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Title

MASLD in focus: From Mechanisms to Diagnosis and Management in Adults

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent chronic liver disease globally and a major cause of liver-related and cardiometabolic morbidity. MASLD is defined by the presence of hepatic steatosis and at least 1 of 5 cardiometabolic features in the absence of secondary causes of liver disease and significant alcohol consumption (>20 grams per day for women and 30 grams per day for men). The recent reclassification of non-alcoholic fatty liver disease to MASLD represents a paradigm shift towards recognising the central role of systemic metabolic dysfunction and cardiometabolic risk factors in disease pathogenesis and development of complications. The pathophysiology of MASLD is complex, multifaceted, and interconnected, involving adipose tissue dysfunction, altered hepatic lipid metabolism, mitochondrial and endoplasmic reticulum stress, dysregulation of the gut-liver axis, and genetic predisposition. The severity of liver fibrosis remains the strongest predictor of all-cause mortality and liver-specific morbidity and mortality, and the burden of cardiometabolic dysfunction impacts the risk of complications in MASLD. Non-invasive serum-based and imaging-based biomarkers are central to identifying advanced liver fibrosis and guiding risk stratification. This narrative review summarises the current understanding of MASLD pathogenesis, the clinical utility of non-invasive diagnostics, and compares international guidelines for disease management. This review also discusses approved and emerging treatment options for MASLD, recognising the current need for developing strategies for monitoring treatment efficacy.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), the new name for non-alcoholic fatty liver disease (NAFLD), has been through a number of official and unofficial name changes in the last few years. Finally, in June 2023, a consensus process led by the American Association for the Study of Liver Disease (AASLD), the European Association for the Study of the Liver (EASL), and the Asociación Latinoamericana para el Estudio del Hígado established the new officially recognised nomenclature for MASLD.[1]

Under this revised disease framework, steatotic liver disease (SLD) was introduced as the overarching term referring to all liver diseases characterised by hepatic steatosis, irrespective of aetiology.[1] A diagnosis of MASLD requires the presence of hepatic steatosis, typically identified by non-invasive imaging technology such as ultrasound, in combination with one or more common cardiometabolic risk factors following the exclusion of secondary causes of liver disease (**Figure 1**).[1, 2] A diagnosis of MASLD also allows for moderate alcohol consumption (less than 20 and 30 grams per day for women and men, respectively)[3] to discriminate pure MASLD from Metabolic dysfunction Alcohol-related Liver Disease (Met-ALD where the amounts of alcohol consumed are 20-50 grams per day for women and 30-60 grams per day for men). The introduction of the new term MASLD constitutes a substantive revision in disease classification, acknowledging the advances in understanding the disease's systemic and multi-organ characteristics, and moving beyond a liver-specific perspective. Evidence indicates an almost complete overlap between populations previously diagnosed with NAFLD and those now classified with MASLD.[4-6] This finding underscores the clinical relevance of the MASLD definition and indicates that the revised criteria refine diagnostic precision without expanding the patient population.

The global prevalence of MASLD in the general adult population has increased from 25% (1990-2015)[7] to 38% (2016-2019)[8] and is continuing to grow, with an expected global prevalence of 55% by 2040.[7-11] Worldwide, MASLD has become the most common chronic liver disease, and approximately 4-5% of adults develop MASLD each year.[8, 12, 13] Regional prevalences of MASLD vary significantly due to lifestyle and genetic differences,[14, 15] with the higher rates observed in Latin America (44%)[16] and the lower rates in Western Europe (25%).[8] Additionally, individuals living with obesity or type 2 diabetes mellitus (T2DM) are disproportionately affected by MASLD,[15, 17, 18] with approximately 65-75% of this high-risk population being affected by the disease.[16]

With MASLD accepted as the new nomenclature for NAFLD, it is timely to review the mechanisms, diagnosis, and management of this common and burdensome liver disease. This narrative review discusses the complex pathophysiological mechanisms of MASLD, and the utility of non-invasive serum-based and imaging-based biomarkers used in clinical practice to identify advanced liver fibrosis. We also discuss international guidelines for identifying, managing, and monitoring MASLD in adults, as well as current and emerging pharmacological therapeutic options for MASLD. Finally, we highlight current knowledge gaps in MASLD research.

Sources and selection criteria

Clinical pharmaceutical trials in MASLD/MASH were identified on 31 August 2025 using ClinicalTrials.gov with the following search terms: "non-alcoholic fatty liver disease" OR "NAFLD" OR "non-alcoholic steatohepatitis" OR "NASH" OR "metabolic dysfunction-associated steatotic liver disease" OR "MASLD" OR "metabolic dysfunction-associated steatohepatitis" OR "MASH"; filters applied: Not yet recruiting, Recruiting, Active (not recruiting); Phase: 3; Study type: Interventional.

Non-invasive serum-based and imaging-based biomarkers for liver fibrosis were identified on 31 August 2025 using PubMed with the following search criteria: "metabolic dysfunction-associated steatotic liver disease" OR "MASLD" OR "non-alcoholic fatty liver disease" OR "NAFLD" AND "Enhanced Liver Fibrosis test" OR "ELF test" OR "FIB-4" OR "AST to ALT ratio" OR "BARD score" OR "NAFLD fibrosis" score OR "APRI score" or "FibroScan" OR "vibration-controlled transient elastography" OR "VCTE" or "magnetic resonance imaging" OR "MRE" OR "point shear wave elastography" OR "pSWE"; filters applied: meta-analysis, date: 2020 to 2025, free full text, humans, adult 19+ years. We only considered articles in peer-reviewed journals.

Prognosis and complications

The severity of liver fibrosis remains the strongest predictor of all-cause mortality and liver-specific morbidity and mortality in people with MASLD.[19-23] Based on liver biopsy histology, the severity of liver fibrosis is scored

on a five-stage scale: F0 (absence of fibrosis), F1 (perisinusoidal or portal fibrosis), F2 (perisinusoidal and portal or periportal fibrosis), F3 (septal and bridging fibrosis) and F4 (cirrhosis). The risks of all-cause and liver-specific mortality and morbidity increase with advancing fibrosis severity (**Figure 1**).[19-22, 24-27] Worldwide, MASLD has rapidly become the most common chronic liver disease[10] and represents a significant research priority due to its rising global prevalence and substantial clinical burden.

MASLD is a key risk factor for hepatocellular carcinoma (HCC), the risk of which increases in parallel with liver fibrosis severity and is the highest in those with cirrhosis, where the annual incidence of HCC is thought to range from approximately 0.7% to 2.5%.[28, 29] MASLD also increases the risk of fatal and non-fatal cardiovascular disease events,[30] chronic kidney disease stage ≥3,[31] certain extrahepatic cancers (e.g., gastrointestinal, urinary tract, and breast cancers),[32, 33] and impaired quality of life.[34, 35] Solidifying its multisystem nature, the cardiac-specific, extrahepatic cancer-specific, and liver-specific mortality rates are thought to account for about 33%, 23% and 7%, respectively, of total mortality in patients with MASLD.[9]

Pathophysiology

Figure 2 illustrates a framework for understanding how perturbations in adipose tissue function, lipid metabolism, inflammatory signaling, gut-liver axis crosstalk, and genetic predisposition may interact to drive hepatic steatosis, systemic cardiometabolic dysfunction, and ultimately progression to liver fibrosis and advanced chronic disease states. While this review provides an overview of key pathophysiological mechanisms underlying MASLD, a comprehensive discussion is available in the recent literature.[36-38]

Adipose tissue dysfunction and lipid metabolism

When subcutaneous adipose tissue expansion is inadequate and/or insulin resistance impairs the suppression of lipolysis, the resulting increased flux of non-esterified fatty acids (NEFAs) into visceral adipose tissue and the liver, where they provide a key fuel source for the formation and expansion of hepatic lipid droplets.[39] Indeed, clinical studies have demonstrated a positive association between markers of adipose tissue insulin resistance, such as the adipose tissue insulin resistance index and adiponectin concentrations, and both the presence and progression of MASLD.[31, 40, 41] Excess hepatic NEFAs also contribute to the formation of toxic lipid intermediates such as ceramides and diacylglycerols that are known to contribute to hepatocyte dysfunction and inflammation.

