommendation Strong, Certainty Moderate)

What is the optimum diagnostic strategy for cholestatic liver blood tests?

Cholestasis is caused by reduced flow or formation of bile. Intrahepatic cholestasis is characterised by dysfunction of hepatocytes, bile canaliculi, bile ductules or cholangiocytes in the absence of bile duct obstruction and is most commonly caused by drug injury, alcohol or bacterial infections/sepsis.[69] Extrahepatic cholestasis is characterised by obstruction, most commonly caused by bile duct stones, malignancy (most commonly pancreatic or biliary) or benign strictures. Cholestasis persistent for >6 months is termed chronic. Causes include PBC, PSC and sarcoidosis.[69]

The investigation of cholestatic liver blood tests should be conducted as described in Recommendations 7–13 (figure 5). Elevated serum ALP and GGT occur with early cholestasis, with elevated bilirubin more commonly in later disease. An isolated increase in ALP frequently occurs in non-liver conditions such as pregnancy, child growth, bone disease and vitamin D deficiency, and if a non-liver cause is suspected then further liver investigations may not be required. Isolated increases in ALP can occur in certain inherited disorders of bile acid synthesis and transport (eg, familial intrahepatic cholestasis) and genetic testing should be considered in those with unexplained or atypical cholestasis, in those where clinically relevant, after exclusion of more frequent causes.[70] Familial intrahepatic cholestasis may be supported by a personal or family history of young-age intraductal stones, drug-induced cholestasis or obstetric cholestasis (particularly prior to week 21 of pregnancy).

Mildly cholestatic liver enzymes with negative aetiology screen and normal imaging is a relatively frequent finding in the elderly and may not require extensive further investigation. Congestive hepatopathy associated with heart failure can present with mildly cholestatic liver enzymes so should be considered in this scenario.[71] A clinical history of, or symptoms suggestive of, heart failure may indicate this diagnosis. Testing with N-terminal pro-B-type natriuretic peptide (NT-proBNP) can be used to exclude heart failure. Where present, ultrasound (US) findings suggestive of hepatic congestion include dilated inferior vena cava or hepatic veins.

Alpha-fetoprotein, carcinoembryonic antigen (CEA) and CA19.9 may be increased in patients with malignancies but have limited sensitivity and specificity so are not recommended as screening blood tests in people without known malignancy.[4]

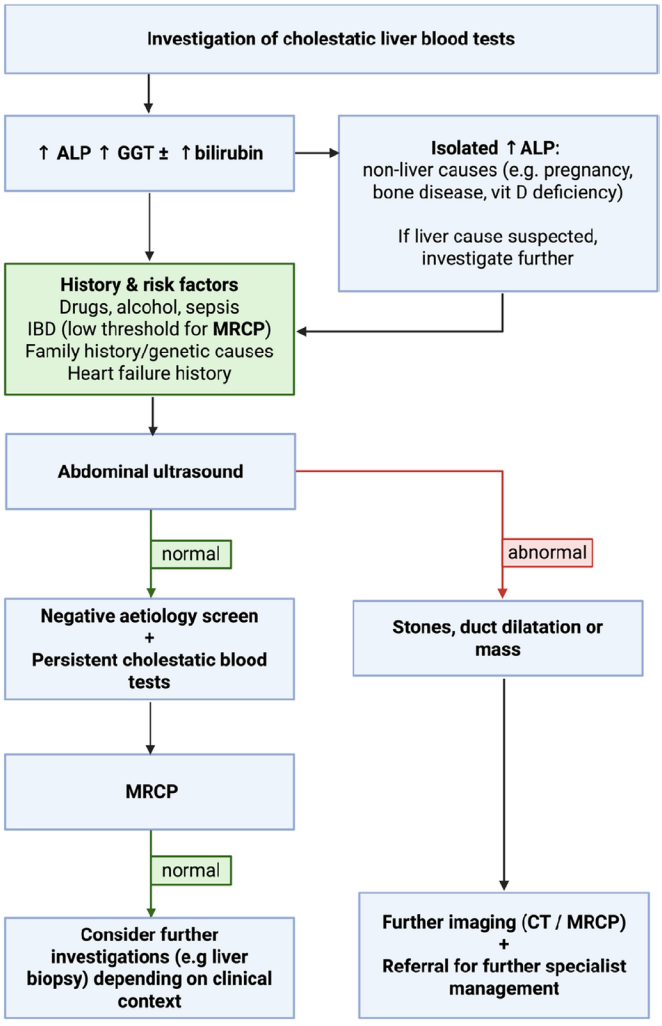


Figure 5 Investigation of cholestatic liver blood tests. ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; IBD, inflammatory bowel disease; MRCP, magnetic resonance cholangiopancreatography.

What routine imaging should be conducted if abnormal liver blood tests are identified?

Imaging provides structural information about the liver, biliary tree and pancreas, and commonly involves US, CT or MRI. US is inexpensive, does not use ionising radiation and can be applied in the community setting. However, it is operator-dependent and can be suboptimal in patients with steatosis or high BMI. The inferior bile duct and/or pancreas may be obscured by bowel gas. CT is widely available in the hospital setting, is less expensive than MRI, and not rendered suboptimal by high BMI, steatosis or bowel gas. It uses ionising radiation so, when used, the benefits need to be weighed against a theoretical small increase in cancer risk. MRI is particularly useful for imaging the biliary tree, and for characterising liver lesions non-invasively. It is more expensive than US or CT, and less widely available. Claustrophobia and MR-incompatible medical devices may prevent the use of MRI.

US commonly identifies steatosis but is not sensitive if steatosis is less than 20%.[72] It is also able to detect changes seen in chronic liver disease such as liver nodularity, irregular liver margin and reversal of portal vein blood flow or ascites. These features are highly specific for liver disease but have a

low sensitivity.[73] US is also important to assess the patency of portal and hepatic veins. Assessment of spleen size may also be helpful in the assessment of portal hypertension. Six-monthly US is the recommended surveillance imaging tool for HCC in people with cirrhosis provided the entire liver can be adequately visualised and this should be conducted using established call–recall systems in secondary care.[74 75] Moreover, US is a good first-line test for people with cholestatic liver blood tests as it can identify gallstones, biliary dilatation or masses, guiding further investigation and management.[69]

Due to its overall accuracy in diagnosing liver disease, cost, accessibility and safety, US is the imaging modality of choice as a first-line investigation. US reports in this context should document liver parenchymal features, focal liver lesions, the presence or absence of features of portal hypertension and hepatic decompensation, and any pancreaticobiliary abnormalities, in line with the recommendations from the Society of Radiographers and British Medical Ultrasound Society.[76] As with liver US for HCC surveillance,[77] use of a structured reporting template may help to ensure report completeness, facilitating consistent risk stratification.

In patients with biliary colic and cholestatic liver enzyme abnormalities, MRCP could be considered as a cost-effective first-line alternative to US.[78] However, a definitive cost-effectiveness analysis is yet to be undertaken for this approach.

Pancreatic protocol CT is recommended by NICE as the first-line imaging modality in individuals with cholestatic liver blood tests and suspected hepato-pancreato-biliary (HPB) malignancy, owing to its high diagnostic accuracy for pancreatic and peri-pancreatic neoplasms.[79] CT also provides assessment of tumour extent, vascular involvement and resectability, factors that are critical to determine management and assess prognosis. Therefore, people with suspected HPB malignancy should be referred urgently for pancreatic protocol CT. Pancreatic protocol implies a late arterial phase acquisition of the abdomen and a portal phase acquisition of the abdomen and pelvis.

MRCP, with or without dedicated MRI pancreas sequences, or alternatively a pancreatic protocol CT scan, is recommended as the next-line investigation following initial US assessment in people with cholestatic liver blood tests when US demonstrates biliary thickening or ductal dilatation.[69] Endoscopic US may also have a role in the evaluation of suspected cholelithiasis, biliary thickening, ductal dilatation, pancreatic masses or when planning intervention.

In individuals with persistent cholestatic liver test abnormalities but a normal US and a negative liver aetiology screen, MRCP should be considered to assess for early cholangiopathy.

Abnormal liver blood tests are a common finding in people with IBD. Although many abnormalities are self-limiting, PSC is the most important condition to exclude, given its strong association with IBD and its potential for progressive liver injury and increased risk of cholangiocarcinoma.[80] MRCP is the recommended first-line imaging modality for this purpose because US and CT lack sensitivity to detect cholangiopathy.[48]

Recommendation 10. Abdominal US is recommended as the first-line imaging test for people with raised liver blood tests, suspected liver associated symptoms and/or fibrosis staging blood tests that indicate possible advanced chronic liver disease. (Recommendation Strong, Certainty Moderate)

Recommendation 11. People with cholestatic liver blood tests in whom HPB malignancy is suspected should be referred for pancreatic protocol CT. (Recommendation Strong, Certainty Moderate)

Recommendation 12. MRCP±MRI pancreas (or pancreatic protocol CT) is recommended following US in people with cholestatic liver blood tests when:

- The US demonstrates biliary thickening or dilatation. (Recommendation Strong, Certainty High)
- Following a normal US scan and a negative liver aetiology screen. (Recommendation Conditional, Certainty Low)

Recommendation 13. MRCP is specifically recommended in people with IBD and abnormal liver blood tests. (Recommendation Strong, Certainty Moderate)

Ultrasound in people with a clinical diagnosis of SLD

Evidence guiding the role of US in asymptomatic people with isolated, mildly elevated aminotransferase levels remains limited. Although US is widely used in routine practice to identify structural liver abnormalities or features of SLD, its value in guiding management in this low-risk population is uncertain. Mildly raised transaminases are frequent in people with metabolic risk factors due to hepatic steatosis, and international guidelines advocate imaging to diagnose SLD,[7] however it is well known to be insensitive for detecting less than 20% steatosis.[72] Therefore, US may not add additional diagnostic information in a patient with a clinical diagnosis of SLD. Further research is therefore required to define the value of abdominal US in this context, assess its cost-effectiveness, and determine whether its routine use leads to earlier detection of clinically significant liver disease or, conversely, contributes to unnecessary investigations and resource use.

Research Recommendation 2. Research is required to determine whether US aids diagnosis or alters clinical management in asymptomatic individuals with isolated, mildly elevated aminotransferase values.

What investigations should be conducted in individuals who have possible liver disease identified incidentally on imaging?

The most common abnormal imaging finding in the asymptomatic community population is steatosis, present in 25%–35% of the global population.[81] The prevalence of incidental cirrhosis found on imaging performed for other diagnostic indications varies depending on the population. A study of abdominal imaging in over 150 000 Finnish people identified cirrhosis in 1.6% but rates are likely to be higher in hospital populations.[82]

Incidental imaging findings include steatosis, features of cirrhosis and portal hypertension, liver and pancreatic lesions, and biliary abnormalities. As discussed earlier, for imaging performed in the context of liver disease, a comprehensive documentation of these findings is important to facilitate subsequent risk stratification. Individuals with incidentally detected steatosis should undergo clinical assessment to establish risk factors for hepatic steatosis and should then undergo risk stratification for advanced liver fibrosis as per Recommendation 16 and figure 4. Individuals with suspected liver disease should be assessed by taking a focused history and conducting a clinical examination to assess for signs of liver disease. A full liver aetiology screen and fibrosis assessment should be performed as per Recommendations 7 and 16.

Where features consistent with cirrhosis or portal hypertension are reported on imaging, individuals should be referred for specialist assessment. In cases where descriptions of possible cirrhosis are open to interpretation or equivocal (eg, ‘coarsened liver echotexture’ on US), fibrosis assessment should be undertaken with a two-step pathway as suggested in Recommendation

16 with referral to secondary care initiated where appropriate as suggested in Recommendation 21.

