Medical Policy

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Populations	Interventions	Comparators	Outcomes
Individuals: • With chronic liver disease	Interventions of interest are: • FibroSURE serum panels	Comparators of interest are: • Liver biopsy • Noninvasive radiologic methods • Other multianalyte serum assays	Relevant outcomes include: • Test validity • Morbid events • Treatment-related morbidity
Individuals: • With chronic liver disease	Interventions of interest are: • Multianalyte serum assays for liver function assessment other than FibroSURE	Comparators of interest are: • Liver biopsy • Noninvasive radiologic methods • Other multianalyte serum assays	Relevant outcomes include: • Test validity • Morbid events • Treatment-related morbidity
Individuals:	Interventions of interest are:	Comparators of interest are: • Liver biopsy	Relevant outcomes include:

Populations	Interventions	Comparators	Outcomes
• With chronic liver disease	• Transient elastography	• Other noninvasive radiologic methods • Multianalyte serum assays	• Test validity • Morbid events • Treatment-related morbidity
Individuals: • With chronic liver disease	Interventions of interest are: • Multiparametric magnetic resonance imaging	Comparators of interest are: • Liver biopsy • Other noninvasive radiologic methods • Multianalyte serum assays	Relevant outcomes include: • Test validity • Morbid events • Treatment-related morbidity
Individuals: • With chronic liver disease	Interventions of interest are: • Noninvasive radiologic methods other than transient elastography or multiparametric magnetic resonance imaging for liver fibrosis measurement	Comparators of interest are: • Liver biopsy • Other noninvasive radiologic methods • Multianalyte serum assays	Relevant outcomes include: • Test validity • Morbid events • Treatment-related morbidity

DESCRIPTION

Noninvasive techniques to monitor liver fibrosis are being investigated as alternatives to liver biopsy in patients with chronic liver disease. There are 2 options for noninvasive monitoring: (1) multianalyte serum assays with algorithmic analysis of either direct or indirect biomarkers; and (2) specialized radiologic methods, including magnetic resonance elastography, multiparametric magnetic resonance imaging (MRI), transient elastography, acoustic radiation force impulse imaging, and real-time transient elastography.

OBJECTIVE

The objective of this evidence review is to determine whether the use of noninvasive techniques for detecting liver fibrosis compared with liver biopsy can improve the net health outcome in patients with chronic liver disease.

BACKGROUND

Disease Background

Chronic liver disease (CLD) is associated with approximately two million annual deaths worldwide. CLD is a progressive deterioration of liver function for more than 6 months, adversely affecting synthesis of clotting factors, other proteins, detoxification of harmful products of metabolism, and excretion of bile. CLD is a continuous process of inflammation, destruction, and regeneration of liver parenchyma, which leads to fibrosis and cirrhosis. Multiple etiologies are associated with CLD including toxin exposures, chronic alcohol abuse, infection, autoimmune diseases, genetic and metabolic disorders. CLD is the 9th cause of death in the

United States (U.S.). According to the National Center for Health Statistics from the U.S. Center for Disease Control and Prevention, approximately 4.5 million adults had CLD and cirrhosis. This represents 1.8 percent of the adult population. There were 52,222 deaths through 2023 (15.6 deaths per 100,000 population) from CLD and cirrhosis.[1,]

Steatosis (also known as fatty liver disease) is a condition caused by an excessive buildup of fat in the liver. Steatotic liver disease (SLD) is a generic term for the accumulation of lipids in liver parenchymal cells. Primary risk factors for SLD include alcohol, insulin resistance, and obesity. In 2023, a global consensus conference described 5 subclasses of SLD: metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease (NAFLD); alcohol-associated liver disease (ALD); SLD with specific etiology (e.g., drug-induced); cryptogenic SLD, and MASLD with increased alcohol intake (MetALD).[2,]

The Brunt-Kleiner scoring system and the NASH Clinical Research Network (CRN) scoring system ((i.e., NAFLD Activity Score, NAS) are two of the most widely used methods for histologically assessing steatosis and fibrosis in MASLD. The Brunt-Kleiner system has four possible grades (0-3) and five possible stages (0-4). The NAS is an 8-point scale classifying the severity of steatosis (score: 0-3), lobular inflammation (score: 0-3) and ballooning (score: 0-2), with greater scores equating more severe disease. Both systems determine the degree of steatosis based on the percentage of steatotic hepatocytes involved: normal <5%, mild =5% to 33%, moderate =34% to 66%, and severe >66%.