The hypertrophic expansion of adipocytes can lead to the recruitment and activation of immune cells, the propagation of inflammatory signaling, and the release of proinflammatory mediators, such as tumor necrosis factor-alpha and interleukin 1-beta. Consequently, adipose tissue can become fibrotic, further limiting its expansion and exacerbating hepatic lipid deposition and metabolic dysfunction.[31, 42] Indeed, markers of adipose fibrogenesis, such as the expression of collagen VI gene isoforms and transforming growth factor-beta, have been found to be associated with the presence and severity of MASLD.[31, 42] As adipose tissue becomes dysfunctional, its profile of secreted adipokines (e.g., leptin, adiponectin and resistin) becomes altered, adding a further layer of dysfunction.[43, 44]

Hepatic mechanisms

Alongside the increased release of NEFAs from expanded and dysfunctional adipose tissue, hepatic de novo lipogenesis (DNL) is pathologically upregulated in individuals with cardiometabolic derangements (**Figure 2**). In obesity, increased expression of transcriptional regulators sterol regulatory element-binding protein-1c (SREBP-1c) and carbohydrate-responsive element-binding protein (ChREBP) promotes the conversion of carbohydrates into NEFAs in the liver. This increase in DNL fuels the synthesis of high levels of intrahepatic triglycerides (TAGs) and toxic lipid intermediates, which contribute to hepatic lipid droplet formation and inflammation.[45] The expansion of hepatic lipid droplets is also thought to induce physical stress and distort the cells' nuclei, potentially exacerbating cell stress, inflammation and hepatic fibrogenesis.[46, 47] Importantly, increased dietary fructose is now recognised as a driver of hepatic lipid accumulation and inflammation in MASLD.[48, 49]

Beyond local effects, alterations in the secretion of hepatic signaling proteins (i.e., hepatokines), such as fibroblast growth factor 21 (FGF21), fetuin-A, and angiopoietin-like proteins, can also play important roles in the pathophysiology of MASLD. These alterations have been proposed to affect inter-organ communication and negatively impact nutrient metabolism in both the liver and extrahepatic tissues, such as muscle and adipose tissue.[43]

Gut-liver axis and microbiome dysfunction

The gut microbiota and gut-liver axis are important players in the pathophysiology of MASLD, and intestinal dysbiosis is commonly observed in patients with MASLD (**Figure 2**). In a randomised trial of patients with NAFLD that also monitored changes in the fecal microbiome by 16S ribosomal DNA sequencing, one year of administration of a symbiotic combination (probiotic and prebiotic) altered the fecal microbiome but did not reduce liver fat content or markers of liver fibrosis.[50] Recent meta-analyses indicate that gut microbiomes in patients with MASLD are typically less taxonomically rich and diverse than those of healthy individuals.[51-53] Additionally, MASLD is often associated with an enrichment of potentially pro-inflammatory genera, such as *Fusobacterium* and *Escherichia,* and a depletion of barrier-protective taxa, such as *Ruminococcaceae* and *Faecalibacterium*.[51-53] These compositional shifts in gut microbes are thought to impair intestinal barrier integrity. Indeed, a 2020 meta-analysis of 14 studies found that markers of intestinal permeability were elevated in patients with SLD compared to healthy controls.[54] **Table 1** lists some of the mechanisms (e.g., intestinal dysbiosis and altered gut microbiota metabolite production) and their consequences to highlight the important roles of the microbiome and the gut-liver axis in the pathophysiology of MASLD.

Genetic predisposition

Genetic predisposition accounts for ~50% of MASLD variability, and genome-wide association studies have identified the most common genetic determinants.[55, 56] The most common and impactful genetic determinant of MASLD is the patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) rs738409 variant, which results in an isoleucine-to-methionine substitution at position 148 (I148M).[57] This risk allele is thought to be present in approximately 25% of the global population, though studies indicate that its distribution varies between populations.[58] **Table 2** summarises the functional consequences and clinical impact of *PNPLA3*-I148M. Importantly, the detrimental impact of *PNPLA3*-I148M is strongly modified by overall adiposity and metabolic dysfunction through gene-environment interactions.[59-61] In addition to *PNPLA3*-I148M, other genetic variants, e.g., transmembrane 6 superfamily member 2 (*TM6SF2)* (E167K)[62] and membrane-bound O-acyltransferase domain-containing 7 (*MBOAT7)* (rs641738) [62] may contribute to the development and progression of MASLD (**Table 2**).[56] Genomic studies have highlighted the importance of genetics in MASLD and the potential utility of polygenic and partitioned polygenic risk scores to identify those at risk of MASLD complications and to cluster patients with MASLD according to differing hepatic and extrahepatic complication risks.[56, 63]

Diagnosis

Early detection of MASLD is challenging, mainly because it is asymptomatic and because there is currently no specific test for MASLD. MASLD is often discovered incidentally during routine blood tests or abdominal ultrasounds for other conditions. For instance, a clinician may investigate liver health following an incidental finding of a steatotic liver on ultrasonography or after a routine liver function test (LFT) that indicates abnormal liver enzyme concentrations, such as an increased serum alanine aminotransferase (ALT). An abnormal LFT can indicate potential liver issues, such as cell damage or impaired liver function[64, 65] and is useful for identifying at-risk patients. However, it is important to underline that a normal LFT does not exclude MASLD, especially in asymptomatic patients.[66] Once there is suspicion of a liver issue, the approach to identifying patients with MASLD is usually sequential[36] but must include the testing for and exclusion of other causes such as viral hepatitis, haemochromatosis and Met-ALD/alcoholic liver disease. The latter should be assessed by careful history and may be supplemented by novel biomarkers, such as phosphatidylethanol, a direct biomarker for alcohol quantification,[67] which can be used alongside clinical history to objectively quantify alcohol consumption and differentiate between metabolic and alcohol-related aetiologies.[68]

Non-invasive serum biomarkers

The gold standard for identifying and staging liver fibrosis remains liver biopsy;[69] however, it is an invasive procedure with poor patient acceptance,[70, 71] is time-consuming and costly, and can be subject to potential sampling errors.[72-76] Additionally, given the global health care burden imposed by MASLD, liver biopsies do not provide a scalable approach to identifying or monitoring liver fibrosis.[8, 12, 13] Non-invasive serum biomarkers can offer a potential alternative and replacement to liver biopsy.[77] These biomarkers are

reproducible, avoid sampling errors, and eliminate intra-observer variations.[72, 78] Initially, serum biomarkers for liver fibrosis were developed by secondary care physicians to detect patients with advanced liver fibrosis (≥F3). In liver fibrosis staging, both direct and indirect biomarkers are used.[79] Indirect biomarkers are routine serum-based laboratory tests, such as serum ALT and aspartate aminotransferase (AST) concentrations.[79] ALT is produced in the cytosol, and although not specific to the liver, liver-produced AST is produced in mitochondria. These markers reflect alterations in hepatic function and are widely used in clinical practice as indicators of liver injury.[80] However, neither enzyme is particularly valuable for assessing liver fibrosis.[79] Conversely, direct biomarkers, such as circulating levels of hyaluronic acid (HA) and procollagen III N-terminal peptide (PIIINP), and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1), are associated with the pathogenesis of liver fibrosis at the molecular and cellular levels.[81]

There are several non-invasive serum biomarkers validated against liver biopsy, including the AST/ALT ratio, AST-to-platelet ratio index (APRI), BARD score, fibrosis-4 (FIB-4) index, and NAFLD fibrosis score (NFS) (**Figure 3** and **Table 3**). These five non-invasive biomarkers use a combination of direct markers and routine patient data (e.g., age, BMI and diabetes status). They are available for use in both primary and secondary care and can rule out ≥F3 liver fibrosis in varying degrees.[77] The enhanced liver fibrosis (ELF™) test, also available in primary and secondary care, uses serum concentrations of HA, PIIINP, and TIMP-1 to assess advanced liver fibrosis. **Table 3** shows the overall performance of these biomarkers in identifying ≥F3 when used in isolation. Among these biomarkers, FIB-4 and NFS scores are the highest-performing, with areas under the receiver operating characteristic (AUROCs) of 0.81 (95% confidence interval (CI) 0.77-0.84) and 0.82 (95% CI 0.78-0.85), respectively.[82] However, their sensitivity is relatively poor at 0.57 (95% CI 0.39-0.74) and 0.30 (95% CI 0.27-0.33), respectively,[82] meaning that they miss people with definite disease. Conversely, the specificity of FIB-4 and NFS scores is high at 0.89 (95% CI 0.77-0.95) and 0.96 (95% CI 0.95-0.96), respectively,[82] indicating they are effective at correctly identifying patients without ≥F3 fibrosis. Overall, the ELF™ test shows the highest sensitivity and specificity at 0.71 (95% CI 0.58-0.80) and 0.76 (95% CI 0.65-0.85), respectively,[83] making it a reliable test for both detecting and ruling out ≥F3 fibrosis. **Figure 3** summarises the serum biomarkers currently recommended for use in clinical practice, along with their cut-off values for identifying ≥F3 fibrosis.

Several less widely available non-invasive serum biomarkers have been validated against liver biopsy, such as NIS2+™ (micro ribonucleic acid (miR)-34a-5p, chitinase-3-like protein 1 (CHI3L1 also known as YKL-40) and sex),[84] MACK-3 (AST, homeostasis model assessment-insulin resistance [HOMA-IR] and cytokeratin-19),[85] and ADAPT score (age, diabetes status, type III collagen neo-epitopes and platelet count).[86] NIS2+™, MACK-3, and ADAPT scores have shown a strong performance for detecting MASH, with an AUROC of 0.81 (95% CI 0.80-0.83),[84] 0.80 (95% CI 0.77-0.81),[87] and 0.86 (95% CI 0.79-0.91),[87] respectively. However, these biomarkers have one or more components in their algorithm that are proprietary or require specialist equipment and/or technical skills, making them expensive and therefore not widely available in clinical practice.