Recommendation 14. People with hepatic steatosis identified incidentally on imaging should be clinically assessed to establish the cause, followed by risk stratification for advanced chronic liver disease. (Recommendation Strong, Certainty Low)

Recommendation 15. People with suspected liver disease identified incidentally on imaging should be assessed for liver disease risk factors including alcohol use, cardiometabolic risk factors and bloodborne virus risks, and have a liver aetiology screen and liver fibrosis testing as per Recommendations 7 and 16. (Recommendation Strong, Certainty Moderate)

FIBROSIS STAGING IN PARENCHYMAL LIVER DISEASE

The histological staging of liver disease has been used as the standard investigation for determining fibrosis but is problematic and prone to error due to its small size (unrepresentative sampling) and subjective interpretation. A single core biopsy of the liver is therefore not a gold standard for fibrosis staging. However, new tests for fibrosis have been validated, directly or indirectly against liver histology, so their less than perfect performance against histology must be viewed in that context. Systematic reviews of the performance of fibrosis biomarkers and their effectiveness at detecting advanced liver disease have been conducted recently.[83–85] Historically, fibrosis tests have been focused on assessing histological stage of fibrosis. However, overall liver disease prognosis is more important than histological fibrosis stage and is what clinicians are trying to ascertain from fibrosis estimations. Testing that predicts risk of liver-related events is an area of rapid development and beyond the scope of these guidelines. Here, we focus on fibrosis assessment using currently available biomarkers in the UK to inform clinical decision-making, such as referral to secondary care or treatment. Most liver fibrosis tests have reasonable accuracy to diagnose/exclude advanced fibrosis or cirrhosis. However, fibrosis biomarkers are unreliable in diagnosing moderate liver fibrosis and differentiating between specific stages of liver fibrosis. With the increasing use of non-invasive tests (NITs) to stage fibrosis and predict prognosis, the term compensated advanced chronic liver disease (cACLD) was introduced as an overarching term for the spectrum of advanced fibrosis and cirrhosis. When using VCTE, a valid LSM≥10 kPa is suggestive of cACLD.[86]

Abnormal liver blood tests are common in primary care but correlate poorly with the presence and severity of liver fibrosis. Aminotransferase levels alone are unreliable markers of disease stage, and moderate or advanced fibrosis may be present despite normal or only mildly abnormal liver blood tests, particularly in MASLD and ALD.[87 88] Conversely, abnormal liver blood tests are frequently incompletely investigated, resulting in underdiagnosis of clinically significant liver disease and late presentation with advanced or decompensated cirrhosis.[62] Liver fibrosis stage is the strongest predictor of liver-related outcomes, including progression to cirrhosis, hepatic decompensation, HCC and liver-related mortality, across a range of liver disease aetiologies.[68 89 90] Non-invasive fibrosis tests have been validated against histological fibrosis stage and, importantly, against clinically meaningful outcomes, demonstrating their utility for identifying patients at increased risk of liver-related morbidity and mortality.[85 91–93]

Real-world pathway evaluations demonstrate that systematic fibrosis assessment in patients with abnormal liver blood tests substantially increases detection of advanced liver disease compared with standard care, while remaining scalable and cost-effective in primary care settings.[33] Therefore, assessment of liver fibrosis should be considered a core component of the investigation of abnormal liver blood tests, rather than a discretionary step.

A summary of routinely available NITs in the UK is shown in table 4. FIB-4 is the archetypical "simple" clinical score that aids detection of advanced hepatic fibrosis and cirrhosis, equivalent to histological stages F3 and F4. It is an indirect fibrosis biomarker that does not actually measure extracellular matrix turnover, comprising instead four readily available parameters (ALT, AST, platelet count and age). It was originally developed for use in patients with HIV/HCV coinfection[24] but has subsequently been validated across a range of aetiologies including viral hepatitis, ALD and MASLD.[27 83] Notably, in addition to supporting stratification of patients for presence or absence of advanced fibrosis, FIB-4 has been shown to have prognostic value and can help clinicians identify patients at greater risk of liver-related morbidity.[92 93]

A FIB-4 threshold of <1.3 (<2.0 in patients older than 65 years of age) has high negative predictive value (NPV) to rule out advanced fibrosis.[27 85 94] This therefore serves as a key first-line triage, helping to rule out advanced fibrosis. Crucially, while no test is perfect, because the test is low cost and can easily be integrated into electronic systems for automated calculation and reflex testing,[33] it can be repeated to monitor patients and refine risk stratification.[92] FIB-4 is validated in ALD, MetALD, MASLD and HCV/HBV and can therefore be used regardless of the likely aetiology of liver disease.[83]

While the FIB-4 threshold of 1.3 has a good NPV, most people above this value will not have cACLD. The optimal FIB-4 threshold for ruling out advanced fibrosis in different aetiologies varies, but <1.3 is a widely accepted level and has been assessed in mixed cohorts.[30 95 96] Therefore, a second-line test should then be used for patients who have a FIB-4≥1.3 (≥2.0 in over-65-year-olds) to positively identify cases with clinically significant disease. Options for a second-line test include Enhanced Liver Fibrosis Panel (ELF, Siemens), Liver-Stiffness by Vibration-Controlled Transient Elastography (LSM-VCTE, Fibroscan, Echosens) or other forms of elastography (US acoustic radiation force elastography (ARFI), shear wave elastography (SWE) or MR elastography). A UK primary care study showed sequential testing with FIB-4 followed by ELF substantially reduces false-positives, improves overall diagnostic accuracy and minimises the need for further testing or unnecessary referral to secondary care.[97] Another study showed that FIB-4 followed by ELF correctly classified 88% of cases and reduced false-positives to 8%.[96] ELF also predicts liver-related outcomes over 5 and 10 years with reasonable accuracy.[98] Pathways using FIB-4 followed by VCTE also reduce false-positives and the need for hepatology referral[99] and predict the risk of liver-related events.[100] ELF and VCTE as the second-line test had similar performance in a large cohort of people with MASLD.[101] ELF has the advantage that it can be applied to the same blood sample. VCTE is widely used in hepatology, particularly in secondary care. VCTE should ideally be performed under fasting conditions because LSM can increase after eating. For people with elevated non-fasting LSM readings, VCTE should be repeated under fasting conditions before making treatment or management decisions.

Recommendation 16. The liver fibrosis staging pathway in primary care should comprise two-step sequential testing starting with FIB-4, with second-line testing depending on local availability. Second-line fibrosis testing may include ELF, VCTE or other validated NITs. (Recommendation Strong, Certainty High)

Recommendation 17. The aetiology of liver disease should not influence the choice of fibrosis test or the threshold value for

Table 4 Overview of commonly used non-invasive liver fibrosis tests

Test	Pros	Cons	Interpretation	Cut-offs for advanced fibrosis
FIB-4 score	Inexpensive and widely available.	High false-positive rate, particularly with age >65 years	Low=low probability of cACLD/F3–F4	≥1.3 requires second-line testing
Age AST ALT Platelets	Useful first-line stratification	Less accurate in age <35 years	High=increased risk requires second-line test	≥2.0 for age >65 years reduces false-positives
	Automated calculation available	False-positives with ALD		
		Lower accuracy than ELF or VCTE		
AST/ALT ratio	Very inexpensive and widely available	Poor fibrosis accuracy vs other tests	Increased ratio suggestive of cACLD	≥1 suggestive of cACLD/F3–F4
		False-positives in ALD		
ELF	High diagnostic accuracy	More expensive.	High ELF suggests advanced fibrosis	≥9.8 probable cACLD/F3–F4
HA PIIINP TIMP-1	Low false-positives	False-positives in other fibrotic disorders		
	Can be 'reflex' tested	Specific equipment required to analyse so not available in all laboratories		
Transient elastography (VCTE)	High diagnostic accuracy	Accuracy reduced in obesity, non-fasting state, hepatic congestion	Higher LSM=higher probability of advanced fibrosis	<8 kPa reliably excludes cACLD/F3–F4
		Requires another visit to healthcare if used as second-line test		≥10 kPa probable cACLD/F3–F4
		Not available in some healthcare settings		≥12 kPa highly probable cACLD/F3–F4

ALD, alcohol-related liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; cACLD, compensated advanced chronic liver disease; ELF, Enhanced Liver Fibrosis (test); F3–F4, fibrosis stages 3 to 4; FIB-4, Fibrosis-4; HA, hyaluronic acid; kPa, kilopascals; LSM, liver stiffness measurement; PIIINP, procollagen III N-terminal peptide; TIMP-1, tissue inhibitor of metalloproteinases-1; VCTE, vibration-controlled transient elastography.

ALD, MetALD, MASLD or chronic viral hepatitis. (Recommendation Strong, Certainty Moderate)

Limitations of non-invasive testing pathways

Although non-invasive fibrosis testing pathways using FIB-4 first line are widely recommended, there is risk of false-negatives for advanced fibrosis/cirrhosis and moderate liver fibrosis.[83] The risk of obtaining false-negative results depends on the context of use, with higher rates in populations with higher pre-test probability of advanced fibrosis such as secondary care cohorts of people with MASLD or those with T2DM,[83] whereas lower prevalence community cohorts typically have lower false-negative rates and very high NPVs.[96 102] Moreover, the choice of cut-off affects the false-negative rate. FIB-4 cut-offs <1.3, while highly convenient, has limited sensitivity, sometimes as low as ~60%, for detecting ≥F3 fibrosis in some populations with MASLD, T2DM, obesity, ALD and adults aged ≥60 years.[83 103] However, lowering the cut-off would substantially increase the need for second-line testing, and increasing the cut-off to 2.0 to reduce false-positives in people aged >65 years with MASLD has been advocated.[94] Repeated FIB-4 testing after at least a 12-month interval may help increase the diagnosis rate for severe liver disease in the general population.[104] ELF when used alone also has a significant false-negative rate (8%) for advanced fibrosis in a large case-finding study.[96] Combining ELF with FIB-4 improves sensitivity but does not eliminate residual risk.[96 103 105] Clinicians who used three fibrosis tests (FIB-4, ELF and VCTE) to stage fibrosis had higher concordance with liver biopsy compared with FIB-4 alone, FIB-4+ELF and FIB-4+VCTE, but this was still imperfect (84% vs 74%, 78% and 80%, respectively).[106] Overall, NITs may miss 5%–20% of advanced fibrosis cases and up to 17% of individuals labelled "low risk" by FIB-4 may still have clinically significant fibrosis.[96 103]

In view of the limitations of NITs, clinical judgement should be used, and when clinical suspicion remains high and initial screening tests are low risk, referral to secondary care should be considered for further investigations such as MR elastography or liver biopsy.

Recommendation 18. For patients in whom there is a strong clinical suspicion of advanced liver disease, referral to secondary care should be considered, even if initial risk-stratifying fibrosis tests are normal or low risk. (Recommendation Strong, Certainty Moderate)

WHO SHOULD BE REFERRED TO/REVIEWED IN SECONDARY CARE?