Fibrosis scores are generally disease-specific and technically cannot be unified across different CLDs. To achieve a unified approach, the American Association for the Study of Liver Diseases (AASLD) Practice Guidelines Committee incorporated the different fibrosis staging systems by consolidating them into a single framework. The AASLD defined three primary categories: "at least significant fibrosis," corresponding to fibrosis stage 2 or higher (F2-4); "at least advanced fibrosis," encompassing stages F3 and F4; and "cirrhosis," represented by stage F4 (Table 1).[3,4,]

Table 1. Staging of Fibrosis across Multiple Etiologies*

			Significant Fibrosis		
				Advanced Fibrosis	
Etiology	**0**	**FI**	**F2**	**F3**	**F4**
ALD	• No fibrosis or portal fibrosis	• Expansive periportal fibrosis	• Bridging fibrosis	• Cirrhosis	• N/A
MASLD [Brunt-Kleiner system]	• No fibrosis	• 1A: delicate perisinusoidal • 1B: dense perisinusoidal • 1C: portal-only fibrosis	• Perisinusoidal and portal/ periportal fibrosis	• Bridging fibrosis	• Cirrhosis
Viral and Autoimmune Hepatitis	• No fibrosis	• Enlarged, fibrotic portal tracts	• Periportal or portal-portal septa but	• Fibrosis with architectural	• Cirrhosis

			Significant Fibrosis		
		(Fibrous portal expansion)	intact architecture	distortion but no obvious cirrhosis (Bridging fibrosis)	
PBC and PSC	• N/A	• N/A	• N/A	• Bridging fibrosis	• Cirrhosis
Various etiologies [Metavir system]	• No fibrosis	• Stellate enlargement of portal tract but without septa formation	• Enlargement of portal tract with rare septa formation	• Numerous septa without cirrhosis	• Cirrhosis

* Adapted from American Association for the Study of Liver Diseases (AASLD) Practice Guidelines (2025)[3,4,]
ALD: Alcohol-associated liver disease; MASLD: Metabolic dysfunction-associated steatotic liver disease; PBC: Primary biliary cirrhosis; PSC: Primary Sclerosing Cholangitis

NON-INFECTIOUS ETIOLOGIES

Alcohol-Associated Liver Disease

ALD is a major cause of liver disease worldwide, both on its own and as a co-factor in the progression of chronic viral hepatitis, MASLD, iron overload, and other liver diseases.[5,6,] ALD represents a spectrum of liver injury resulting from alcohol use, ranging from steatosis to steatohepatitis and cirrhosis. ALD progression relies on persistent alcohol use and factors such as genetics, sex, diet, and concurrent liver conditions.

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) formerly Nonalcoholic Fatty Liver Disease (NAFLD)

In 2023, the AASLD and other professional societies adopted new nomenclature for the spectrum of NAFLD. The new terminology reflected the role of metabolic dysfunction in the development of what is now termed MASLD. Given this recent nomenclature shift, this policy will continue to use the abbreviations NAFLD and NASH (nonalcoholic steatohepatitis) unless a publication specifically refers to MASLD or MASH (metabolic dysfunction-associated steatohepatitis).

MASLD is characterized by hepatic steatosis (>5%) along with at least one cardiometabolic risk factor, no other causes of SLD, and minimal or no alcohol consumption. MASH, a more severe subtype of MASLD, is a progressive liver disease characterized by the presence of at least 5% hepatic steatosis, along with hepatocellular damage and inflammation.[7,2,] This condition can develop into advanced liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC), all of which are linked to significant morbidity and mortality. In the U.S., MASH ranks among the leading causes of HCC and is the second most common reason for liver transplantation after hepatitis C.[8,] Once MASH advances to clinically significant fibrosis (stages F2 and F3), the risk of serious

clinical outcomes rises. Cardiovascular incidents are the primary cause of death in individuals with MASH, with non-liver cancers being the second leading cause.[9,10,]

INFECTIOUS ETIOLOGIES

Hepatitis C Virus

Infection with hepatitis C virus (HCV) can lead to permanent liver damage. Prior to noninvasive testing, liver biopsy was typically recommended before the initiation of antiviral therapy. Repeat biopsies may be performed to monitor fibrosis progression. Liver biopsies are analyzed according to the most commonly used histologic scoring system known as the Metavir system. The Metavir system includes scores for fibrosis (Table 1) and necroinflammatory activity (which refers to a combination of cellular events in which tissue necrosis is accompanied by an inflammatory response). This activity is graded as A0 = no activity, A1 = mild activity, A2 = moderate activity, and A3 = severe activity.