Imaging-based biomarkers

It is important to note that serum biomarkers are primarily used to stratify patients with MASLD according to the likelihood of advanced liver fibrosis (≥F3). However, their utility is limited because additional confirmatory tests are required to accurately determine the fibrosis stage. Relying solely on a non-invasive serum biomarker without further confirmation can lead to significant misdiagnosis.[88] Therefore, imaging methods, such as vibration-controlled transient elastography (VCTE), magnetic resonance elastography (MRE), and point shear wave elastography (pSWE), are used to confirm the stage of liver fibrosis by measuring the physical stiffness of liver tissue and providing a liver stiffness measurement (**Table 3** and **Figure 3)**. Both VCTE and pSWE use ultrasound-based technology to propagate a shear wave through the skin and into the liver. VCTE machines are available as portable and fixed devices, are used in both primary and secondary care settings, and offer good overall performance for identifying ≥F3, with an AUROC of 0.90 (95% CI 0.87-0.92).[89] pSWE performs better than VCTE for identifying ≥F3, with an AUROC of 0.94 (95% CI 0.91-0.96).[89] However, pSWE is only available in secondary care as the device is not currently portable. MRE is also a fixed device and is only available in a secondary care setting. MRE combines magnetic resonance imaging with low-frequency vibration to produce an elastogram, a visual map of tissue elasticity.[90] MRE performs better than VCTE and pSWE for identifying ≥F3, with an AUC of 0.94 (95% CI 0.91-0.95).[91]

International guidelines on diagnosing advanced fibrosis and cirrhosis

Guidelines for assessing, diagnosing, and monitoring MASLD differ across regions. The current UK guidelines from the National Institute for Care and Excellence (NICE) recommend the use of ELF™ as a first-line test, followed by VCTE.[92] NICE currently recommends to diagnose ≥F3 if ELF™ is ≥10.51.[92] Conversely, if ELF™ is <10.51, ≥F3 is unlikely to be present.[92] The entry criteria for MASLD assessment in the NICE guidelines are individuals in higher-risk groups, such as those with T2DM or metabolic syndrome.[92] Whereas both the AASLD and EASL guidelines recommend testing all metabolically unwell populations.[49, 93] The AASLD guidelines advise using FIB-4, followed by VCTE, if FIB-4 is between 1.3 and 2.67.[93] If FIB-4 is ≥2.67, referral to a hepatologist is recommended.[93] Similarly, the EASL guidelines also recommend FIB-4 as the first-line test.[49] If FIB-4 falls between 1.3 and 2.67, VCTE, MRE/shear wave elastography (SWE), or ELF™ are suggested as an alternative test to confirm the fibrosis stage.[49] If VCTE-measured liver stiffness is ≥8.0 kilopascals (kPa) or FIB-4 is ≥2.67, EASL recommends referral to a hepatologist[49] (**Figure 4**). Arguably, the ELF™ test is superior to the FIB-4 index (**Table 3**), but it requires specialist laboratory analysis, which makes ELF™ costly. FIB-4, however, can be calculated using routine data, making it inexpensive and accessible to all health care practitioners.

Identifying clinically significant liver fibrosis in MASLD

International guidelines do not give a clear steer on how to identify significant liver fibrosis (stage F2). However, individuals with MASLD and fibrosis stage F2 are at increased risk of developing T2DM, cirrhosis, extrahepatic complications, including cardiovascular disease, and overall mortality[94, 95] and new treatments are licensed for F2 liver fibrosis (as well as F3 liver fibrosis), see below. There is evidence to show that approximately 20% of patients diagnosed with mild to significant fibrosis (F1-F2) will progress to advanced fibrosis/cirrhosis (F3/F4) within 5 years,[96] thus putting them at substantial risk of death from end-stage liver disease and HCC. Patients with MASLD and stages F2 and F3 are now eligible for anti-fibrotic therapies in some countries, which are now licensed for these indications. Early detection of F2 is key to preventing, controlling, treating, and managing disease progression, as the earlier stages of liver disease lend themselves well to therapeutic interventions.[96-98] There are currently no global guidelines for the detection of ≥F2, and there is no single non-invasive blood biomarker recommended for this purpose. A 2023 meta-analysis of the ELF™ test indicated that the optimal calculated cut-off value for detecting F2 fibrosis in all causes of liver disease was 9.5, with an AUROC of 0.81 (95% CI 0.74-0.87) and sensitivity of 0.73 (95% CI 0.62-0.81) and specificity of 0.76 (0.67-0.83) suggesting that the ELF™ test may also have utility in detecting F2 fibrosis.[83] However, further research is needed in this area, particularly with combining the ELF™ test with a second-line non-invasive test.

Future directions

Machine learning (ML) has the potential to improve the precision of identifying fibrosis stage F2. ML refers to computational methods in which algorithms are trained on sample data to identify patterns and make predictions.[99] Unsupervised ML models analyse unlabeled data to uncover patterns and iteratively learn from themselves[99], whereas supervised ML models use data (e.g., patient characteristics and clinical outcomes) to predict specific outcomes, such as fibrosis stage.[99] In healthcare, supervised ML is predominantly used for predictive modelling [100] and has been used to identify individuals at risk of ≥F2 fibrosis. In a recently published meta-analysis, the pooled AUROC for the diagnostic performance of different ML models for identifying ≥F2 was 0.83 (95% CI 0.79-0.86).[101] This suggests that ML-based approaches may provide more accurate risk stratification for ≥F2 than widely used clinical biomarkers of liver fibrosis, such as ELF™, BARD, AST/ALT ratio, FIB-4, and NFS, which are currently validated only for ≥F3 fibrosis.

Monitoring liver fibrosis in patients with MASLD

Currently, there is no single non-invasive biomarker that has been sufficiently validated for reliably monitoring liver fibrosis at the individual level. Yet monitoring changes in liver fibrosis is essential for understanding if the treatment (e.g., lifestyle modifications or pharmacotherapy interventions) being provided is working. Whether non-invasive serum- and imaging-based biomarkers can reliably track these changes in liver fibrosis remains uncertain.[77, 102, 103] Currently, serum biomarkers are only validated for ≥F3 fibrosis. Therefore, repeating these biomarkers and using the result for prognosis requires independent validation of changes in biomarker scores against liver biopsy. Drug trials use non-invasive measures to monitor treatment responses alongside liver biopsy. The ongoing phase 3 placebo-controlled ESSENCE trial is investigating the use of subcutaneous

semaglutide 2.4 mg/week for the treatment of adults with non-cirrhotic MASH and moderate-to-advanced fibrosis.[104] At week 72, the semaglutide group showed a mean improvement of 0.6 units in ELF™, a 40% decrease in serum ALT and gamma-glutamyl transferase concentrations, and a 30% decrease in serum AST compared to placebo. Although these changes in non-invasive measures are encouraging, it should be noted that these findings pertain to the entire group of participants randomised to semaglutide, rather than distinguishing between responders and non-responders based on liver biopsy results. Nevertheless, this information is encouraging and highlights the need to investigate delta responses in non-invasive markers in responders versus non-responders.

The EASL and AASLD guidelines recommend repeating the FIB-4 test every 1-3 years to monitor liver fibrosis.[49, 105] However, evidence on the effectiveness of FIB-4 for monitoring disease progression is conflicting. A large retrospective cohort study (n=202,319) of patients with MASLD calculated FIB-4 longitudinally. At baseline, 75%, 21% and 4% of patients with MASLD had low, intermediate, and high FIB-4 scores, respectively.[106, 107] At the 3-year follow-up, 21% of low-risk patients (FIB-4 <1.45) progressed to moderate or high-risk categories, while 55% of high-risk patients (FIB-4 >2.67) remained in the high-risk category.[106, 107] Compared to low-risk patients, those who remained in the high-risk FIB-4 category had a significantly higher incidence of HCC (4.56 vs 0.05 per 1000 person-years; adjusted sub-distribution hazard ratio 57.7, 95% CI 24.6-33.2).[106, 107] This study confirmed that a longitudinal increase in FIB-4 score is dose-dependently associated with the risk of developing HCC and cirrhosis.[106, 107] In a smaller retrospective study (n=135) of MASLD patients with a high prevalence of ≥F2, FIB-4, APRI and NFS were weakly associated with disease progression, with suboptimal diagnostic precision (AUROCs 0.65 (95% CI 0.53-0.75), 0.64 (95% CI 0.52-0.76) and 0.56 (95% CI 0.44-0.68) for FIB-4, APRI and NFS, respectively).[108]

The UK NICE guidelines recommend repeating the ELF™ test every three years to monitor disease progression.[92] In a retrospective and prospective study (n=300) with paired ELF™ score and liver biopsies, the ELF™ test efficiently identified liver disease progression in patients without ≥F3.[109] Among patients with a liver biopsy score of F0-F2 (no liver scarring to mild liver scarring), 55% with ELF™ ≥9.8 developed clear evidence of ≥F3 within an average of 6 years.[109] In contrast, only 3.5 % of patients with F0-2 and ELF™ <9.8 developed advanced disease, but over a much longer period (14.2 years).[109] Cox-proportional hazards modelling indicated that each unit increase in ELF™ test increased significantly the hazard of progression to ≥F3 by 4.34 times (95% CI 2.4-7.8), adjusted for age.

Treatment

Interventions for MASLD aim not only to achieve hepatic histologic improvements but also to confer extrahepatic benefits, particularly on cardiovascular and systemic metabolic health. This evolving therapeutic landscape encompasses established lifestyle interventions, nutritional supplements, bariatric surgical procedures (in selected patients with coexisting severe obesity), approved pharmacotherapies, and an expanding pipeline of interventions targeting key pathogenic pathways, as illustrated in **Table 4**. In this section, we discuss the spectrum of interventions aimed at improving liver histology, mitigating metabolic risk factors, and addressing cardiometabolic complications of MASLD.