Unexplained jaundice or suspicion of HPB malignancy

New unexplained jaundice can indicate serious underlying disease. Common causes include liver failure from multiple aetiologies, HPB malignancies, obstructing choledocholithiasis and significant haemolysis. Therefore, unexplained jaundice should lead to an urgent referral to secondary care.[4]

Recommendation 19. People with unexplained jaundice should be referred urgently to secondary care. (Recommendation Strong, Certainty High)

Liver aetiology screen indicates a disease on aetiology screen

Identification of a liver disease (not including ALD or MASLD, which are discussed separately) on the aetiology screen (table 3), such as autoimmune liver disease, viral hepatitis or hereditary haemochromatosis, requires referral to secondary care because these conditions carry a significant risk of progression to advanced fibrosis and cirrhosis if not promptly diagnosed and managed. Typically, these conditions are managed in secondary care by specialist teams according to national and international guidelines. Therefore, people with a liver disease identified on the aetiology screen should be offered referral to specialist services as per local pathways.

Persistent moderate to severely raised liver enzymes

Persistently moderate to severely raised ALT and/or AST (>5× ULN) warrants urgent evaluation in secondary care even if the liver aetiology screen is negative.[107] Marked persistent biochemical abnormalities are associated with a higher likelihood of significant hepatic injury, especially when accompanied by jaundice, synthetic dysfunction or suspicion of malignancy.

For people with persistently raised ALP and GGT for >6 months without explanation (eg, normal imaging, negative autoimmune serology and no compatible drug history), less common causes of liver disease such as anti-mitochondrial antibody (AMA)-negative PBC, small duct PSC or sarcoidosis are possible diagnoses. Therefore, consider obtaining advice and guidance from secondary care gastroenterology/liver services regarding the need for further investigation in patients where a definitive diagnosis may alter their management.

Recommendation 20. Secondary care referral should be considered when:

- The liver aetiology screen indicates a disease such as autoimmune liver disease, viral hepatitis, haemochromatosis or other rare liver diseases. (Recommendation Strong, Certainty High)
- People have unexplained persistent moderate-severely raised ALT or AST (>5× ULN). (Recommendation Strong, Certainty Moderate)
- Advice and guidance should be sought from hepatology services if ALP values are >1.5× ULN for 6 months or more *with* commensurate anomalies in GGT *and* no alternative explanation (eg, normal imaging, negative autoimmune serology and no compatible drug history). (Recommendation Strong, Certainty Low).

Fibrosis tests or imaging that indicate cACLD

Patients with cACLD, advanced fibrosis and cirrhosis are at increased risk of complications of chronic liver disease including HCC, decompensation, liver transplantation and death.[68 89 90] Therefore, referral to hepatology services is recommended to facilitate treatment decision-making, HCC surveillance, portal hypertension assessment and management, and enrolment into clinical trials.[12 13] However, comorbidities and performance status should be considered before referral. Asymptomatic patients with cACLD and poor performance status or significant comorbidity (eg, severe heart failure or chronic obstructive pulmonary disease) are unlikely to benefit as surveillance is not recommended in this group.[75]

People with suspected cACLD can be identified by imaging suggesting cirrhosis or through non-invasive testing. When using NITs, second-line tests should guide referral decisions. Multiple studies have assessed the diagnostic performance of these biomarkers in different populations. ELF performs well across disease aetiologies.[108] A cut-off of ≥9.8 is suggestive of advanced fibrosis/cirrhosis and should trigger referral to secondary care or further fibrosis testing.[97 109] Age impacts the performance of ELF so alternative cut-offs may be appropriate for extremes of age, but further research is required to more clearly define these.[110] For VCTE, various thresholds have been suggested for different aetiologies and settings.[84] Selecting diagnostic thresholds for NITs is always a balance of sensitivity and specificity. An LSM<8 kPa reliably excludes advanced fibrosis/cirrhosis in MASLD and ALD (sensitivity 93% and 94%, respectively) whereas LSM≥12 kPa has good specificity (88%).[111] The prognostic value of FIB-4 followed by VCTE has recently been evaluated in a large study, and people with LSM<10 kPa had a very low incidence of liver-related events over 5 years.[100] Therefore, an LSM threshold of ≥10 kPa is a reasonable threshold for referral to secondary care. The cut-off used for ELF, VCTE and ARFI to prompt referral to hepatology services should be the same regardless of aetiology. The choice is between optimising diagnostic performance versus a complex pathway that would be more difficult to implement and audit. These ELF and LSM thresholds are consistent with recommendations made by the BSG/BASL MASLD special interest group for when to consider specific pharmacotherapy for patients with MASLD.[112] People with features of cirrhosis or portal hypertension on imaging with LSM<10 kPa could have porto-sinusoidal vascular disease so should be referred irrespective of the LSM or ELF result.

Recommendation 21. People with suspected advanced chronic liver disease (advanced fibrosis or cirrhosis) on non-invasive fibrosis testing (eg, fasting LSM≥10 kPa or ELF≥9.8) should be referred to hepatology services. (Recommendation: Strong, Certainty Low)

Recommendation 22. People with features of cirrhosis or portal hypertension on imaging should be referred for specialist management. (Recommendation Strong, Certainty Moderate)

Mild asymptomatic liver blood test abnormalities, negative aetiology screen and low-risk fibrosis assessment

Mild, asymptomatic abnormalities in liver blood tests often do not represent clinically significant liver disease and are frequently seen in primary care.[15] As discussed earlier, people with raised liver blood tests should have an aetiology screen and fibrosis assessment. A pragmatic 'watch and wait' management strategy is appropriate for asymptomatic individuals with mild liver test abnormalities (ALT or AST<5× ULN, ALP<1.5× ILN), a negative aetiology screen, absence of a drug- or alcohol-related cause, and low-risk fibrosis markers. In this group, routine referral to secondary care is unlikely to alter clinical management, and appropriate next steps include reassurance, lifestyle optimisation and periodic re-evaluation in primary care. When uncertainty persists, clinicians may seek secondary care advice via advice and guidance pathways.

Recommendation 23. In asymptomatic people with mildly raised liver blood tests, a negative liver aetiology screen, low-risk fibrosis markers, normal imaging and without an identified drug or lifestyle aetiology, referral to secondary care is unlikely to change management and guidance may be sought. (Recommendation Conditional, Certainty Low)

Periodic reassessment of liver fibrosis risk in people with ongoing risk factors for progression

Liver fibrosis stage is the key determinant of long-term patient outcomes in chronic liver disease.[68 90] Therefore, timely detection of fibrosis progression is essential for patient risk stratification

and management. However, the ideal time interval for repeating NITs remains variably defined across international guidelines, and supporting evidence is still evolving.

The European and American guidelines currently converge on a 1–3-year monitoring interval, adjusted to either baseline fibrosis severity[30] or presence of metabolic risk factors.[113] The European Association for the Study of the Liver (EASL) guideline recommends repeating NITs every 3 years in patients with early-stage MASLD and annually in those with advanced fibrosis.[30] The American Association for the Study of Liver Diseases (AASLD) guideline recommends primary fibrosis risk assessment using FIB-4, and in patients with FIB-4<1.3, with repeat FIB-4 every 2–3 years in patients without pre-diabetes/T2DM and up to two metabolic risk factors.[113] They recommend that patients with pre-diabetes/T2DM or more than two metabolic risk factors have FIB-4 every 1–2 years.

There is growing evidence to support the value of serial NIT measurements but this does not pinpoint an optimal time interval. Current evidence is based on either retrospective studies, where longitudinal NITs are compared against paired liver biopsies and the time intervals between liver biopsies are variable, or RCTs for metabolic dysfunction-associated steatohepatitis (MASH), where intervals between baseline and repeat liver biopsy are fixed but short in duration. Several large retrospective population studies have demonstrated that changes in FIB-4 score correlate with future liver events, cardiovascular events and overall mortality.[92 104 114] Emerging UK data show that rising FIB-4 at 12 months predicts worsening outcomes, while a decline suggests improved prognosis.[92] Data from Sweden showed that repeat FIB-4 testing within 5 years improves identification of individuals at risk for severe liver disease.[104] Other than FIB-4, NITs including NAFLD fibrosis score, AST to Platelet Ratio Index (APRI) and VCTE have also demonstrated utility in detecting fibrosis progression and prognosis,[115–119] though thresholds for clinically meaningful changes remain uncertain. From interventional RCTs, changes in NITs such as FIB-4, ELF and LSM consistently mirrored histological changes,[120 121] providing further justification for repeat NIT assessments.

Based on existing evidence, until stronger prospective data define optimal thresholds and intervals, a 3-year repeat assessment is recommended in people without advanced fibrosis/cACLD and ongoing risk factors for progressive liver disease.

Recommendation 24. In those without advanced disease, but with ongoing risk factors for progressive liver disease, repeat testing for fibrosis is recommended 3-yearly. (Recommendation Conditional, Certainty Low)

LIVER BIOPSY

Liver biopsy remains an important diagnostic tool in selected clinical scenarios. While there has been a move to non-invasive diagnosis and staging of liver disease, persistent or unexplained abnormalities often require histological clarification, particularly when non-invasive modalities cannot provide a definitive diagnosis.[122] In individual cases, the clinician and patient must discuss the risks and benefits of liver biopsy. Scenarios where a liver biopsy may be considered in the investigation of suspected liver disease are outlined below.

Unexplained persistently raised liver blood tests

Abnormal liver blood tests may persist and remain unexplained despite extensive investigation. A liver biopsy may be considered to aid diagnosis and distinguish between conditions such as steatohepatitis, autoimmune liver disease, drug-induced liver injury or infiltrative disorders that may not be apparent on routine investigations.

Diagnosis of autoimmune liver disease

Guidelines recommend that although serology and immunoglobulin G (IgG) levels can strongly suggest AIH, histological evaluation is typically necessary to confirm the diagnosis, determine the degree of inflammatory activity and inform treatment planning.[36] Liver biopsy may also aid diagnosis in people with cholestatic liver blood tests in whom an autoimmune aetiology is suspected but not proven by serology (PBC) or imaging (PSC).

Staging of liver disease when NITs are indeterminate or discordant

Although NITs such as VCTE, ELF and simple fibrosis scores have improved risk stratification, they can be indeterminate (indeterminate risk or technical failure) or discordant, particularly in individuals with mixed pathologies, metabolic risk factors or comorbid inflammatory conditions. Therefore, a liver biopsy may be considered when precise knowledge of fibrosis stage will change a patient's management.

Use of liver biopsy in clinical trials

Although NITs such as MR elastography and proton-derived fat fraction are increasingly used, clinical research protocols sometimes require histological assessment both at baseline and during follow-up to determine treatment efficacy, fibrosis progression or to assess mechanistic biomarkers. As such, liver biopsy remains an essential investigational tool in trial settings,

Recommendation 25. Liver biopsy may be considered to investigate suspected liver disease in the following: unexplained persistently raised liver blood tests, diagnosis of AIH, staging of liver disease when NITs are indeterminate or discordant and a precise diagnosis may alter management, or as part of a clinical trial/research study. (Recommendation Strong, Certainty Moderate)

SHOULD THERE BE CASE FINDING FOR CHRONIC LIVER DISEASE?

Over the past four decades, mortality from liver disease in the UK has risen more than fourfold.[2 123] This increase is largely driven by high levels of harmful alcohol use and the increasing prevalence of obesity, particularly in socioeconomically deprived areas. Early-stage liver disease is usually silent and opportunities for detection are frequently missed despite many individuals having clear risk factors such as obesity, metabolic syndrome, harmful alcohol intake or exposure risks for viral hepatitis.[6] Consequently, a substantial proportion of patients are only diagnosed once cirrhosis is already established, when the likelihood of developing liver-related complications is significantly higher and options to reverse fibrosis are limited.[62 123] Identifying individuals with chronic liver disease early can improve outcomes,[6 124] which raises the question as to whether widespread population screening for liver disease or targeted case finding in people with risk factors for liver disease may be effective.