Hepatitis B Virus

Most people who become infected with hepatitis B virus (HBV) recover fully, but a small portion develops chronic HBV, which can lead to permanent liver damage. Identification of liver fibrosis is needed to determine timing and management of treatment, and liver biopsy is the criterion standard for staging fibrosis. The Metavir grading system is applied to HBV.

Autoimmune Etiologies

Autoimmune liver diseases include autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC). AIH is a rare, chronic inflammatory condition leading to liver parenchyma destruction by autoantibodies, commonly affecting women and associated with antinuclear antibodies, anti-smooth muscle antibodies, and hypergammaglobulinemia. PBC involves progressive autoimmune destruction of intrahepatic biliary channels, portal inflammation, and fibrosis, resulting in cholestatic jaundice, primarily in middle-aged women, with increased alkaline phosphatase. PSC, often linked to ulcerative colitis, is characterized by inflammation and fibrosis reducing intrahepatic and extrahepatic bile duct size, leading to bile duct strictures and cholestasis.

Genetic Etiologies

Alpha-1 antitrypsin deficiency, hereditary hemochromatosis, and Wilson disease are genetic etiologies of childhood onset of CLD. Alpha-1 antitrypsin deficiency is the most common. Hemochromatosis and Wilson disease are autosomal recessive conditions. Hemachromatosis involves HFE gene mutations causing excess iron deposition in the liver and Wilson disease involves ATP7B gene mutations causing excess copper buildup.

Other Etiologies

A wide range of drugs and drug classes can cause hepatotoxicity. Various vascular abnormalities, including but not limited to Budd-Chiari syndrome can also lead to advanced liver damage. Budd-Chiari syndrome is a rare vascular disorder caused by the obstruction of the hepatic venous outflow tract, which can be triggered by a hypercoagulable state resulting from specific medications. In 5-10% cases, the cause is unknown (cryptogenic or idiopathic).[11,]

DIAGNOSIS, MONITORING AND SURVEILLANCE

Biopsy for Chronic Liver Disease
The diagnosis of non-neoplastic liver disease can be made from needle biopsy samples. In addition to establishing a disease etiology, liver biopsy can determine the degree of inflammation present and stage the degree of fibrosis (see Table 1).

Accurate assessment of the degree of hepatic fibrosis and steatosis is essential in predicting prognosis and making treatment recommendations in individuals with CLD. While liver biopsy has long been the reference standard for assessing fibrosis and steatosis, the procedure is costly, invasive, and carries a small, but important, risk of complications. The frequency of biopsy-related complications varies based on operator experience, underlying comorbidities, size of the needle, number of needle passes, and hemostatic abnormalities such as thrombocytopenia and/or prolonged prothrombin time.[3,]

Noninvasive Alternatives to Liver Biopsy
Multiple noninvasive blood-based biomarkers and imaging technologies have been developed to reduce the need for liver biopsies. The term "noninvasive liver disease assessment(s)" (NILDA), has been used to describe these tests. They have been developed to determine the presence and severity of liver fibrosis, steatosis, and clinically significant portal hypertension.[3,] They offer safer and more repeatable assessments for disease progression and treatment response.

Multianalyte Assays
Multianalyte tests for CLD typically combine several blood-based biomarkers and clinical data (like age, sex, BMI) into a proprietary algorithm to assess steatosis, fibrosis, or liver cancer risk. These assays are often used in conjunction with imaging technologies to provide a comprehensive, non-invasive assessment of liver status. Most commercially available laboratory-developed biomarker tests for liver fibrosis are regulated under the Clinical Laboratory Improvement Amendments standards. These laboratory-developed tests (LDTs) have not been cleared or approved by the Food and Drug Administration (FDA).