Lifestyle and nutritional strategies

According to the 2024 EASL guidelines,[49] behavioural modifications are the first-line treatment for MASLD. Lifestyle and dietary strategies trialled in patients with MASLD to date have included: exercise interventions, dietary pattern recommendations aimed at inducing weight loss or modifying intakes of particular food groups, and supplementation studies involving micronutrients and functional foods targeting the gut microbiome. When considering the application of lifestyle or nutritional advice, consideration should also be given to screening for disordered eating behaviours, given that there is a significant prevalence of binge eating disorder within patients with MASLD, estimated to be over 20%.[110-112]

Fewer than half of the behavioural interventions that aim to promote weight loss in patients with MASLD achieve their objective, but predictors of success include designs with frequent in-person interventions and clear guidance on recommendations for both physical activity and dietary intakes.[113] Interestingly, the benefits of exercise interventions are independent of weight loss, with an estimated mean reduction of 24% in MRI-measured liver fat, and the greatest impact is observed with interventions equivalent to at least 150 minutes of brisk walking per week.[114] When Mediterranean dietary patterns are recommended, systematic reviews

highlight beneficial changes in metabolic markers and liver function tests despite modest changes in body composition.[115] Conversely, diets with a higher proportion of ultra-processed foods have been linked to MASLD within cross-sectional, case-control, and prospective study designs.[116] These observations align with public health messages on dietary recommendations and physical activity.

Approved pharmacotherapy interventions

Resmetirom

Resmetirom, an oral thyroid hormone receptor-β (THR-β) selective agonist, became the first drug to receive conditional approval from both the U.S. Food and Drug Administration (FDA) in March 2024 and the European Medicines Agency in August 2025. Resmetirom is currently approved for the treatment of adults once a diagnosis of non-cirrhotic MASH and moderate to advanced (F2/F3) liver fibrosis has been established, either through liver biopsy or using validated non-invasive tests. Resmetirom functions by specifically activating THR-β, which is highly expressed in the liver and plays a key role in regulating hepatic lipid metabolism. By activating this receptor, resmetirom modulates hepatic gene expression involved in lipid metabolism, thereby increasing hepatic fat metabolism and reducing lipotoxicity.[117] The conditional approval of resmetirom followed the pivotal phase 3 placebo-controlled MAESTRO-NASH trial, which involved 966 patients with obesity with biopsy-confirmed MASH and liver fibrosis.[118] Both the 80 mg and 100 mg daily doses increased the proportion of patients achieving MASH resolution without worsening of liver fibrosis (80 mg: 26%, 100 mg: 30% vs. placebo: 10%) and ≥1 stage improvement in liver fibrosis without worsening of MASH (80 mg: 24%, 100 mg: 26% vs. placebo: 14%). In this trial, MASH resolution was defined as an achievement of a hepatocellular ballooning score of 0, a lobular inflammation score of 0 or 1, and a reduction in the NAFLD activity score by ≥2 points.[118] Beyond histological liver endpoints, resmetirom did not change body weight or improve insulin resistance, but did significantly reduce circulating levels of low-density lipoprotein cholesterol, lipoprotein(a) and triglycerides.[118]

Importantly, the incidence of serious adverse events was similar across trial groups: 10.9% in the 80 mg, 12.7% in the 100 mg, and 11.5% in the placebo group, and the incidence of non-serious adverse events was similar between treatment and placebo groups. After 52 weeks, trial discontinuation was more common in the 100 mg resmetirom group (6.8%) than in the 80 mg or placebo groups (1.9 and 2.2%, respectively). These findings indicate that, within this cohort, resmetirom was well tolerated, with gastrointestinal adverse events being the most frequently reported. This study also reported non-clinically significant changes in thyroid function tests without evidence of systemic thyrotoxicity. Resmetirom is contraindicated in patients with decompensated cirrhosis, and caution is advised in individuals with pre-existing thyroid disease. Additionally, data in elderly patients remain limited. Importantly, the MAESTRO-NAFLD open-label extension trial (ClinicalTrials.gov number, NCT04951219) is ongoing to assess the long-term safety of resmetirom, while the MAESTRO-NASH-OUTCOMES trial (NCT05500222) is currently evaluating its efficacy in patients with MASH-related compensated cirrhosis (**Table 4**).

Semaglutide

In August 2025, subcutaneous semaglutide 2.4 mg/week, a glucagon-like peptide-1 (GLP-1) receptor agonist, was also granted accelerated approval by the FDA for the treatment of adults with non-cirrhotic MASH and moderate-to-advanced fibrosis in conjunction with lifestyle modification.[119] Whilst the mechanisms underlying semaglutide's hepatic metabolic benefits are not completely understood, this drug has been shown to decrease appetite and increase satiety, improve insulin resistance, reduce hepatic DNL by downregulating ChREBP and SREBP-1c signalling (along with the expression of other lipid-synthesising genes), and suppress the expression of pro-inflammatory genes.[120] This approval followed Part 1 of the phase 3 placebo-controlled ESSENCE trial, which evaluated the efficacy of semaglutide on liver outcomes in 800 adults with obesity and with MASH and moderate-to-advanced (F2-F3) liver fibrosis.[104] After 72 weeks, 63% of participants treated with semaglutide (2.4 mg weekly) achieved resolution of MASH without worsening of fibrosis, compared to 34% in the placebo arm. In this study, resolution of MASH was defined as an NAFLD activity score of 0 for ballooning and 0 to 1 for inflammation. Similarly, 37% of participants treated with semaglutide achieved ≥1-stage improvement in fibrosis without worsening of MASH, compared with 22% of those receiving placebo.[104] A total of 86.3% and 79.7% of patients reported adverse events in the semaglutide and placebo groups, respectively, and 13.4% of patients in each group reported a serious adverse event. At week 72, patients taking semaglutide had greater weight loss compared with placebo (-10.5% vs. -2%), and improvements in insulin resistance and plasma lipid levels. The safety profile of semaglutide in patients with MASH is consistent with its

established use in obesity and T2DM. The most frequently reported adverse events are gastrointestinal and typically occur during dose escalation. Semaglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in those with multiple endocrine neoplasia syndrome type 2. While semaglutide is widely used in older adult patients, data in patients with advanced liver disease are limited, and the drug is currently not licensed for the treatment of patients with MASH-related decompensated cirrhosis.

Crucially, the ongoing Part 2 of the ESSENCE trial (NCT04822181) will assess the long-term efficacy of semaglutide over approximately 4.5 years in patients with MASH and F2-F3 liver fibrosis (**Table 4**). Despite promising efficacy in patients with MASH, an earlier phase 2b trial involving 71 adults with biopsy-confirmed MASH-related compensated cirrhosis found that, over 48 weeks, semaglutide 2.4 mg/week did not significantly improve liver fibrosis or achieve MASH resolution compared with placebo.[121] Beyond hepatic histology, the established cardiometabolic benefits of semaglutide, including sustained weight loss and a 20% relative reduction in the risk of major adverse cardiovascular events [122] in patients with existing cardiovascular disease and obesity, further underscore its potentially transformative role in the management of MASLD.

Pipeline therapies in late-phase clinical development

Although resmetirom and semaglutide mark major advances, many patients with MASH and liver fibrosis do not achieve adequate histologic or clinical responses, and patients with MASH-related compensated cirrhosis remain without effective therapy. Ongoing phase 3 controlled trials are therefore exploring agents that target complementary pathways and may be used either as alternatives or in future combination regimens (**Table 4**).

Dual incretin receptor agonists

Dual incretin agonists, such as tirzepatide (i.e. a GLP-1/Gastric Inhibitory Polypeptide (GIP) agonist) and survodutide (GLP-1/glucagon agonist), have demonstrated promising efficacy in phase 2b randomized clinical trials. Involving 190 patients with obesity with biopsy-confirmed MASH and F2-F3 liver fibrosis, results from the SYNERGY-NASH trial showed that once-weekly subcutaneous tirzepatide (5 mg, 10 mg, or 15 mg) over 52 weeks improved MASH resolution (defined as no steatotic liver disease or simple steatosis without MASH and an inflammation score of 0 or 1 and a ballooning score of 0) and reduced liver fibrosis by ≥1 stage more effectively compared to placebo. Moreover, all tirzepatide doses resulted in greater weight loss, with favourable effects on the plasma lipid profile and glycaemic control. Adverse events were reported in 92% and 83% of patients in the tirzepatide groups and placebo group, respectively. Moreover, incident serious adverse events were similar in the tirzepatide groups (6%) and the placebo group (6%). Despite these promising results, as of August 2025, no phase 3 tirzepatide trials are underway. Conversely, survodutide, which also showed promising efficacy in a 48-week phase 2b trial involving 293 patients with obesity with biopsy-proven MASH and liver fibrosis,[123] is currently being investigated in two phase 3 trials (NCT06632457 and NCT06632444) (**Table 4**). These trials look to investigate the long-term efficacy and safety of survodutide in nearly 1,800 patients with biopsy-confirmed MASH and F2-F3 liver fibrosis (NCT06632444) and 1,590 patients with MASH-related compensated cirrhosis (NCT06632457). Results from these phase 3 trials are expected between 2029 and 2032 and will inform potential FDA approval.

Triple incretin receptor agonists

In a Phase 2a clinical trial, retatrutide, a triple incretin receptor agonist (GLP-1, GIP/glucagon), demonstrated robust efficacy in promoting weight loss and improving cardiometabolic markers in individuals living with obesity compared to placebo.[124] Moreover, retatrutide treatment for 24 weeks also resulted in marked reductions in liver fat content (measured with MRI-proton fat fraction), body weight, and adiposity at all investigated doses (1 mg, 4 mg, 8 mg, and 12 mg weekly) in patients with MASLD, whilst liver fibrosis biomarkers were not improved.[125] Adverse events (predominantly gastrointestinal) during the treatment period were reported in 70% of participants in the placebo group and in 73-94% of participants in the retatrutide groups, with the highest incidence rates in the 8 and 12 mg groups. Notably, the incidence of serious adverse events was similar between the retatrutide and placebo groups. These findings highlight the potential of multi-incretin therapies to address both hepatic and systemic metabolic dysfunction, warranting further Phase 2 and 3 trials to assess long-term histological outcomes.