Population screening for liver disease

Evidence from large cohort studies and modelling analyses demonstrates that population-level screening yields low detection rates (advanced fibrosis approximately 2%–6.5% and cirrhosis about 1%) and is not cost-effective.[125–127] Commonly used fibrosis assessment tools, such as FIB-4, have limited specificity in unselected populations, resulting in high false-positive

rates.[96 128] Therefore, widespread population screening for liver disease is not recommended. Targeted case-finding may be a more efficient approach, particularly among individuals with metabolic risk factors, harmful alcohol consumption, abnormal liver biochemistry or viral hepatitis risks.

Recommendation 26. Routine population-wide screening for chronic liver disease in asymptomatic adults is not recommended. (Recommendation Strong, Certainty Moderate)

Case finding for liver disease in people with T2DM

When considering case finding for liver disease in high-risk groups, clinicians should consider performance status and comorbidities to determine whether detection of asymptomatic liver disease would positively impact on the individual's length and/or quality of life.

The prevalence of advanced liver fibrosis in individuals with T2DM is estimated at 6% to 15%, and 3.8% to 7.7% for cirrhosis, depending on the population studied and the choice and thresholds of NITs used to define the groups.[34 129–133]

Several studies using different methodologies and in separate cohorts have derived prevalence figures for advanced fibrosis and cirrhosis that are broadly aligned. Participants in the NHANES study 2017–2018 with T2DM who underwent VCTE (n=825) were defined as having advanced fibrosis if VCTE≥9.7 kPa and cirrhosis≥13.6 kPa leading to prevalence figures of 15.4% and 7.7%, respectively.[133] Ajmera and colleagues prospectively included approximately 500 patients over the age of 50 years with T2DM and assessed for liver fibrosis using MR elastography and/or VCTE to assess for advanced fibrosis or cirrhosis, with VCTE liver stiffness thresholds of ≥8.8 kPa and ≥15 kPa, respectively.[130] A Spanish cohort used similar thresholds for VCTE (≥9.7 kPa for advanced fibrosis, ≥13.6 kPa for cirrhosis) and studied an older cohort of patients with a long duration of T2DM.[131] A meta-analysis of studies looking at T2DM, in which 21 studies assessed presence of liver fibrosis, also used a conservative VCTE threshold for determining the presence of advanced liver fibrosis (≥9 kPa) and found high prevalence of advanced fibrosis at nearly 15%.[132] However, all cohorts are potentially subject to selection bias depending on recruitment strategy, with older patients and those with longer duration of T2DM likely to be enriched for advanced liver fibrosis. In many cases the VCTE-LSM thresholds are associated with high sensitivity but lower specificity and thus a potentially significant false-positive rate that may overestimate the burden of advanced liver disease in patients with T2DM in the community.

Case-finding data from a recent community-based study of people with risk factors for chronic liver disease in the UK (n=2445) assessed the presence of cACLD at 6.5% of those with T2DM (n=660). These data are likely more representative of the general population and use more stringent criteria for the diagnosis of cACLD through comprehensive clinical assessment by an expert hepatologist, including repeat VCTE, imaging or liver biopsy, where appropriate.[129] A population-based case-finding pilot from the UK found 47 243 individuals with risk factors for liver disease, of whom 11 908 underwent non-invasive testing with FIB-4±ELF ± VCTE according to a prespecified testing strategy. Some 42% had T2DM and, of these, 3.7% had cACLD (LSM≥11.5 kPa) and 2.3% had probable cirrhosis (≥15 kPa).[34]

Cost-effectiveness modelling provides support for case-finding approaches.[127 134–136] In addition, published evidence suggests that approaches are more cost-effective when targeting individuals with T2DM when compared with obese populations.[137] In a rapidly evolving field of drugs targeting cardiometabolic risk, as well as emerging liver-specific therapies, detailed cost-effectiveness studies that mirror planned case-finding strategies are needed.

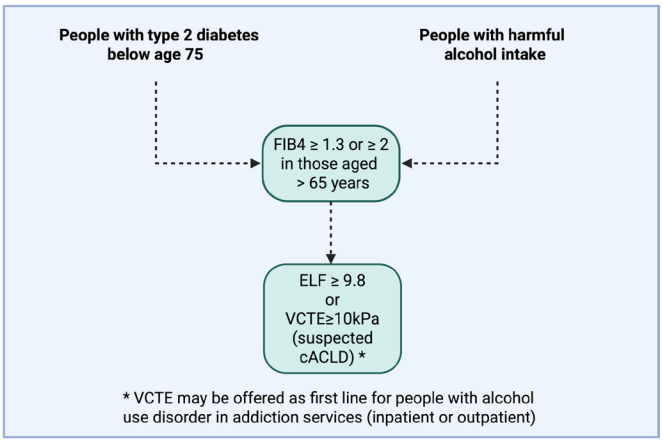


Figure 6 Case finding for advanced liver disease in high-risk groups. cACLD, compensated advanced chronic liver disease; ELF, Enhanced Liver Fibrosis (ELF) test; FIB-4, Fibrosis-4 test; VCTE, vibration-controlled transient elastography.

Two-step risk stratification pathways for chronic liver disease are widely used with evidence that those in high-risk groups have worse outcomes.[4 30 100] Most studies assessing these pathways have been conducted in people with known liver disease rather than for case finding. The pre-test probability of advanced liver fibrosis or cirrhosis should be lower than in those known to have liver disease, so the positive predictive value of a test will decrease. Higher thresholds for NITs may be appropriate for case finding in the community but further research is needed. Therefore, until further evidence is available, the same two-step pathways for risk stratification using the same thresholds as patients with known liver disease should be used (Recommendations 16 and 21; figure 6).

Individuals without evidence of advanced fibrosis but with ongoing risk factors may develop progressive liver fibrosis, estimated at one fibrosis stage every 7 years in those with steatohepatitis.[138] NITs have an appreciable false-negative rate for advanced fibrosis. However, the risk of liver-related harm over a 5-year period in those with LSM<12 kPa is low.[100] While the detection of advanced liver fibrosis remains clinically relevant in an individual, repeating fibrosis assessment will detect those with progressive disease.

Recommendation 27. People with T2DM should be assessed for the presence of advanced chronic liver disease at diagnosis of T2DM, where appropriate for age (eg, <75 years), comorbidity and performance status (0–1). (Recommendation Strong, Certainty Moderate)

Recommendation 28. When case finding in people with T2DM, a two-step non-invasive fibrosis testing pathway (Recommendation 16) should be used to identify those at risk of advanced chronic liver disease. (Recommendation Strong, Certainty Moderate)

Recommendation 29. People with T2DM without evidence of advanced liver fibrosis (eg, FIB-4<1.3, LSM<10 kPa or ELF<9.8 (or age-adjusted thresholds)) should undergo repeat assessment at 5-yearly intervals up to the age of 75 years. (Recommendation Conditional, Certainty Low)

Research Recommendation 3. Assess the performance characteristics of NIT thresholds in case finding versus known disease populations to determine optimal thresholds for use.

Case finding for liver disease in people with obesity

The prevalence of advanced liver fibrosis in individuals with obesity is lower than for T2DM, estimated at 2.9% to 5.2%,[129 139] although these conditions frequently coexist. European guidance suggests screening individuals with obesity and at least one further cardiometabolic risk factor.[8] However, the numbers of individuals encompassed is vast, cost-effectiveness has not been demonstrated, and implementation would not be feasible. Higher-risk groups should be prioritised.

Recommendation 30. Case finding for people with obesity, but without T2DM or harmful alcohol intake, is not recommended. (Recommendation Conditional, Certainty Low)

Research Recommendation 4. Assessment of the cost-effectiveness of case finding for advanced liver disease in at-risk populations including people with T2DM; people with obesity, but without T2DM; and people with harmful alcohol intake.

What is the best way to screen for liver disease in people with high-risk alcohol use?

Alcohol use disorder (AUD) reflects an alcohol consumption that is likely to cause physical, psychological or social harm. This includes both harmful drinking (>50 units/week for men or >35 units/week for women) and alcohol dependence (a strong desire to drink and difficulties controlling its use). Hazardous drinking increases the risk of physical or psychological sequelae (between 14 and 50 units/week for men and between 14 and 35 units/week for women).[140] People with AUD are at substantially increased risk of advanced liver disease and the majority of liver-related deaths and hospital admissions in the UK have alcohol as the main cause for liver disease, yet diagnosis is frequently delayed.[123 141] Despite this, relatively few studies have addressed screening or case finding in people with AUD or potentially harmful alcohol use.

Two settings for the diagnosis and risk stratification of ALD are discussed below. The first is people with sustained alcohol consumption to potentially harmful levels (>35 units/week for women, >50 units/week for men) and the second is those with AUD attending alcohol services in whom alcohol intake is typically harmful.

Case finding for liver disease in people with potentially harmful alcohol consumption

Existing NICE guidelines recommend non-invasive testing for cirrhosis for people who drink potentially harmful amounts of alcohol, defined as >50 units/week (men) or >35 units/week (women) for several months.[37] However, despite these cut-offs for alcohol consumption being recommended to select people for fibrosis testing, there are remarkably few studies to support this. One study reported that men consuming 50 units or more per week had almost a threefold increase in the risk of advanced liver fibrosis, while women drinking 35 units or more per week faced a fivefold increase in risk.[142] Moreover, in the same study, drinking >14 units/week doubled the likelihood of advanced fibrosis in overweight/obesity. A recent large prospective study evaluating outcomes of implementation of liver health checks in primary care in England found that 5.1% of people with a history of ALD coded in their records had undiagnosed cACLD.[34] However, there was no difference in the proportion of people with cACLD between those consuming less than or greater than 30 units per week. One of the limitations of using units to select patients for fibrosis testing is that alcohol history is poorly documented in health records and self-reported alcohol consumption can be unreliable. The use of alternative alcohol risk assessments, such as the Alcohol Use Disorders Identification Test (AUDIT), or use of direct alcohol biomarkers (such as phosphatidylethanol (PEth) or urine/hair ethyl glucuronide (EtG)) to select patients for fibrosis testing has not been widely evaluated. In another prospective case-finding study evaluating the performance of liver fibrosis biomarkers in primary care, AUDIT score did not predict the presence of cACLD.[129] Therefore, until further evidence is available, non-invasive fibrosis testing should be offered to people with harmful alcohol consumption (eg, >50 units/week for men, >35 units/week for women) for >1 year to identify significant/advanced liver disease.

Several NITs have been evaluated for ALD including FIB-4, ELF and VCTE.[29 30 83 84] Overall, there are far fewer studies assessing these tests in ALD compared with MASLD. In comparison with MASLD, the false-positive rate using FIB-4 for advanced fibrosis in people with ALD is higher due to alcohol-associated increases in AST and reduction in platelet count.

NICE guidelines recommend the use of VCTE to screen for cirrhosis in people with high-risk alcohol consumption (>50 units/week for men, >35 units/week for women).[37] This approach is feasible and acceptable to patients, and stratifies clinically significant disease in harmful drinkers outside hospital settings.[143] EASL recommend a two-tier strategy using simple scores like FIB-4 followed by ELF or VCTE.[30] One UK study evaluating referrals from primary care with ALD found that use of FIB-4 to risk stratify could halve unnecessary referrals for further investigation.[142] As stated previously, we recommend two-step sequential fibrosis testing at first diagnosis starting with FIB-4, with second-line testing with ELF, VCTE or other validated NITs depending on local availability irrespective of aetiology of liver disease. People with ELF≥9.8 or LSM≥10 kPa should be offered referral to secondary care. For those with AUD who have cACLD excluded, consider retesting after 3 years for those with ongoing harmful alcohol consumption.