The FDA cleared the ADVIA Centaur Enhanced Liver Fibrosis (ELF) test for marketing in the U.S. as a novel Class II medical device following a De Novo review (513(f)(2) pathway, DEN190056).

Table 2 lists the proprietary algorithm-based serum markers for liver fibrosis which are currently available in the U.S.:

Table 2. Multianalyte Assays

Test (Manufacturer)	Description	Regulatory Status
FibroSURE (LabCorp)	• ASH FibroSURE (ASH Test) uses a combination of 10 serum biochemical markers of liver function together with age, sex, height, and weight in a proprietary algorithm; it is proposed to provide surrogate markers for liver fibrosis, hepatic steatosis, and alcoholic steatohepatitis. The test has been	• LDTs

Test (Manufacturer)	Description	Regulatory Status
	available in Europe under the name AshTest™ (BioPredictive); the test is exclusively offered by LabCorp in the U.S. as ASH FibroSURE. • HCV FibroSURE uses a combination of 6 serum biochemical markers of liver function plus age and sex in a patented algorithm to generate a measure of fibrosis and inflammation activity in the liver that corresponds to the Metavir system (Table 1). These markers are combined using a linear regression equation to produce a score between 0 and 1, with higher values corresponding to more severe disease. The test has been clinically available in Europe under the name FibroTest since 2003. It is exclusively offered by LabCorp in the U.S. as HCV FibroSURE. • NASH FibroSURE (NASH Test) uses a proprietary algorithm of the same 10 biochemical markers (as the ASH test) of liver function in combination with age, sex, height, and weight and is proposed to provide surrogate markers for liver fibrosis, hepatic steatosis, and NASH. The test has been available in Europe under the name NashTest (BioPredictive); the test is exclusively offered by LabCorp in the U.S. as NASH FibroSURE.	
FIBROSpect II (Prometheus Laboratories)	• FIBROSpect II uses a combination of 3 serum markers to assess the degree of liver fibrosis: hyaluronic acid; tissue inhibitor of metalloproteinase 1; and alpha-2-macroglobulin. These markers are combined using a logistic regression algorithm to generate a index score, ranging from 1 to 100 (or sometimes reported between 0 and 1), with higher scores indicating more severe disease.	• LDTs

Test (Manufacturer)	Description	Regulatory Status
OWLiver panel (CIMA Sciences in partnership with Luxor Scientific)	• The OWLiver test is a serum test for detecting MASLD, MASH with moderate or no fibrosis (F0-F1), and "at-risk" MASH (with significant fibrosis F≥2). The test uses two algorithms, OWLiver-MASH and MASEF score, which combine a panel of 16 and 12 lipid biomarkers in tandem with BMI, AST, and ALT using multivariable logistic regression analysis. This provides a predicted probability score (ranging from 0 to 1) of MASH (OWLiver-MASH) or MASH with significant fibrosis (F≥2) (MASEF Score).	• LDTs
• Enhanced Liver Fibrosis (Siemens Healthineers)	• The Enhanced Liver Fibrosis (ELF) test uses a proprietary algorithm of markers to produce a score based on 3 components: type III procollagen peptide, hyaluronic acid, and tissue inhibitor of metalloproteinase-1. The test stratifies risk for developing cirrhosis or other liver-related events based on the following ranges: <9.80 (lower risk) and ≥11.30 (higher risk). Specific ELF thresholds are used in clinical pathways to guide further assessment and management in NAFLD (MASLD): <7.7 and 9.8 (low and high thresholds).	• In August 2021, the ADVIA Centaur Enhanced Liver Fibrosis (ELF) test (Siemens Healthcare) was cleared by the FDA for marketing as a Class II novel medical device after the De Novo review (513(f)(2)) pathway (DEN190056). • In 2018, the test was granted a first Breakthrough Device Designation (BDD) for predicting disease progression in patients with advanced fibrosis due to NAFLD. • In 2023, the ELF test was granted a second BDD to aid in the identification of advanced fibrosis (≥F3) and cirrhosis (F4) in patients with NAFLD.

Noninvasive Imaging Technologies

Noninvasive imaging technologies to detect liver fibrosis or cirrhosis among patients with CLD are being evaluated as alternatives to liver biopsy. The noninvasive imaging technologies for review are transient elastography (TE), magnetic resonance elastography (MRE), acoustic radiation force impulse (ARFI) imaging, multiparametric magnetic resonance imaging (MRI), and real-time tissue elastography (RTE). Noninvasive imaging tests have been used in combination with multianalyte serum tests.