PPAR agonists

In addition to incretin-based therapies, several drugs targeting peroxisome proliferator-activated receptors (PPARs) and the FGF21 pathway are currently in late-phase clinical trials. Whilst pioglitazone, a PPAR-Y agonist,

showed some efficacy in MASH resolution and reducing fibrosis severity in a meta-analysis of phase 2 trials,[126] patients with MASH treated with 30 mg/day of pioglitazone for 96 weeks showed no significant improvement in liver fibrosis relative to placebo in the phase 3 PIVENS trial.[127] This highlights the need for more potent pan-PPAR agonists. Building on promising findings from the phase 2b NATIVE trial,[128] lanifibranor, a pan-PPAR agonist, is now under phase 3 investigations for long-term efficacy and safety (NCT04849728). Part A evaluates two doses (800 mg/day and 1,200 mg/day) over 72 weeks for MASH resolution (defined by NASH CRN scores for ballooning of 0 and inflammation of 0 to 1) and fibrosis improvement, while Part B will assess adverse events and cardiovascular outcomes over 48 weeks following the treatment period.

FGF21 analogues and SGLT2 inhibitors

Similarly, FGF21 analogues, including efruxifermin and pegozafermin, are being evaluated in phase 3 trials in patients with biopsy-proven MASH and F2-F3 fibrosis (NCT06318169 and NCT06161571) or MASH-related compensated cirrhosis (NCT06528314 and NCT06419374) (**Table 4**) over a 1.5-year period. In the recent phase 2b SYMMETRY trial, including 181 patients with obesity and with biopsy-confirmed MASH-related compensated cirrhosis, treatment with efruxifermin at a weekly dose of 50 mg for 96 weeks led to a reversal of cirrhosis (defined as a reduction in liver fibrosis of at least one stage) without worsening of MASH in a greater percentage of patients than placebo (29% vs. 11%).[129] Whilst Phase 3 trials have yet to be conducted, treatment with 10 mg/day of the sodium-glucose cotransporter-2 inhibitor dapagliflozin over 48 weeks was shown to result in greater resolution of MASH and fibrosis improvement compared to placebo in a phase 2b trial involving 158 patients with biopsy-proven MASH.[130]

PNPLA3 silencing

Complementing hormonal modulation, precision medicine approaches are also emerging to target genetic determinants of MASLD. Preclinical studies indicate that silencing *PNPLA3* expression with antisense oligonucleotides can reduce MASH and liver fibrosis.[131] Building on this, a phase 1 clinical trial explored the tolerability and safety of AZD2693, an antisense therapy targeting *PNPLA3*-I148M, at three doses (25, 50, and 80 mg/kg/week) over 8 weeks in participants with SLD.[132] AZD2693 was found to reduce the expression of *PNPLA3,* be safe and well-tolerated, and appeared to reduce liver fat content in a dose-dependent manner. A Phase 2b trial involving 220 participants with MASH and F2-3 liver fibrosis who are homozygous for the *PNPLA3*-I148M variant and aged 18-75 years is currently underway and is expected to be completed in October 2025 (NCT05809934).

In summary, the therapeutic landscape for MASLD/MASH is rapidly evolving, with emerging pharmacotherapies offering meaningful histologic and metabolic benefits. Given the multifactorial pathogenesis of MASLD and residual unmet needs – particularly in patients with advanced liver fibrosis or compensated cirrhosis – there is a strong rationale for combination strategies targeting complementary pathways.[133] This is especially important given that not all patients respond equally to pharmacological interventions. Integrating these pharmacotherapies with diet and lifestyle interventions may enhance histologic improvement, slow liver fibrosis progression, and simultaneously address coexisting cardiometabolic risk factors, representing a promising avenue for comprehensive MASLD management. Further clinical trials are required to explore the effectiveness of combination treatment strategies for the management of MASLD.

Conclusion

MASLD is a metabolic, heterogeneous, and multisystem disease that extends beyond the liver, with liver fibrosis severity, cardiometabolic dysfunction, and genetic predisposition determining liver-related and extrahepatic clinical outcomes. Recent advances in non-invasive diagnostics have transformed disease detection and risk stratification, enabling earlier intervention. The emergence of targeted MASLD pharmacotherapies licensed for the treatment of F2 and F3 liver fibrosis offers new opportunities, not only to stabilise or prevent liver disease progression, but also to target the risk of extra-hepatic diseases in treating MASLD as a multisystem disease. That said, current challenges remain, and these include diagnosing F2 liver fibrosis, monitoring liver fibrosis regression (or progression), and establishing rules for stopping potentially expensive therapies when patients do not show evidence of treatment benefit. Finally, the cost-effectiveness of diagnosis, monitoring, and treatment needs to be established. Given that MASLD is a multisystem disease, assessing cost-effectiveness should consider benefits (and harms) beyond the liver as part of a holistic approach to MASLD.

Questions for future research

- What is the optimum time span for monitoring liver progression?
- How do we reliably monitor fibrosis regression/progression at the individual level?
- How do we test for and monitor amelioration or progression of stage ≥F2 fibrosis?
- How do we test at-risk populations for MASLD cost-effectively?
- What are the long-term clinical and cost-effectiveness outcomes of emerging pharmacotherapies for MASLD and its extrahepatic complications across diverse patient populations?
- What are the mechanistic links between MASLD and its extrahepatic complications?
- How do gene-environment interactions, particularly involving diet, adiposity, and metabolic status, modulate disease progression and treatment response?

Patient Involvement

No patient or public involvement was sought for this review.

Figure 1: Diagnosis of MASLD. A diagnosis of MASLD requires evidence of hepatic steatosis in combination with 1 of 5 common cardiometabolic features after excluding the presence of significant alcohol consumption and other secondary causes of liver disease (as specified in the figure). Whilst not a requirement of MASLD, liver fibrosis is a crucial clinical characteristic of MASLD severity and spans from no fibrosis (F0), mild fibrosis (F1), significant fibrosis (F2), advanced fibrosis (F3), and cirrhosis (F4). *Abbreviations*: T2DM; type 2 diabetes mellitus, TAG; triglyceride, HDL-C; high-density lipoprotein cholesterol, LAL-D; lysosomal acid lipase deficiency. Created with BioRender.com.

Figure 2: Overview of the key factors discussed in the pathogenesis of MASLD. **A**) Dysfunctional adipose tissue characterised by increased insulin resistance, inflammation, fibrogenesis, and a shift in the production of adipokines is strongly associated with MASLD. Collectively, these alterations can increase the flux of NEFAs to the liver, promoting hepatic steatosis and exacerbating systemic low-grade inflammation and cardiometabolic dysfunction. Simultaneously, intestinal dysfunction, driven by gut dysbiosis and loss of intestinal barrier integrity, results in increased endotoxin release and alterations in the production of microbial metabolites, such as TMA, SCFAs, and secondary bile acids, all of which have been shown to play a role in the development and progression of MASLD. **B**) Common genetic risk variants, such as *PNPLA3*-I148M, *TM6SF2*-E167K, and other variants, increase the risk of developing both MASLD/MASH and its extrahepatic complications through a wide range of mechanisms. Crucially, the presence of these genetic variants alone is insufficient to cause MASLD; gene-environment interactions with overall adiposity, metabolic dysfunction, and diet are critical determinants of the disease phenotype. **C**) Within hepatocytes, increased DNL, excess NEFA uptake, and insulin resistance drive the accumulation of lipid droplets. Once established, hepatic lipid droplets are thought to displace the cell's nucleus, induce endoplasmic reticulum stress, and are strongly associated with the generation of lipotoxic lipid intermediates, such as ceramides and diacylglycerol. Simultaneously, mitochondrial dysfunction can promote oxidative stress and reduce fatty acid oxidation, further driving hepatic steatosis and inflammation. Collectively, these processes may induce hepatocyte dysfunction, leading to the activation of resident immune cells and stellate cells that drive the progression of MASLD to MASH, advanced fibrosis and cirrhosis. *Abbreviations*: MASLD; metabolic dysfunction–associated steatotic liver disease, SLD; steatotic liver disease, NEFAs; non-esterified fatty acids, TMAO; trimethylamine N-oxide, SCFAs; short-chain fatty acids, ROS; reactive oxygen species, DNL; de novo lipogenesis, ER; endoplasmic reticulum, PNPLA3; patatin-like phospholipase domain-containing protein 3, TM6SF2; Transmembrane 6 superfamily member 2, MBOAT7; Membrane-bound O-acyltransferase domain-containing 7, HSD17B13; Hydroxysteroid 17-beta dehydrogenase 13, GCKR; Glucokinase regulatory protein. Created with BioRender.com.