Recommendation 31. In people with harmful alcohol consumption (eg, >50 units/week for men, >35 units/week for women) for >1 year, offer non-invasive fibrosis assessment to identify significant/advanced liver disease using sequential two-step fibrosis testing as per Recommendation 16. (Recommendation Strong, Certainty Low)

Case finding for liver disease in people with alcohol use disorder within inpatient and outpatient addiction services

ALD is frequently silent until decompensation and routine liver blood tests alone neither exclude nor reliably stage advanced fibrosis. Overall, approximately 20% of people with AUD develop advanced liver disease supporting targeted testing in this group.[41] A few studies have evaluated case finding for advanced liver fibrosis using VCTE in inpatient and outpatient cohorts of people with AUD. These show that 7.5%–12% of inpatients with AUD undergoing VCTE had LSM≥12 kPa, consistent with advanced fibrosis or cirrhosis,[144–147] suggesting a significant burden of undiagnosed advanced liver disease in this population. Similar rates of advanced liver disease were seen in three outpatient studies in alcohol addiction services, with cirrhosis prevalence ranging from 6.3% to 15.7%.[147–150]

Importantly, one inpatient study using histology to define fibrosis showed that LSM<10 kPa can reliably exclude advanced fibrosis (NPV of 99%) independent of recent alcohol

consumption.[144] False-positives frequently occur with VCTE due to severe hepatic steatosis in those drinking harmful amounts of alcohol, so further evaluation is necessary before making a formal diagnosis of cACLD. Cost-effectiveness of case finding with VCTE in addiction services has not been evaluated. Overall, VCTE is a reasonably good tool to assess for cACLD in people with AUD and can identify a substantial burden of previously unrecognised advanced liver disease.

Recommendation 32. Case finding for advanced chronic liver disease with VCTE should be considered in individuals attending inpatient and outpatient services for alcohol use disorder. (Recommendation Conditional, Certainty Low)

Research Recommendation 5. Determine the optimum fibrosis screening strategy for people at risk of advanced liver disease due to alcohol.

Case finding to identify individuals with alcohol use disorder to enable targeted testing for ACLD

There is currently limited evidence to support the use of AUD case finding as an effective strategy for identifying individuals at risk of liver disease. Although early detection of harmful drinking is theoretically valuable, the practical performance of alcohol screening tools in real-world population settings remains suboptimal. Studies using postal invitations to complete the AUDIT questionnaire have reported relatively low uptake rates of typically between 21.8% and 34.8%.[151] Similarly, approaches using existing data sources or opportunistic screening have not demonstrated adequate engagement. Screening primary care electronic health records to identify individuals with potential high-risk alcohol use, or targeting those who self-report elevated intake, such as individuals with an AUDIT-C>7 during workplace health assessments, has also yielded low response and completion rates.[151–154]

Research Recommendation 6. Determine whether case finding for individuals with AUD to test for ACLD is clinically and cost effective.

SPECIAL CIRCUMSTANCES

How should elevated ferritin values be investigated?

Elevated ferritin is a common finding in people with raised liver blood tests, but it is frequently non-specific and may reflect inflammatory, metabolic or haematological conditions rather than iron overload alone. Elevated ferritin is particularly common in people with MASLD or ALD. To ensure appropriate evaluation and avoid unnecessary investigations, investigation of raised ferritin should start with testing the transferrin saturation to determine evidence of biochemical iron overload, with further assessment conducted according to the BSG-endorsed British Society of Haematology guidelines (figure 3).[58 59]

Recommendation 33. Elevated ferritin values should be investigated according to the BSG-endorsed British Society of Haematology guidelines. (Not Graded)

What is the optimum approach to the investigation of abnormal liver blood tests and suspected liver disease in pregnancy?

In 2023, EASL produced a guideline on the management of liver diseases in pregnancy[155] that provides detailed advice on pre-existing liver conditions. This section will only focus on the investigation of new abnormal liver blood tests in pregnancy, which can be due to either a pregnancy-related disorder or a hepatic disorder occurring coincidentally in pregnancy. Regardless of the origin, liver diseases in pregnancy are associated with increased risk of both maternal and fetal morbidity and mortality.

The liver aetiology screen in pregnancy should review alcohol, metabolic risk factors and medication history, including over-the-counter medication and herbal products. Blood investigations should follow Recommendations 7–9. In addition, serum bile acids should be measured at baseline. Serial measurement of bile acids should be performed in those with cholestatic liver enzymes as rising levels are associated with an increased risk of preterm delivery, with potential harm when values reach >100 μmol/L. US, VCTE and non-contrast MRI (ie, MRCP) are all considered safe throughout pregnancy and should be used as outlined in

Table 5 Key performance indicators for audit and quality improvement

KPI	KPI title	Definition	Audit standard
Infrastructure KPIs			
1	Use of PLP-supplemented ALT/AST assays	Laboratories using PLP assays for ALT/AST	100%
2	Use of reflex/automated testing	Raised ALT with reflex AST or automated FIB-4 calculation performed in primary care	≥85%
3	Direct access to elastography (VCTE)	Waiting time for VCTE assessment	≥85% within 6 weeks
4	Quality of imaging reporting	Proportion of liver ultrasounds with structured report of findings including: ► Parenchymal features ► Focal liver lesions ► Presence or absence of features of portal hypertension or decompensation (ascites) ► Spleen size ► Documentation of portal vein flow or thrombosis	≥85%
Patient management KPIs			
5	Completion of liver aetiology screen	Adults with newly abnormal liver blood tests receiving a *complete* standard aetiology screen	≥85%
6	Documentation of alcohol history	Documented alcohol intake in people with raised liver blood tests	≥85%
7	Use of two-step fibrosis pathway in people with raised liver blood tests	FIB-4 completed, and ELF/VCTE performed when above threshold (≥1.3 or ≥2.0 in ≥65 years)	≥85%
8	Quality of hepatology referrals	Referrals include: ► Alcohol history ► Aetiology screen ► Fibrosis test results (FIB-4+VTCE/ELF) ► Imaging reports	≥85%
9	Case finding in T2DM	Adults with T2DM (<75 years, suitable performance status) receiving two-step fibrosis assessment	≥70%

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ELF, Enhanced Liver Fibrosis (test); FIB-4, Fibrosis-4 (test); KPI, key performance indicator; PLP, pyridoxal 5′-phosphate; T2DM, type 2 diabetes mellitus; VCTE, vibration-controlled transient elastography.

Box 1 Key changes compared with the 2018 British Society of Gastroenterology guidelines on abnormal liver blood tests

- ⇒ Expansion of guideline scope from investigation of abnormal liver blood tests to investigation of suspected liver disease, including incidental imaging findings and targeted case finding.
- ⇒ Adoption of the new nomenclature for steatotic liver disease.
- ⇒ Reflex and automated laboratory testing pathways (eg, Fibrosis-4 (FIB-4), intelligent Liver Function Testing (iLFT)) recommended.
- ⇒ New definitions of thresholds and investigation panels for severely elevated aminotransferases.
- ⇒ More prescriptive imaging pathways for ultrasound, CT and magnetic resonance cholangiopancreatography (MRCP).
- ⇒ Introduction of recommendations for investigation of incidental imaging findings suggestive of liver disease.
- ⇒ Sequential two-step non-invasive fibrosis testing with FIB-4 followed by Enhanced Liver Fibrosis (ELF) test, vibration-controlled transient elastography (VTCE) or other validated test to be undertaken prior to secondary care review.
- ⇒ Introduction of uniform thresholds for fibrosis staging/referral across alcohol-related liver disease (ALD), metabolic dysfunction-associated steatotic liver disease (MASLD), MASLD with increased alcohol intake (MetALD) and viral hepatitis.
- ⇒ Periodic repeat fibrosis assessment (3-yearly) recommended in people with ongoing risk factors.
- ⇒ Targeted case finding for advanced liver disease recommended for people with type 2 diabetes mellitus and those with high-risk alcohol use.

previous sections. However, VCTE readings may be inaccurate in the second and third trimester due to a physiological increase in liver stiffness from the increased blood flow to the liver, with values >7.9 kPa in healthy pregnant women. Moreover, there is a lack of specific reference ranges for pregnant individuals, and clinicians often have to rely on standards created for non-pregnant populations. Liver stiffness measurements may also be affected by anatomical changes, such as abdominal distension in the later stages of pregnancy. Serum NITs may also be reliable in pregnancy.

MRI scans are usually avoided in the first trimester, unless clinically urgent. If imaging demonstrates choledocholithiasis or biliary obstruction then an endoscopic retrograde cholangiopancreatography (ERCP) can be performed, ideally in the second or third trimester. The risk of not performing ERCP in this context will usually substantially outweigh the small risk from using ionising radiation as part of the procedure.

Investigation of suspected liver disease/raised liver blood tests in people who are being worked up for or treated with immunomodulators or disease-modifying antirheumatic drugs

People with suspected liver disease or abnormal liver blood tests who are being considered for, or are currently receiving, immunomodulators or disease-modifying antirheumatic drugs (DMARDs) require enhanced assessment and monitoring.[156] This applies to conventional synthetic DMARDs (eg, methotrexate, leflunomide, azathioprine, sulfasalazine, hydroxychloroquine), biologic agents such as anti-tumour necrosis factor (TNF) therapies, rituximab and tocilizumab, targeted synthetic DMARDs including Janus kinase (JAK) inhibitors, and other immunomodulators such as ciclosporin, mycophenolate mofetil, tacrolimus and cyclophosphamide.

Hepatitis B and C screening should be performed in all patients planned for immunosuppressive treatment, and those who have current or past hepatitis B should receive appropriate antiviral prophylaxis or monitoring for reactivation.[157 158]

In addition, people with raised liver blood tests or suspected liver disease should have a full history, liver aetiology screen and fibrosis testing as per recommendations above to determine the cause and stage of liver disease. These findings should guide drug selection and determine the level of monitoring required. Ongoing monitoring during therapy is essential, particularly for patients receiving higher-risk or potentially hepatotoxic agents. A hepatology review should be considered for persistent or progressive abnormalities or before initiating high-risk DMARD therapy in patients with known liver disease.

MONITORING, AUDIT AND KPIS

Nine auditable KPIs were developed and these are summarised in table 5.

CONCLUSIONS

These updated guidelines aim to standardise diagnostic pathways for liver disease to facilitate earlier detection of clinically significant liver disease (a summary of changes compared with the previous guidelines is shown in box 1). A pragmatic approach has been taken to ensure that these guidelines are applicable to routine clinical settings and it is hoped that widespread implementation will improve the care of the increasing pool of people with liver disease and reduce unwarranted variation.