Table 3. Noninvasive Imaging Technologies

Technology	Description	Device (Vendor, FDA Decision Date, 510(k) Number)
Ultrasound Technologies		
ARFI imaging (shear wave elastography)	• ARFI imaging uses an ultrasound probe to produce an acoustic "push" pulse, which generates shear waves that propagate in tissue to assess liver stiffness. ARFI elastography evaluates the wave propagation speed (measured in meters per second) to assess liver stiffness. The faster the shear wave speed, the harder the object. • ARFI encompasses two related techniques: point shear wave elastography (pSWE), which assesses regions of interest measuring 10×5 mm^2, and two-dimensional shear wave elastography (2D-SWE), which assesses more than one region of interest in rapid succession to decrease sampling error. ARFI elastography can be performed at the same time as a liver sonographic evaluation, even in patients with a significant amount of ascites.	• pSWE: Acuson S2000 Virtual Touch (Siemens AG, 2008, K072786). • 2D-SWE: ElastQ Imaging shear wave elastography (Phillips, 2017, K163120).
RTE	• RTE is a type of strain elastography that uses a combined autocorrelation method to measure tissue strain caused by manual compression or a person's heartbeat. The relative tissue strain is displayed on conventional color B mode ultrasound images in real-time. Challenges in the use of this test are to identify a region of interest while avoiding areas likely to introduce artifacts, such as large blood vessels, the area near the ribs, and the surface of the liver. Areas of low strain increase as fibrosis progresses and strain distribution becomes more	• HI VISION™ Preirus Diagnostic Ultrasound Scantier (Hitachi Medical Systems America, 2010, K093466).

Technology	Description	Device (Vendor, FDA Decision Date, 510(k) Number)
	complex. RTE can be performed in patients with ascites or inflammation. This technology does not perform as well in severely obese individuals.	
TE	• TE uses a mechanical vibrator to produce mild amplitude and low-frequency (50 Hz) waves, inducing an elastic shear wave that propagates throughout the liver. Ultrasound tracks the wave, measuring its speed in kilopascals, which correlates with liver stiffness. Increases in liver fibrosis also increase liver stiffness and resistance of liver blood flow. Cut-off values, expressed in kilopascals (kPa), vary by disease and patient population, but generally range from >7-8 kPa for significant fibrosis (≥F2 or F3) to >10-17.6 kPa for cirrhosis (F4). • TE does not perform as well in patients with ascites, higher BMI, or narrow intercostal margins. Although this test may be used to measure fibrosis, it does not provide information on inflammatory activity and steatosis, nor is it accurate during acute hepatitis or hepatitis exacerbations.	• AIXPLORER Ultrasound System (SuperSonic Imagine, 2009, K091970). • FibroScan (EchoSens, 2013, K123806).
Magnetic Resonance Technologies		
MRE	• MRE uses a driver to generate 60-Hz mechanical waves on the patient's chest wall. The magnetic resonance equipment creates elastograms by processing the acquired images of propagating shear waves in the liver using an inversion algorithm. These elastograms represent the shear stiffness as a pixel value in kilopascals. • MRE has several advantages over ultrasound elastography,	• Magnetic Resonance Elastography (MRE) (Resoundant, 2009, K083421; available by GE Healthcare, Siemens Healthineers, Philips)

Technology	Description	Device (Vendor, FDA Decision Date, 510(k) Number)
	including the ability to analyze larger liver volumes, liver volumes of obese patients or patients with ascites, and viscoelasticity using a 3-dimensional displacement vector.	
MMRI	• MMRI combines proton density fat-fraction, T2*, and T1 mapping. Proton density fat-fraction provides an assessment of hepatic fat content and can be used to determine the grade of liver steatosis. T1 relaxation times are used to assess increases in extracellular fluid, which correlates with the extent of fibrosis and inflammation of the liver. Hepatic iron quantification is measured through T2* relaxation times as T1 relaxation times are decreased by excess iron in the liver tissue.	• LiverMultiScan is a magnetic resonance diagnostic device software application (Perspectum, 2015, K143020).