Figure 3. Identifying advanced liver disease in patients with MASLD: a summary of the processes for assessing, confirming, and managing patients. The flow begins by using a serum biomarker to **identify** patients at risk of liver disease. A decision on what to do next is based on the result of the serum biomarker. When the serum biomarker indicates a high probability of ≥F3 fibrosis, imaging technology is used to **confirm** the fibrosis stage, which then informs the clinical diagnosis and **management**. *Abbreviations*: AASD; American Association for the Study of Liver Diseases, APRI; aspartate aminotransferase to platelet ratio index, AST/ALT; aspartate aminotransferase to alanine transaminase, EASD; European Association for the Study of Diabetes, EASL; European Association for the Study of Liver, EASO; European Association for the Study of Obesity, ELF™; enhanced liver fibrosis, FIB-4; fibrosis 4, LFTs; liver function tests, MRE; magnetic resonance elastography, NFS; non-alcoholic fatty liver disease fibrosis score, pSWE; shear wave elastography, VCTE; vibration controlled transient elastography, F2; significant liver fibrosis, F2-F3; significant to advanced liver fibrosis, F3; advanced liver fibrosis, F4; cirrhosis, £; pound sterling (GBP). *References:* [1]Tacke F, Horn P, Wai-Sun Wong V, Ratziu V, Bugianesi E, et al. EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). Journal of Hepatology. 2024;81(3):492-542. [2]NICE. Non-alcoholic fatty liver disease (NAFLD): assessment and management. [Internet]; 2016 Available from: https://www.nice.org.uk/guidance/ng49. [3]European Association for the Study of the Liver. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol. 2021 Sep;75(3):659-689. doi: 10.1016/j.jhep.2021.05.025. Epub 2021 Jun 21. PMID: 34166721.

Figure 4: **Summary of the UK, American, and European guidelines for identifying, managing, and monitoring liver fibrosis in MASLD.** The current entry criteria for MASLD assessment in the UK NICE Guidelines are populations at high risk, such as individuals with T2DM or those with metabolic syndrome. Whereas the AASLD and EASL guidelines entry criteria are to test all metabolically unwell populations using FIB-4 index. VCTE is the recommended second-stage diagnosis method in all three guidelines. *Abbreviations*: AASLD; American Association for the Study of Liver Diseases, cT1; iron-corrected T1, EASL; European Association for the Study of Liver, ELF™; enhanced liver fibrosis, FIB-4; fibrosis 4, kPa; kilopascal, MRE; magnetic resonance imaging, T2DM; type 2 diabetes mellitus, UK NICE; United Kingdom National Institute of Care and Excellence, SWE; shear wave elastography, VCTE; vibration-controlled transient elastography, F4; cirrhosis.

Table 1: The mechanisms and resulting health issues/consequences of the microbiome and gut-liver axis in the pathophysiology of MASLD.

Mechanism(s)	Consequences
Intestinal dysbiosis	Detrimentally impacts the inter-organ metabolic crosstalk between the gut and other organs, including the liver[134]
Increased intestinal permeability	Translocation of microbial products and metabolites (like lipopolysaccharides) into the portal circulation, which can directly link gut dysbiosis and hepatic dysfunction[135]
Increased systemic lipopolysaccharide concentrations	Activation of pro-inflammatory pathways via toll-like receptors, leading to low-grade systemic inflammation and promoting MASH[136]
Alterations in microbial metabolism	Impaired hepatic lipid and glucose metabolism[134]
Shifts in the production of gut microbiota metabolites	Increased production of trimethylamine, reduced synthesis of short-chain fatty acids (like butyrate), altered bile acid profiles, and increased endogenous ethanol production[137]

Table 2: Examples of key genetic variants related to MASLD.

Variant	Gene	Genetic effect	Functional consequence	Clinical impact
rs738409 (I148M)	*PNPLA3*	Isoleucine-to-methionine substitution at position 148[57]	Impaired triglyceride hydrolase activity, protein accumulation on hepatic lipid droplets, impaired degradation, and dominant-negative effect on other lipases[138-140]	Strong association with progressive MASLD forms, including HCC, with an odds ratio of 1.5–3.0 per risk allele.[57, 58, 141] Impact is influenced by gene-environment interactions, such as adiposity[57-59, 142]
E167K	*TM6SF2*	Loss-of-function[62]	Impairs VLDL secretion[62]	Promotes hepatic fat accumulation but paradoxically lowers LDL cholesterol concentrations[62]
rs641738	*MBOAT7*	Variant not explicitly detailed as loss-of-function[62]	Impacts phospholipid remodelling[62]	Promotes hepatic inflammation and fibrosis[62]

Abbreviations: HCC; hepatocellular carcinoma, LDL; low-density lipoprotein, MASLD; metabolic dysfunction-associated steatotic liver disease, *MBOAT7;* Membrane-bound O-acyltransferase domain-containing 7, *PNPLA3*; patatin-like phospholipase domain-containing protein 3, *TM6SF2;* Transmembrane 6 superfamily member 2, VLDL; very low-density lipoprotein.

Table 3: Comparison of non-invasive serum-based and imaging-based biomarkers and their optimal cut-off values for identifying advanced fibrosis in MASLD and availability for use in Primary and Secondary care.

Serum-based biomarker	Components	Cut-off value	Sensitivity (95% CI)	Specificity (95% CI)	Performance (AUROC) (95% CI)	Advantages/disadvantages	Recommended test
APRI score[82]	AST and PLT count	≥1 for advanced fibrosis	0.45 (0.29-0.62)	0.89 (0.83-0.93)	0.83 (0.80-0.86)	Uses routine blood tests, low cost, easy to calculate, better at excluding disease than identifying disease	
AST/ALT ratio score[82]	AST and ALT	≥0.8 for advanced fibrosis	0.63 (0.44-0.79)	0.77 (0.68-0.84)	0.78 (0.74-0.81)	Uses routine blood tests, low cost, easy to calculate, should not be used as a standalone diagnostic test	
BARD score[82]	BMI, AST, ALT, diabetes status	≥2 for advanced fibrosis	0.72 (0.58-0.83)	0.65 (0.55-0.75)	0.74 (0.70-0.77)	Uses routine blood tests, low cost, easy to calculate, should not be used as a standalone diagnostic test	
ELF™ score[83]	HA, TIMP-1, PIIINP	≥9.6 for advanced fibrosis (Youden index calculation)	0.71 (0.58-0.80)	0.76 (0.65-0.85)	0.80 (0.73-0.86)	Propriety test, higher costs, available for clinical use, performs well for identifying the presence or absence of advanced fibrosis	UK NICE guidelines
FIB-4[82]	Age, AST, ALT, PLT count	≥3.25 for advanced fibrosis	0.57 (0.39-0.74)	0.89 (0.77-0.95)	0.81 (0.77-0.84)	Uses routine blood tests, low cost, easy to calculate, should not be used as a standalone diagnostic test	EASL and AASLD guidelines
NFS score[82]	Age, BMI, diabetes status, AST/ALT ratio, PLT count, ALB	≥0.676 for advanced fibrosis	0.30 (0.27-0.33)	0.96 (0.95-0.96)	0.82 (0.78-0.85)	Uses routine blood tests, low cost, easy to calculate, better at excluding disease than identifying disease	
NIS2+™[84]	miR-34a-5p, YKL-40, sex	>0.68 suggests at-risk NASH[a]	0.62 (0.59-0.65)	0.85 (0.83-0.87)	0.74 (0.72-0.76)	Proprietary test, requires complex laboratory equipment and high technical skills, high cost	
MACK-3[87]	AST, HOMA-IR, CK-18	>0.53 for MASH and clinically significant fibrosis	0.41 (0.34-0.48)	0.89 (0.85-0.92)	0.74 (0.70-0.73)	Proprietary test, high cost, primarily used in research settings	
ADAPT[87]	Age, diabetes status, PRO-C3 and PLT count	>6.91 for MASH and clinically significant fibrosis	0.47 (0.39-0.55)	0.88 (0.83-0.91)	0.77 (0.73-0.81)	Cost of PRO-C3, currently only available as a research test, not approved for diagnostic use	
Imaging-based biomarker							
FibroScan (VCTE)[89]	LSM	7.1 kPa to 7.9 kPa for advanced fibrosis	0.89 (0.85-0.91)	0.67 (0.59-0.74)	0.90 (0.87-0.92)	Available in primary and secondary care. Easy to use but operator-dependent, it provides instant results. Its accuracy can be affected by BMI or the presence of ascites. Less expensive than MRE or pSWE	EASL, AASLD, and UK NICE guidelines
MRE[89]	LSM	3.62 kPa to 3.8 kPa for advanced fibrosis	0.88 (0.81-0.93)	0.91 (0.86-0.94)	0.94 (0.91-0.96)	Only available in secondary care, large sampling volume, which can accommodate obese patients or those with ascites, provides a three-dimensional view of the liver. High cost	
pSWE[91]	LSM	1.36 m/s to 1.77 m/s for advanced fibrosis	0.89 (0.73-0.96)	0.88 (0.82-0.92)	0.94 (0.91-0.95)	Only available in secondary care, it offers real-time visualisation of the liver. Lower cost than MRE but higher cost than VCTE	

Abbreviations: AASLD; American Association for the Study of Liver Diseases, ALB; albumin, ALT; alanine transaminase, APRI; aspartate aminotransferase to platelet ratio index, AST; aspartate aminotransferase, AST/ALT; aspartate aminotransferase to alanine transaminase, AUC; area under the curve, AUROC; area under the receiver operating characteristic curve, BARD; body mass index aspartate aminotransferase to alanine transaminase ratio, BMI; body mass index, CI; confidence interval, CK-18; cytokeratin-18,

EASL; European Association for the Study of Liver, ELF™; enhanced liver fibrosis, FIB-4; fibrosis four, HA; hyaluronic acid, HOMA-IR; homeostasis model assessment for insulin resistance, kPa; kilopascal, LSM; liver stiffness measurement, MRE; magnetic resonance elastography, m/s; metre per second, NAS; non-alcoholic fatty liver disease activity score, NASH; non-alcoholic steatohepatitis, NFS; non-alcoholic fatty liver disease fibrosis score, NICE; National Institute of Care and Excellence, PIIINP; type 3 procollagen peptide, PLT; platelet, PRO-C3; N-terminal propeptide of type III collagen, pSWE; point shear wave elastography, TIMP-1; Tissue Inhibitor of Metalloproteinases-1, VCTE; vibration controlled transient elastography, *At-risk NASH is defined as NASH with NAS ≥4 and F≥2.