Author affiliations
[1]Liver Unit and NIHR Newcastle Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Trust and Translational & Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK
[2]NIHR Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[3]Faculty of Health, University of Plymouth, Plymouth, UK
[4]School of Medicine, University of Dundee, Dundee, UK
[5]Barts Liver Centre, Blizard Institute, Queen Mary University of London, London, UK
[6]Institute for Liver and Digestive Health, University College London, London, UK
[7]Translational & Clinical Research Institute, Newcastle University and Liver Unit & NIHR Newcastle Biomedical Research Centre, Newcastle upon Tyne Hopsitals NHS Foundation Trust, Newcastle upon Tyne, UK
[8]Biochemistry, County Durham and Darlington NHS Foundation Trust, Durham, UK
[9]School of Health and Wellbeing, University of Glasgow, Glasgow, UK
[10]Patient Representative, LIVErNORTH Liver Patient Support, Newcastle upon Tyne, UK
[11]Institute of Medical Imaging and Visualisation, Bournemouth University, Poole, UK
[12]Liver Unit, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK
[13]Radiology, Addenbrooke's Hospital, Cambridge, UK
[14]Liver UK, Ringwood, UK
[15]Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, UK
[16]Princess Alexandra Hospital NHS Trust, Harlow, UK
[17]Great Western Hospitals NHS Foundation Trust, Swindon, UK
[18]Liver Unit, Royal Victoria Hospital, Belfast, UK
[19]Acute Medicine, Royal Free London NHS Foundation Trust, London, UK
[20]University Hospital of Wales and Cardiff University, Cardiff, UK
[21]University Hospitals of Leicester NHS Trust, Leicester, UK
[22]Surgery, Addenbrooke's Hospital, Cambridge, UK
[23]Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK
[24]National Institute for Health Research (NIHR) Birmingham Liver Biomedical Research Unit, University of Birmingham, Birmingham, UK
[25]Liver Unit, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[26]University Hospital Southampton NHS Foundation Trust, Southampton, UK

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ORCID iDs
Stuart McPherson https://orcid.org/0000-0002-5638-2453
John F Dillon https://orcid.org/0000-0002-2164-4476
Wenhao Li https://orcid.org/0000-0003-0717-9069
Palak Trivedi https://orcid.org/0000-0002-4009-8087

REFERENCES

1 Devarbhavi H, Asrani SK, Arab JP, *et al*. Global burden of liver disease: 2023 update. *J Hepatol* 2023;79:516–37.
2 Liver UK. Liver disease in numbers. 2025. Available: https://britishlivertrust.org.uk/information-and-support/statistics
3 Karlsen TH, Sheron N, Zelber-Sagi S, *et al*. The EASL-Lancet Liver Commission: protecting the next generation of Europeans against liver disease complications and premature mortality. *Lancet* 2022;399:61–116.
4 Newsome PN, Cramb R, Davison SM, *et al*. Guidelines on the management of abnormal liver blood tests. *Gut* 2018;67:6–19.
5 Macpherson I, Abeysekera KWM, Harris R, *et al*. Identification of liver disease: why and how. *Frontline Gastroenterol* 2022;13:367–73.
6 Abeysekera KWM, Macpherson I, Glyn-Owen K, *et al*. Community pathways for the early detection and risk stratification of chronic liver disease: a narrative systematic review. *Lancet Gastroenterol Hepatol* 2022;7:770–80.
7 Rinella ME, Lazarus JV, Ratziu V, *et al*. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol* 2023;79:1542–56.
8 European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J Hepatol* 2024;81:492–542.
9 Bird-Lieberman E. BSG guidelines and guidance development, writing and review process. British Society of Gastroenterology; 2025.
10 Atkins D, Best D, Briss PA, *et al*. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328:1490.
11 AGREE Consortium. Appraisal of Guidelines for Research Evaluation (AGREE II). AGREE Enterprise; 2017.
12 Mansour D, Masson S, Corless L, *et al*. British Society of Gastroenterology Best Practice Guidance: outpatient management of cirrhosis - part 2: decompensated cirrhosis. *Frontline Gastroenterol* 2023;14:462–73.
13 Mansour D, Masson S, Shawcross DL, *et al*. British Society of Gastroenterology Best Practice Guidance: outpatient management of cirrhosis - part 1: compensated cirrhosis. *Frontline Gastroenterol* 2023;14:453–61.
14 Scutt P, Ban L, Card T, *et al*. Liver blood marker testing in UK primary care: a UK wide cohort study, 2004-2016. *BMJ Open* 2022;12:e058967.
15 Donnan PT, McLernon D, Dillon JF, *et al*. Development of a decision support tool for primary care management of patients with abnormal liver function tests without clinically apparent liver disease: a record-linkage population cohort study and decision analysis (ALFIE). *Health Technol Assess* 2009;13:iii–iv, .
16 Chong P, Gnanendran D, Gao-Du YX, *et al*. Defining "Normal" Liver Function Tests. *Cureus* 2025;17:e97561.
17 Lilford RJ, Bentham L, Girling A, *et al*. Birmingham and Lambeth Liver Evaluation Testing Strategies (BALLETS): a prospective cohort study. *Health Technol Assess* 2013;17:i–xiv, .
18 Li X. A-134 Comparative Analysis of ALT and AST Measurements: Impact of P5P Activators on Platform Discrepancies. *Clin Chem* 2024;70:i50.
19 Talli I, Marchioro L, Zaninotto M, *et al*. Measurement of AST and ALT with Pyridoxal-5'-Phosphate according to IFCC: A decades-long gap seems to be filled. *Clin Chim Acta* 2025;569:120158.
20 Evans C, MacKenzie F, Marrington R. Variation in liver function testing and the effect of pyridoxal-5-phosphate on ALT, AST and FIB-4 results. *Ann Clin Biochem* 2024;61:459–68.
21 Bergmeyer HU, Hørder M, Rej R. International Federation of Clinical Chemistry (IFCC) Scientific Committee, Analytical Section: approved recommendation (1985) on IFCC methods for the measurement of catalytic concentration of enzymes. Part 2. IFCC method for aspartate aminotransferase (L-aspartate: 2-oxoglutarate aminotransferase, EC 2.6.1.1). *J Clin Chem Clin Biochem* 1986;24:497–510.
22 Chapko MK, Dufour DR, Hatia RI, *et al*. Cost-effectiveness of strategies for testing current hepatitis C virus infection. *Hepatology* 2015;62:1396–404.
23 Williams AL, Hoofnagle JH. Ratio of serum aspartate to alanine aminotransferase in chronic hepatitis. Relationship to cirrhosis. *Gastroenterology* 1988;95:734–9.
24 Sterling RK, Lissen E, Clumeck N, *et al*. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology* 2006;43:1317–25.
25 McLernon DJ, Donnan PT, Sullivan FM, *et al*. Prediction of liver disease in patients whose liver function tests have been checked in primary care: model development and validation using population-based observational cohorts. *BMJ Open* 2014;4:e004837.
26 Gao J, Ahmed H, Cannings-John R, *et al*. A liver function test pathway significantly increases the early detection of chronic liver disease and cirrhosis. *Hepatol Commun* 2026;10:e0887.
27 McPherson S, Stewart SF, Henderson E, *et al*. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. *Gut* 2010;59:1265–9.
28 McPherson S, Armstrong MJ, Cobbold JF, *et al*. 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. *Lancet Gastroenterol Hepatol* 2022;7:755–69.
29 Sterling RK, Patel K, Duarte-Rojo A, *et al*. AASLD Practice Guideline on blood-based noninvasive liver disease assessment of hepatic fibrosis and steatosis. *Hepatology* 2025;81:321–57.
30 Berzigotti A, Tsochatzis E, Boursier J, *et al*. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis – 2021 update. *J Hepatol* 2021;75:659–89.
31 Mansour D, Grapes A, Herscovitz M, *et al*. Embedding assessment of liver fibrosis into routine diabetic review in primary care. *JHEP Rep* 2021;3:100293.
32 Miller MH, Fraser A, Leggett G, *et al*. Development and validation of diagnostic triage criteria for liver disease from a minimum data set enabling the "intelligent LFT" pathway for the automated assessment of deranged liver enzymes. *Frontline Gastroenterol* 2018;9:175–82.
33 Dillon JF, Miller MH, Robinson EM, *et al*. Intelligent liver function testing (iLFT): A trial of automated diagnosis and staging of liver disease in primary care. *J Hepatol* 2019;71:699–706.
34 Starr H, Newman A, Perumal M, *et al*. Prospective evaluation of a pilot implementation of liver health checks in primary care in England. *Frontline Gastroenterol* 2026.
35 European Association for the Study of the Liver, Clinical Practice Guidelines Panel: Chair, EASL Governing Board representative, *et al*. EASL recommendations on treatment of hepatitis C: Final update of the series☆. *J Hepatol* 2020;73:1170–218.
36 Gleeson D, Bornand R, Brownlee A, *et al*. British Society of Gastroenterology guidelines for diagnosis and management of autoimmune hepatitis. *Gut* 2025;74:1364–409.
37 National Institute for Health and Care Excellence (NICE). Cirrhosis in over 16s: assessment and management (NG50). 2016. Available: https://www.nice.org.uk/guidance/ng50/resources/cirrhosis-in-over-16s-assessment-and-management-pdf-1837506577093