ARFI: Acoustic radiation Force Impulse; RTE: Real-time tissue elastography; TE: Transient elastography; MRE: Magnetic resonance elastography; MMRI: Multiparametric magnetic resonance imaging.

Current Clinical Care Pathway

CLD comprehensive treatment includes etiological management, lifestyle modifications, pharmacotherapy, nutritional support, prevention and management of complications, regular monitoring, and health education. For individuals with advanced liver disease, such as those experiencing cirrhosis or hepatic failure, liver transplantation may ultimately become the only effective option. Chronic hepatitis B or C can be treated with antivirals, such as lamivudine, entecavir, tenofovir (for HBV), or direct-acting antivirals like sofosbuvir or harvoni (for HCV).[12,]

There are two pharmacologic treatment options for MASH as adjuncts to lifestyle interventions.[13,14,15,] Lifestyle modification, including weight loss through a hypocaloric diet and physical activity, remains the cornerstone of MASH management and can reduce hepatic steatosis and improve insulin sensitivity.

For individuals with biopsy-confirmed MASH and fibrosis (≥F2), the FDA has granted accelerated approval for resmetirom (Rezdiffra, Madrigal Pharmaceuticals) and semaglutide (Wegovy, Novo Nordisk). These are prescribed in combination with diet and exercise for the treatment of adults with MASH and moderate to advanced liver fibrosis, (stages F2 to F3). Resmetirom, a liver-specific thyroid hormone receptor beta-agonist, is the first FDA-approved drug for non-cirrhotic MASH with moderate to advanced fibrosis, demonstrating histological and biochemical benefits. Resmetirom is administered orally once daily.

Semaglutide, a Glucagon-like peptide-1 (GLP-1) receptor agonist, is the second FDA-approved agent for MASH and is administered as a weekly subcutaneous injection.

POLICY

A. **Multianalyte Assays**

1. FibroSURE multianalyte assay may be considered **medically necessary** for the evaluation of fibrosis staging in individuals with chronic liver disease.

2. FibroSURE multianalyte assays are considered **experimental / investigational** for monitoring of individuals with chronic liver disease.

3. Other multianalyte assays with algorithmic analyses are considered **experimental / investigational** for the initial evaluation or monitoring of individuals with chronic liver disease.

B. **Noninvasive Imaging Technologies**

1. Transient elastography (FibroScan) imaging may be considered **medically necessary** for the initial evaluation of individuals with chronic liver disease.

2. Transient elastography (FibroScan) imaging is considered **experimental / investigational** for monitoring of individuals with chronic liver disease.

3. The use of other noninvasive imaging, including, but not limited to, magnetic resonance elastography, multiparametric magnetic resonance imaging, acoustic radiation force impulse imaging, or real-time tissue elastography, is considered **experimental / investigational** for the initial evaluation or monitoring of individuals with chronic liver disease.

POLICY GUIDELINES

A. Increased fibrosis stage has important prognostic implications in nonalcoholic fatty liver disease (NAFLD) (now metabolic dysfunction-associated steatotic liver disease, MASLD, see Background).

B. The American Association for the Study of Liver Diseases (AASLD) has developed an algorithm intended to be used by clinicians in need of a readily available and simple decision support tool for liver disease assessment (see below). The AASLD recommends that fibrosis staging begin with nonproprietary blood-based tests because of their wide availability and performance compared to proprietary tests. Nonproprietary tests include the Fibrosis-4 (FIB-4) Index, and NAFLD/NASH fibrosis score (NFS) which are used as initial blood-based tests to rule-out advanced fibrosis. The fibrosis 4 (FIB-4) Index calculator estimates the likelihood of advanced liver fibrosis (scarring) by combining a patient's age with aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count values. A low FIB-4 score (typically <1.3 or <1.45) suggests a low risk of advanced fibrosis, while a high score (typically >2.67 or >3.25) indicates a high risk and may warrant further assessment, potentially a liver biopsy.