Table 4: Ongoing Phase 3 Pharmaceutical Trials in adults with MASLD / MASH.

Trial NCT ID & Duration	Treatment arms (Route of administration)	Target Population (Estimated N)	Primary outcomes	Status (Expected completion)
NCT04951219 52 weeks	- Resmetirom 80 mg/day for 12 weeks and 100 mg daily for 40 weeks - Resmetirom 100 mg/day for 52 weeks (oral tablet)	Adults with biopsy-proven MASH (N=1,000)	- Incidence of adverse events	Active, not recruiting (April 2026)
NCT04849728 Part A: 72 weeks Part B: 48 weeks after completion	- Lanifibranor 800 mg/day - Lanifibranor 1,200 mg/day - Placebo (oral tablet)	Adults ≥18 years with biopsy-proven MASH (N=1,000)	- Part A: Resolution of MASH and improvement in fibrosis by biopsy - Part B: Adverse events, adjudicated liver events, DILI, and MACE	Active, not recruiting (Sep 2026)
NCT06161571 52 weeks	- Efruxifermin 50 mg/week - Placebo (subcutaneous injection)	Adults 18/19–90 years with suspected or biopsy-confirmed MASH or non-invasively diagnosed MASLD (N=700)	- Extent of exposure - Number of participants with AEs, severity, and clinically significant changes in clinical assessments	Active, not recruiting (Oct 2026)
NCT05500222 3 years	- Resmetirom 80 mg/day - Placebo	Adults with MASH-related compensated cirrhosis (N=700)	- Any incident event of all-cause mortality, liver transplant, ascites, hepatic encephalopathy, gastroesophageal variceal haemorrhage, and confirmed increase of MELD score from <12 to >/= 15 due to liver disease	Active, not recruiting (Jan 2027)
NCT06318169 52 weeks	- Pegozafermin 44 mg/week - Pegozafermin 30 mg/week - Placebo (subcutaneous injection)	Adults 18–80 years with biopsy-confirmed MASH, fibrosis stage F2–F3 (N=1,050)	- ≥1 stage improvement in fibrosis without worsening of MASH - Resolution of MASH without worsening of fibrosis - Time to disease progression	Active, recruiting (Feb 2029)
NCT04822181 4.5 years	- Semaglutide (2.4 mg) - Placebo (subcutaneous injection)	Adults ≥18 years with biopsy-confirmed MASH and fibrosis stage F2-F 3	- Resolution of MASH and no worsening of liver fibrosis - Improvement in liver fibrosis and no worsening of MASH - Cirrhosis-free survival	Active, not recruiting (April 2029)
NCT06632457 1.5–4.5 years	- Survodutide (dose not specified) - Placebo (subcutaneous injection)	Adults ≥18 years with biopsy-proven MASH-related compensated cirrhosis and hepatic steatosis (N=1,590)	- Time to first occurrence of composite endpoint: all-cause mortality, liver transplant, hepatic decompensation, worsening MELD score ≥15, or progression to CSPH	Active, recruiting (Jun 2029)
NCT06528314 96 weeks–5 years	- Efruxifermin 50 mg/week - Placebo (subcutaneous injection)	Adults with biopsy-proven MASH-related compensated cirrhosis (N=1,150)	- Time to first occurrence of disease progression - ≥1 stage improvement in fibrosis without worsening of MASH	Active, recruiting (Oct 2029)
NCT06419374 2–5 years	- Pegozafermin (dose not specified) - Placebo (Subcutaneous injection)	Adults 18–75 years with biopsy-confirmed MASH-related compensated cirrhosis (N=762)	- Fibrosis regression - Time to disease progression	Active, recruiting (Jun 2031)
NCT06632444 1–7 years	- Survodutide (dose not specified) - Placebo (subcutaneous injection)	Adults ≥18 years with biopsy-proven MASH and stable body weight (N=1,800)	- Resolution of MASH without worsening of fibrosis - ≥1 stage improvement in fibrosis without worsening of MASH - Composite clinical endpoint: all-cause mortality, liver transplant, hepatic decompensation, worsening MELD score ≥15, or CSPH progression	Active, recruiting (Dec 2031)
NCT06215716 1–4.5 years	- Efruxifermin 28 mg/week - Efruxifermin 50 mg/week - Placebo (subcutaneous injection)	Adults 18–80 years with biopsy-proven MASH (N=1,650)	- Resolution of MASH with ≥1 stage improvement in fibrosis - Event-free survival	Active, recruiting (Nov 2032)

Note: Three phase 3 clinical trials were identified but were omitted as they no longer met the eligibility criteria for “ongoing” studies. The MAESTRO-NASH trial of resmetirom (MGL-3196; NCT03900429) has been completed with published results and subsequent regulatory filings. The ARMOR trial of aramchol (NCT04104321) was suspended following an interim futility analysis. A planned Phase 3 trial of denifanstat (NCT06692283) was withdrawn before recruitment. *Abbreviations*: AEs; adverse

events, CSPH; clinically significant portal hypertension, DILI; drug-induced liver injury, MACE; major adverse cardiac events, MASH; metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease, MELD; model for end-stage liver disease, NCT ID; national clinical trials ID.

Abbreviations

AASLD	American Association for the Study of Liver Diseases
ALB	Albumin
AST	Aspartate aminotransferase
ALT	Alanine transaminase
APRI	Aspartate aminotransferase to platelet ratio index
AST/ALT	Aspartate aminotransferase to alanine transaminase
AUC	Area under the curve
AUROC	Area under the receiver operating characteristics
BARD	Body mass index, aspartate aminotransferase to alanine transaminase ratio
BMI	Body mass index
ChREBP	Carbohydrate-responsive element-binding protein
CI	Confidence interval
cT1	Iron-corrected T1
DNL	De novo lipogenesis
EASL	European Association for the Study of Liver
ELF™	Enhanced liver fibrosis
FDA	Food and drug administration
GGT	Gamma-glutamyl transferase
FGF21	Fibroblast growth factor 21
FIB-4	Fibrosis-4
GCKR	Glucokinase regulatory protein
GIP	Gastric inhibitory polypeptide
GLP-1	Glucagon-like peptide-1
HA	Hyaluronic acid
HCC	Hepatocellular carcinoma
HOMA-IR	Homeostasis model assessment-insulin resistance
HSD17B13	Hydroxysteroid 17-beta dehydrogenase 13
kPa	Kilopascal
LDL	Low-density lipoprotein
LFT	Liver function test
MAFLD	Metabolic dysfunction-associated fatty liver disease
MASH	Metabolic dysfunction-associated steatohepatitis
MASLD	Metabolic dysfunction-associated steatotic liver disease
MBOAT7	Membrane-bound O-acyltransferase domain-containing 7
MELD	Model for end-stage liver disease
Met-ALD	Metabolic dysfunction-associated and Alcohol-related Liver Disease
ML	Machine learning
MRE	Magnetic resonance elastography
m/s	Meter per second
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NEFAs	Non-esterified fatty acids
NFS score	Non-alcoholic fatty liver disease score
NICE	National Institute for Care and Excellence
PEth	Phosphatidylethanol
NICE	National Institute for Care and Excellence
PIIINP	Procollagen III amino-terminal peptide
PNPLA3	Patatin-like phospholipase domain-containing protein 3
pSWE	Point shear wave elastography
SCFAs	Short-chain fatty acids
SLD	Steatotic liver disease
SREBP-1c	Sterol regulatory element-binding protein-1c

TAGs	High triglycerides
TIMP-1	Tissue inhibitor of matrix metalloproteinase
TM6SF2	Transmembrane 6 superfamily member 2
TMA	Trimethylamine
VCTE	Vibration-controlled transient elastography
VLDL	Very low-density lipoprotein

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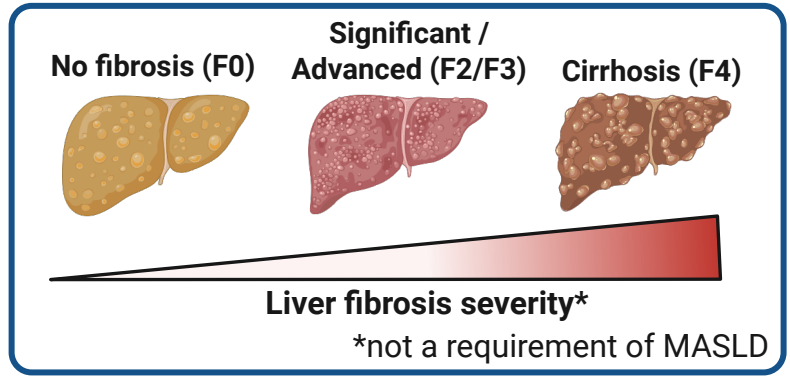
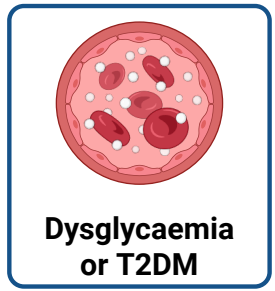
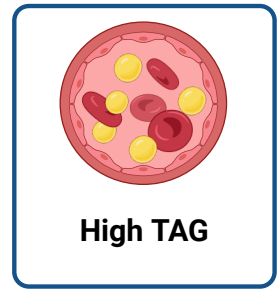
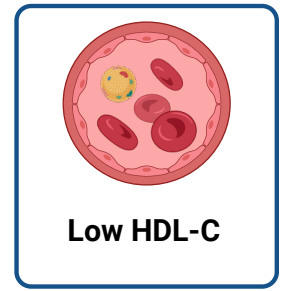
Metabolic dysfunction-associated steatotic liver disease (MASLD)