38 National Institute for Health and Care Excellence (NICE). Hepatitis B and C testing: people at risk of infection (PH43). 2012. Available: https://www.nice.org.uk/guidance/ph43/resources/hepatitis-b-and-c-testing-people-at-risk-of-infection-pdf-1996356260293
39 Smout E, Ruf M, Buti M, *et al*. Blood-borne virus testing in European emergency departments: current evidence and service considerations. *Eur J Public Health* 2025;35:766–73.
40 European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of alcohol-related liver disease. *J Hepatol* 2018;69:154–81.
41 Parker R, Allison M, Anderson S, *et al*. Quality standards for the management of alcohol-related liver disease: consensus recommendations from the British Association for the Study of the Liver and British Society of Gastroenterology ARLD special interest group. *BMJ Open Gastroenterol* 2023;10:e001221.
42 National Guideline Centre (UK). Non-alcoholic fatty liver disease: assessment and management (NICE Guideline No. 49). London National Institute for Health and Care Excellence (NICE); 2016. Available: https://www.ncbi.nlm.nih.gov/books/NBK374135/
43 Hirschfield GM, Dyson JK, Alexander GJM, *et al*. The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines. *Gut* 2018;67:1568–94.
44 Barberio B, Massimi D, Cazzagon N, *et al*. Prevalence of Primary Sclerosing Cholangitis in Patients With Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. *Gastroenterology* 2021;161:1865–77.
45 Bowlus CL, Arrivé L, Bergquist A, *et al*. AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma. *Hepatology* 2023;77:659–702.
46 Culver EL, Bungay HK, Betts M, *et al*. Prevalence and long-term outcome of sub-clinical primary sclerosing cholangitis in patients with ulcerative colitis. *Liver Int* 2020;40:2744–57.
47 Chapman MH, Thorburn D, Hirschfield GM, *et al*. British Society of Gastroenterology and UK-PSC guidelines for the diagnosis and management of primary sclerosing cholangitis. *Gut* 2019;68:1356–78.
48 Chazouilleres O, Beuers U, Bergquist A, *et al*. EASL Clinical Practice Guidelines on sclerosing cholangitis. *J Hepatol* 2022;77:761–806.
49 Lunder AK, Hov JR, Borthne A, *et al*. Prevalence of Sclerosing Cholangitis Detected by Magnetic Resonance Cholangiography in Patients With Long-term Inflammatory Bowel Disease. *Gastroenterology* 2016;151:660–9.
50 European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Drug-induced liver injury. *J Hepatol* 2019;70:1222–61.
51 Fontana RJ, Liou I, Reuben A, *et al*. AASLD practice guidance on drug, herbal, and dietary supplement-induced liver injury. *Hepatology* 2023;77:1036–65.
52 Warren RB, Weatherhead SC, Smith CH, *et al*. British Association of Dermatologists' guidelines for the safe and effective prescribing of methotrexate for skin disease 2016. *Br J Dermatol* 2016;175:23–44.
53 Atallah E, Grove JI, Crooks C, *et al*. Risk of liver fibrosis associated with long-term methotrexate therapy may be overestimated. *J Hepatol* 2023;78:989–97.
54 Babakinejad P, Lapsley R, Forster L, *et al*. Cumulative methotrexate dose is not associated with liver fibrosis in patients with a history of moderate-to-severe psoriasis. *Br J Dermatol* 2024;191:275–83.
55 Lewis JH, Mortensen ME, Zweig S, *et al*. Efficacy and safety of high-dose pravastatin in hypercholesterolemic patients with well-compensated chronic liver disease: Results of a prospective, randomized, double-blind, placebo-controlled, multicenter trial. *Hepatology* 2007;46:1453–63.
56 Bays H, Cohen DE, Chalasani N, *et al*. The National Lipid Association's Statin Safety Task F. An assessment by the Statin Liver Safety Task Force: 2014 update. *J Clin Lipidol* 2014;8:S47–57.
57 LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Roussel Uclaf Causality Assessment Method (RUCAM) in Drug Induced Liver Injury. 2019. Available: https://www.ncbi.nlm.nih.gov/books/NBK548272/ [Accessed 23 Mar 2026].
58 Cullis JO, Fitzsimons EJ, Griffiths WJ, *et al*. Investigation and management of a raised serum ferritin. *Br J Haematol* 2018;181:331–40.
59 Fitzsimons EJ, Cullis JO, Thomas DW, *et al*. Diagnosis and therapy of genetic haemochromatosis (review and 2017 update). *Br J Haematol* 2018;181:293–303.
60 Schilsky ML, Roberts EA, Bronstein JM, *et al*. A multidisciplinary approach to the diagnosis and management of Wilson disease: 2022 Practice Guidance on Wilson disease from the American Association for the Study of Liver Diseases. *Hepatology* 2025;82:E41–90.
61 Miravitlles M, Nuñez A, Torres-Durán M, *et al*. The Importance of Reference Centers and Registries for Rare Diseases: The Example of Alpha-1 Antitrypsin Deficiency. *COPD* 2020;17:346–54.
62 Patel KM, Zhang J, Marsden J, *et al*. Missed and Delayed Diagnoses of Chronic Liver Disease in Primary Care Patients with Cirrhosis. *Dig Dis Sci* 2024;69:3721–8.
63 Prati D, Taioli E, Zanella A, *et al*. Updated definitions of healthy ranges for serum alanine aminotransferase levels. *Ann Intern Med* 2002;137:1–10.
64 Tan EX, Huang DQ, Yee NTS, *et al*. Upper limit of normal ALT levels in health and metabolic diseases: Pooled analysis of 423,355 individuals with bootstrap modelling. *Aliment Pharmacol Ther* 2024;59:984–92.
65 Browning JD, Szczepaniak LS, Dobbins R, *et al*. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology* 2004;40:1387–95.
66 Donnan PT, McLernon D, Steinke D, *et al*. Development of a decision support tool to facilitate primary care management of patients with abnormal liver function tests without clinically apparent liver disease [HTA03/38/02]. Abnormal Liver Function Investigations Evaluation (ALFIE). *BMC Health Serv Res* 2007;7:54.
67 Smith A, Jones B, Patel C. ALFIE 2: follow up on liver function test persistence in UK primary care. Unpublished internal report. 2024.
68 Taylor RS, Taylor RJ, Bayliss S, *et al*. Association Between Fibrosis Stage and Outcomes of Patients With Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. *Gastroenterology* 2020;158:1611–25.
69 European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of cholestatic liver diseases. *J Hepatol* 2009;51:237–67.
70 European Association for the Study of the Liver. EASL Clinical Practice Guidelines on genetic cholestatic liver diseases. *J Hepatol* 2024;81:303–25.
71 Haddadin R, Aboujaoude C, Trad G. Congestive Hepatopathy: A Review of the Literature. *Cureus* 2024;16:e58766.
72 Stern C, Castera L. Non-invasive diagnosis of hepatic steatosis. *Hepatol Int* 2017;11:70–8.
73 Yen Y-H, Kuo F-Y, Chen C-H, *et al*. Ultrasound is highly specific in diagnosing compensated cirrhosis in chronic hepatitis C patients in real world clinical practice. *Medicine (Baltimore)* 2019;98:e16270.
74 Suddle A, Reeves H, Hubner R, *et al*. British Society of Gastroenterology guidelines for the management of hepatocellular carcinoma in adults. *Gut* 2024;73:1235–68.
75 Sharma R, Aravinthan AD, Qurashi M, *et al*. Hepatocellular carcinoma surveillance: minimum standards. *Frontline Gastroenterol* 2025;16:flgastro–2024.
76 Society of Radiographers (SoR), British Medical Ultrasound Society (BMUS). Guidelines for professional ultrasound practice. 2025.1–193. Available: https://www.sor.org/getmedia/bf46f8de-b95e-4cd6-9351-797ceb43674f/2025-SoR-and-BMUS-guidelines-9th-Ed-FINAL
77 American College of Radiology. LI-RADS® ultrasound surveillance v2024 core. 2024. Available: https://edge.sitecorecloud.io/americancoldf5f-acrorgf92a-productioncb02-3650/media/ACR/Files/RADS/LI-RADS/LI-RADS-US-Surveillance-v2024-Core.pdf [Accessed 15 Apr 2026].
78 Novak A, Acharya A, Beer S, *et al*. Pilot feasibility study to determine the utility of direct access and quantitative magnetic resonance cholangiopancreatography (MRCP) in the assessment of suspected acute biliary or ductal gallstone presentations. *BMC Gastroenterol* 2025;25:72.
79 National Institute of Health and Care Excellence (NICE). Suspected cancer: recognition and referral (NG12). 2026. Available: https://www.nice.org.uk/guidance/ng12/resources/suspected-cancer-recognition-and-referral-pdf-1837268071621
80 Moran GW, Gordon M, Sinopoulou V, *et al*. British Society of Gastroenterology guidelines on inflammatory bowel disease in adults: 2025. *Gut* 2025;74:s1–101.
81 Amini-Salehi E, Letafatkar N, Norouzi N, *et al*. Global Prevalence of Nonalcoholic Fatty Liver Disease: An Updated Review Meta-Analysis comprising a Population of 78 million from 38 Countries. *Arch Med Res* 2024;55:103043.
82 Karhiaho IP, Kurki SH, Parviainen HI, *et al*. The hidden epidemic: Uncovering incidental fatty liver disease and its metabolic comorbidities by datamining in a hospital data lake - A real-world cohort study. *Diabetes Res Clin Pract* 2024;210:111609.
83 Patel K, Asrani SK, Fiel MI, *et al*. Accuracy of blood-based biomarkers for staging liver fibrosis in chronic liver disease: A systematic review supporting the AASLD Practice Guideline. *Hepatology* 2025;81:358–79.
84 Duarte-Rojo A, Taouli B, Leung DH, *et al*. Imaging-based noninvasive liver disease assessment for staging liver fibrosis in chronic liver disease: A systematic review supporting the AASLD Practice Guideline. *Hepatology* 2025;81:725–48.
85 Vali Y, Lee J, Boursier J, *et al*. Biomarkers for staging fibrosis and non-alcoholic steatohepatitis in non-alcoholic fatty liver disease (the LITMUS project): a comparative diagnostic accuracy study. *Lancet Gastroenterol Hepatol* 2023;8:714–25.
86 de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015;63:743–52.
87 Gawrieh S, Wilson LA, Cummings OW, *et al*. Histologic Findings of Advanced Fibrosis and Cirrhosis in Patients With Nonalcoholic Fatty Liver Disease Who Have Normal Aminotransferase Levels. *Am J Gastroenterol* 2019;114:1626–35.
88 Sullivan MK, Daher HB, Rockey DC. Normal or near normal aminotransferase levels in patients with alcoholic cirrhosis. *Am J Med Sci* 2022;363:484–9.
89 Lackner C, Spindelboeck W, Haybaeck J, *et al*. Histological parameters and alcohol abstinence determine long-term prognosis in patients with alcoholic liver disease. *J Hepatol* 2017;66:610–8.
90 Dulai PS, Singh S, Patel J, *et al*. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. *Hepatology* 2017;65:1557–65.
91 Thiele M, Johansen S, Israelsen M, *et al*. Noninvasive assessment of hepatic decompensation. *Hepatology* 2025;81:1019–37.