Plus any <u>one</u> cardiometabolic trait





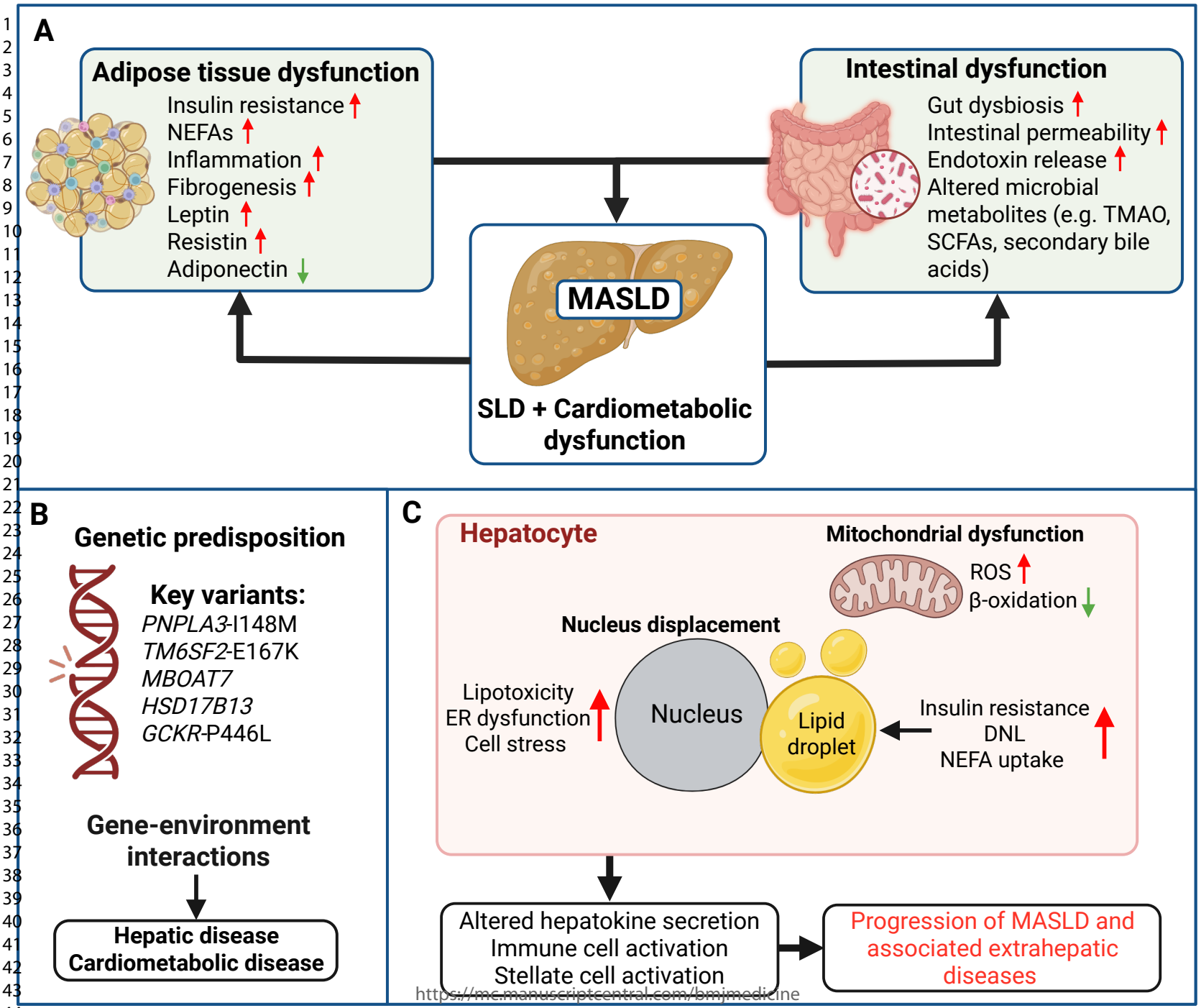


In the absence of secondary causes including:

Excessive alcohol consumption (>20/30 g per day in women and men respectively)

Toxin or drug-induced

Viral or genetically induced (e.g. inborn errors of metabolism and LAL-D)



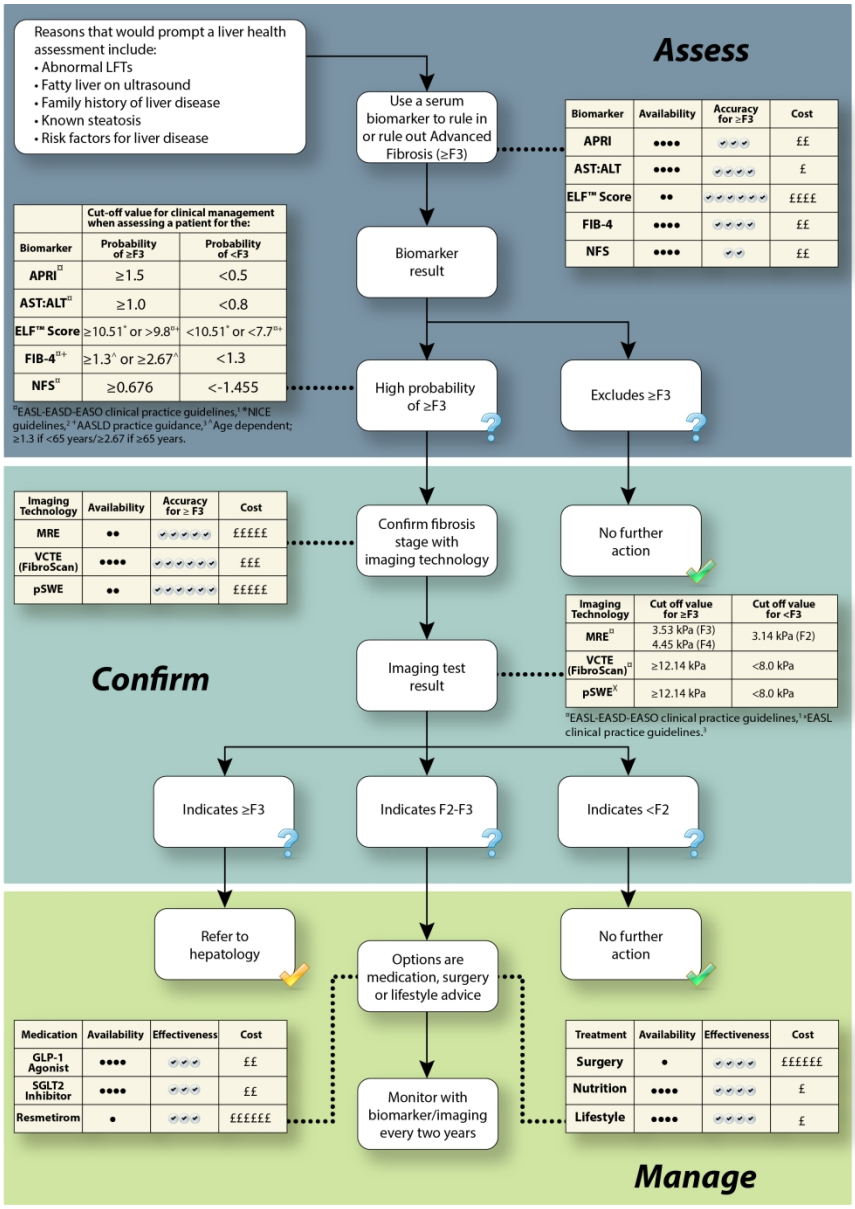


Figure 3. Identifying advanced liver disease in patients with MASLD: a summary of the processes for assessing, confirming, and managing patients.

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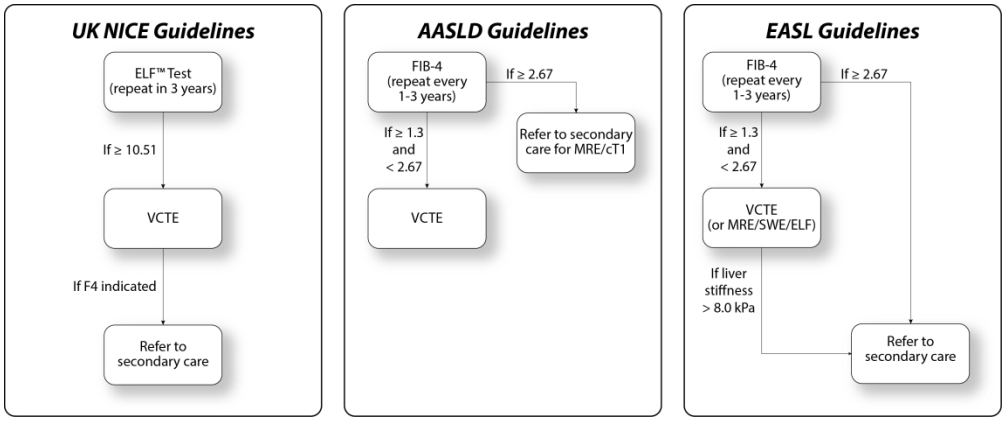

Figure 4: Summary of the UK, American, and European guidelines for identifying, managing, and monitoring liver fibrosis in MASLD.

284x117mm (300 x 300 DPI)