92 Anstee QM, Berentzen TL, Nitze LM, *et al*. Prognostic utility of Fibrosis-4 Index for risk of subsequent liver and cardiovascular events, and all-cause mortality in individuals with obesity and/or type 2 diabetes: a longitudinal cohort study. *Lancet Reg Health Eur* 2024;36:100780.
93 Lee J, Vali Y, Boursier J, *et al*. Prognostic accuracy of FIB-4, NAFLD fibrosis score and APRI for NAFLD-related events: A systematic review. *Liver International* 2021;41:261–70.
94 McPherson S, Hardy T, Dufour J-F, *et al*. Age as a Confounding Factor for the Accurate Non-Invasive Diagnosis of Advanced NAFLD Fibrosis. *Am J Gastroenterol* 2017;112:740–51.
95 Mózes FE, Lee JA, Selvaraj EA, *et al*. Diagnostic accuracy of non-invasive tests for advanced fibrosis in patients with NAFLD: an individual patient data meta-analysis. *Gut* 2022;71:1006–19.
96 Kjaergaard M, Lindvig KP, Thorhauge KH, *et al*. Using the ELF test, FIB-4 and NAFLD fibrosis score to screen the population for liver disease. *J Hepatol* 2023;79:277–86.
97 Srivastava A, Gailer R, Tanwar S, *et al*. Prospective evaluation of a primary care referral pathway for patients with non-alcoholic fatty liver disease. *J Hepatol* 2019;71:371–8.
98 Saarinen K, Färkkilä M, Jula A, *et al*. Enhanced liver Fibrosis® test predicts liver-related outcomes in the general population. *JHEP Rep* 2023;5:100765.
99 Vidal-Trécan T, Julla J-B, El Khoury T, *et al*. Effectiveness of Six International Guidelines Using Fibrosis-4 and FibroScan for Risk Stratification of Metabolic Dysfunction-associated Steatotic Liver Disease in Type 2 Diabetes. *Clin Gastroenterol Hepatol* 2025;23:2176–86.
100 Yip TC-F, Lee HW, Lin H, *et al*. Prognostic performance of the two-step clinical care pathway in metabolic dysfunction-associated steatotic liver disease. *J Hepatol* 2025;83:304–14.
101 Anstee QM, Lawitz EJ, Alkhouri N, *et al*. Noninvasive Tests Accurately Identify Advanced Fibrosis due to NASH: Baseline Data From the STELLAR Trials. *Hepatology* 2019;70:1521–30.
102 Park H, Yoon EL, Kim M, *et al*. Reappraisal of fibrosis-4 index and non-alcoholic fatty liver disease fibrosis score for advanced fibrosis in average-risk population. *Front Med* 2022;9:1024836.
103 Chung SM, Kang MK, Moon JS, *et al*. Performance of Simple Fibrosis Score in Non-Alcoholic Fatty Liver Disease with and without Type 2 Diabetes. *Endocrinol Metab* 2023;38:277–81.
104 Hagström H, Talbäck M, Andreasson A, *et al*. Repeated FIB-4 measurements can help identify individuals at risk of severe liver disease. *J Hepatol* 2020;73:1023–9.
105 Inadomi C, Takahashi H, Ogawa Y, *et al*. Accuracy of the Enhanced Liver Fibrosis test, and combination of the Enhanced Liver Fibrosis and non-invasive tests for the diagnosis of advanced liver fibrosis in patients with non-alcoholic fatty liver disease. *Hepatol Res* 2020;50:682–92.
106 McPherson S, Dyson JK, Jopson L, *et al*. How effective are experienced hepatologists at staging fibrosis using non-invasive fibrosis tests in patients with metabolic dysfunction-associated steatotic liver disease? *Aliment Pharmacol Ther* 2024;60:267–73.
107 Kwo PY, Cohen SM, Lim JK. ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. *Am J Gastroenterol* 2017;112:18–35.
108 Sharma C, Cococcia S, Ellis N, *et al*. Systematic review: Accuracy of the enhanced liver fibrosis test for diagnosing advanced liver fibrosis and cirrhosis. *J Gastroenterol Hepatol* 2021;36:1788–802.
109 Pearson M, Nobes J, Macpherson I, *et al*. Enhanced liver fibrosis (ELF) score predicts hepatic decompensation and mortality. *JHEP Rep* 2024;6:101062.
110 Lichtinghagen R, Pietsch D, Bantel H, *et al*. The Enhanced Liver Fibrosis (ELF) score: normal values, influence factors and proposed cut-off values. *J Hepatol* 2013;59:236–42.
111 Papatheodoridi M, Hiriart JB, Lupsor-Platon M, *et al*. Refining the Baveno VI elastography criteria for the definition of compensated advanced chronic liver disease. *J Hepatol* 2021;74:1109–16.
112 Cobbold JF, Miller H, Hallsworth K, *et al*. The use of pharmacotherapies in non-cirrhotic metabolic dysfunction-associated steatohepatitis: a UK expert consensus. *Lancet Gastroenterol Hepatol* 2026;11:616–26.
113 Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, *et al*. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology* 2023;77:1797–835.
114 Zhou X-D, Li Y-T, Kim SU, *et al*. Longitudinal Changes in Fibrosis Markers: Monitoring Stiffness/Fibrosis Progression and Prognostic Outcomes in MASLD. *Clin Gastroenterol Hepatol* 2026;24:394–406.
115 Siddiqui MS, Yamada G, Vuppalanchi R, *et al*. Diagnostic Accuracy of Noninvasive Fibrosis Models to Detect Change in Fibrosis Stage. *Clin Gastroenterol Hepatol* 2019;17:1877–85.
116 Hagström H, Nasr P, Ekstedt M, *et al*. Accuracy of Noninvasive Scoring Systems in Assessing Risk of Death and Liver-Related Endpoints in Patients With Nonalcoholic Fatty Liver Disease. *Clin Gastroenterol Hepatol* 2019;17:1148–56.
117 Boursier J, Vergniol J, Guillet A, *et al*. Diagnostic accuracy and prognostic significance of blood fibrosis tests and liver stiffness measurement by FibroScan in non-alcoholic fatty liver disease. *J Hepatol* 2016;65:570–8.
118 Shili-Masmoudi S, Wong GL-H, Hiriart J-B, *et al*. Liver stiffness measurement predicts long-term survival and complications in non-alcoholic fatty liver disease. *Liver Int* 2020;40:581–9.
119 Munteanu M, Pais R, Peta V, *et al*. Long-term prognostic value of the FibroTest in patients with non-alcoholic fatty liver disease, compared to chronic hepatitis C, B, and alcoholic liver disease. *Aliment Pharmacol Ther* 2018;48:1117–27.
120 Rinella ME, Dufour J-F, Anstee QM, *et al*. Non-invasive evaluation of response to obeticholic acid in patients with NASH: Results from the REGENERATE study. *J Hepatol* 2022;76:536–48.
121 Sanyal AJ, Anstee QM, Trauner M, *et al*. Cirrhosis regression is associated with improved clinical outcomes in patients with nonalcoholic steatohepatitis. *Hepatology* 2022;75:1235–46.
122 Neuberger J, Patel J, Caldwell H, *et al*. Guidelines on the use of liver biopsy in clinical practice from the British Society of Gastroenterology, the Royal College of Radiologists and the Royal College of Pathology. *Gut* 2020;69:1382–403.
123 Williams R, Aspinall R, Bellis M, *et al*. Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. *Lancet* 2014;384:1953–97.
124 Rogers G, Landi S, Purssell H, *et al*. Proactive case-finding and risk-stratification in people at risk of chronic liver disease in Greater Manchester: a cost-effectiveness analysis. *BMJ Public Health* 2026;4:e003480.
125 Semmler G, Thöne P, Embacher J, *et al*. Prevalence of Fibrosis and Applicability of Lab-Based Noninvasive Tests From Primary to Tertiary Care. *Clin Gastroenterol Hepatol* 2025.
126 Zamani M, Alizadeh-Tabari S, Ajmera V, *et al*. Global Prevalence of Advanced Liver Fibrosis and Cirrhosis in the General Population: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2025;23:1123–34.
127 Serra-Burriel M, Graupera I, Torán P, *et al*. Transient elastography for screening of liver fibrosis: Cost-effectiveness analysis from six prospective cohorts in Europe and Asia. *J Hepatol* 2019;71:1141–51.
128 Graupera I, Thiele M, Serra-Burriel M, *et al*. Low Accuracy of FIB-4 and NAFLD Fibrosis Scores for Screening for Liver Fibrosis in the Population. *Clin Gastroenterol Hepatol* 2022;20:2567–76.
129 Starr H, Tanney C, Little E, *et al*. P52 Prevalence and characteristics of people with advanced chronic liver disease in primary care. BSG LIVE'26, 22–25 June 2026, LEX Liverpool; 2026:A117–8.
130 Ajmera V, Cepin S, Tesfai K, *et al*. A prospective study on the prevalence of NAFLD, advanced fibrosis, cirrhosis and hepatocellular carcinoma in people with type 2 diabetes. *J Hepatol* 2023;78:471–8.
131 Sanchez-Bao AM, Soto-Gonzalez A, Delgado-Blanco M, *et al*. Identifying advanced MAFLD in a cohort of T2DM and clinical features. *Front Endocrinol (Lausanne)* 2023;14:1058995.
132 En Li Cho E, Ang CZ, Quek J, *et al*. Global prevalence of non-alcoholic fatty liver disease in type 2 diabetes mellitus: an updated systematic review and meta-analysis. *Gut* 2023;72:2138–48.
133 Ciardullo S, Monti T, Perseghin G. High Prevalence of Advanced Liver Fibrosis Assessed by Transient Elastography Among U.S. Adults With Type 2 Diabetes. *Diabetes Care* 2021;44:519–25.
134 Forlano R, Stanic T, Jayawardana S, *et al*. A prospective study on the prevalence of MASLD in people with type-2 diabetes in the community. Cost effectiveness of screening strategies. *Liver Int* 2024;44:61–71.
135 Zhang E, Wartelle-Bladou C, Lepanto L, *et al*. Cost-utility analysis of nonalcoholic steatohepatitis screening. *Eur Radiol* 2015;25:3282–94.
136 Tanajewski L, Harris R, Harman DJ, *et al*. Economic evaluation of a community-based diagnostic pathway to stratify adults for non-alcoholic fatty liver disease: a Markov model informed by a feasibility study. *BMJ Open* 2017;7:e015659.
137 Younossi ZM, Paik JM, Henry L, *et al*. Pharmaco-Economic Assessment of Screening Strategies for High-Risk MASLD in Primary Care. *Liver Int* 2025;45:e16119.
138 Singh S, Allen AM, Wang Z, *et al*. Sa1052 Fibrosis Progression in Nonalcoholic Fatty Liver Versus Nonalcoholic Steatohepatitis: A Systematic Review and Meta-Analysis of Paired-Biopsy Studies. *Gastroenterology* 2014;146:S–947.
139 Quek J, Chan KE, Wong ZY, *et al*. Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2023;8:20–30.
140 National Institute for Health and Care Excellence (NICE). Alcohol-use disorders: diagnosis and management of physical complications. 2010. Available: https://www.nice.org.uk/guidance/cg100/resources/alcoholuse-disorders-diagnosis-and-management-of-physical-complications-pdf-35109322251973
141 National Confidential Enquiry into Patient Outcome and Death (NCEPOD). Measuring the Units: A review of patients who died with alcohol-related disease. 2013.1–25. Available: https://www.ncepod.org.uk/2013report1/downloads/MeasuringTheUnits_FullReport.pdf
142 Rhodes FA, Cococcia S, Patel P, *et al*. Is there scope to improve the selection of patients with alcohol-related liver disease for referral to secondary care? A retrospective analysis of primary care referrals to a UK liver centre, incorporating simple blood tests. *BMJ Open* 2021;11:e047786.

143 Knight H, Harman D, Morling JR, *et al*. Acceptability of chronic liver disease screening in a UK primary care setting: a qualitative evaluation. *BMJ Open* 2020;10:e041574.
144 Legros L, Bardou-Jacquet E, Turlin B, *et al*. Transient Elastography Accurately Screens for Compensated Advanced Chronic Liver Disease in Patients With Ongoing or Recent Alcohol Withdrawal. *Clin Gastroenterol Hepatol* 2022;20:1542–52.
145 Carrier P, Girard M, Debette-Gratien M, *et al*. Liver elastometry and alcohol withdrawal: Median-term follow-up in a psychiatric unit. *Alcohol* 2020;89:49–56.
146 Lahmek P, Meunier N, Michel L, *et al*. Using transient elastography as a screening tool for liver fibrosis in addiction service. *Presse Med* 2014;43:e17–31.
147 Archer AJ, Phillips J, Subhani M, *et al*. Proactive case finding of alcohol-related liver disease in high-risk populations: A systematic review. *Liver Int* 2024;44:1298–308.
148 Matthews K, MacGilchrist A, Coulter-Smith M, *et al*. A nurse-led FibroScan® outreach clinic encourages socially deprived heavy drinkers to engage with liver services. *J Clin Nurs* 2019;28:650–62.
149 Subhani M, Harman DJ, Scott RA, *et al*. Transient Elastography in Community Alcohol Services: Can It Detect Significant Liver Disease and Impact Drinking Behaviour? *Biomedicines* 2022;10:477.
150 Owens L, Thompson A, Siju C, *et al*. A six month follow-up study to determine the clinical utility and patient acceptability of fibroelastography in detection and treatment of alcohol-related liver disease. *J Hepatol* 2018;68:S365.
151 Sheron N, Moore M, O'Brien W, *et al*. Feasibility of detection and intervention for alcohol-related liver disease in the community: the Alcohol and Liver Disease Detection study (ALDDeS). *Br J Gen Pract* 2013;63:e698–705.
152 El-Gohary M, Moore M, Roderick P, *et al*. Local care and treatment of liver disease (LOCATE) - A cluster-randomized feasibility study to discover, assess and manage early liver disease in primary care. *PLoS One* 2018;13:e0208798.
153 Harman DJ, Ryder SD, James MW, *et al*. Direct targeting of risk factors significantly increases the detection of liver cirrhosis in primary care: a cross-sectional diagnostic study utilising transient elastography. *BMJ Open* 2015;5:e007516.
154 Cook PA, Morleo M, Billington D, *et al*. Evaluation of work-based screening for early signs of alcohol-related liver disease in hazardous and harmful drinkers: the PrevAIL study. *BMC Public Health* 2015;15:532.
155 European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of liver diseases in pregnancy. *J Hepatol* 2023;79:768–828.
156 National Institue for Health and Care Excellence (NICE). Scenario: General principles of managing adults on DMARDs. 2023. Available: https://cks.nice.org.uk/topics/dmards/management/general-principles-of-managing-dmards/
157 Fragoulis GE, Nikiphorou E, Dey M, *et al*. 2022 EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2023;82:742–53.
158 European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2025;83:502–83.