C. The NFS score is calculated using a formula that considers the following factors: age, body mass index (BMI), diabetes status, and blood test results (AST/ALT ratio, albumin, platelet count). The NFS is interpreted as follows:
   1. Score <-1.455: Low risk of advanced fibrosis
   2. Score between -1.455 and 0.676: Indeterminate risk
   3. Score >0.676: High risk of advanced fibrosis

D. The AASLD Practice Guidelines Committee commissioned a diverse group of experts across multiple disciplines in the field of adult and pediatric liver disease to develop guidelines and guidance statements along with a systematic review covering blood-based noninvasive tests to address specific clinically focused questions. Of these tests, FIB-4 was considered to have superior performance, particularly for the identification of F3-4 stages of fibrosis, which is the spectrum of fibrosis for which the tests were designed. NFS was considered an equivalent to FIB-4 in patients with NAFLD in the assessment of advanced fibrosis. FIB-4 thresholds of ≤1.30 and ≥2.67, and NFS thresholds of ≤-1.455 and ≥0.676, have been proposed as having higher predictive values for F3-4 in NAFLD. The AASLD recommends that in the appropriate clinical setting (i.e., low pre-test probability), both tests should suffice to rule out significant/advanced fibrosis.

E. Confirmatory testing (secondary assessment) such as noninvasive imaging technologies should be performed for patients with values between the lower and upper thresholds of these tests. Patients with FIB-4 scores less than 1.3 are unlikely to have advanced fibrosis. High-risk individuals, such as those with type 2 diabetes, medically complicated obesity, family history of cirrhosis, or more than mild alcohol consumption, should be screened for advanced fibrosis.

F. The AASLD Practice Guidelines Committee made an ungraded statement that in adults with CLD, either ultrasound-based elastography methods or magnetic resonance elastography (MRE) can be utilized to stage fibrosis. Depending on local availability and expertise, it is reasonable to perform MRE as an investigation when concomitant cross-sectional imaging is needed or for patients in whom the accuracy of US-based elastography might be compromised.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review was created using searches of the PubMed database. The most recent literature update was performed through September 22 , 2025.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Noninvasive Testing for Chronic Liver Disease

Liver biopsy is an imperfect reference standard. There is a high rate of sampling error, which can lead to underdiagnosis of liver disease.[16,17,] These errors will bias estimates of performance characteristics of the noninvasive tests to which it is compared, and therefore such errors must be considered in appraising the body of evidence. Mehta et al (2009) estimated that even under the best scenario where sensitivity and specificity of liver biopsy are 90%, and the prevalence of significant disease (increased liver fibrosis, scored as Metavir ≥F2) is 40%; a perfect alternative marker would have calculated the area under the receiver operating characteristic (AUROC) curve of 0.90.[18,] Therefore, the effectiveness of alternative technologies may be underestimated. In fact, when the accuracy of biopsy is presumed to be 80%, a comparative technology with an AUROC curve of 0.76 may actually have an AUROC curve of 0.93 to 0.99 for diagnosing true disease.

Due to a large number of primary studies published on this topic, this evidence review focuses on systematic reviews when available. The validation of multiple noninvasive tests is assessed individually in the following sections. Although options exist for performing systematic reviews with imperfect reference standards,[19,] most available reviews did not use any correction for the imperfect reference.

A systematic review by Crossan et al (2015) was performed for the UK National Institute for Health Research.[20,] The first objective of the review was to determine the diagnostic accuracy of different noninvasive liver tests compared with liver biopsy in the diagnosis and monitoring of liver fibrosis and cirrhosis in patients with HCV, HBV, NAFLD, and ALD. Reviewers selected 302 publications and presentations from 1998 to April 2012. Patients with HCV were the most common population included in the studies while patients with ALD were the least common. FibroScan and FibroTest were the most commonly assessed tests across liver diseases. Aminotransferase to platelet ratio index (APRI) was also widely assessed in HBV and HCV but not in NAFLD or ALD. The estimates of diagnostic accuracy for each test by disease are discussed in further detail in the following sections. Briefly, for diagnosing significant fibrosis (stage ≥F2) in HCV, the summary sensitivities and specificities were: FibroScan, 79% and 83%; FibroTest, 68% and 72%; APRI (low cutoff), 82% and 57%; ARFI imaging, 85% and 89%; HepaScore, 73% and 73%; FIBROSpect II, 78% and 71%; and FibroMeter, 79% and 73%, respectively. For diagnosing advanced fibrosis in HBV, the summary sensitivities and specificities were: FibroScan, 71% and 84% and FibroTest, 66% and 80%, respectively. There are no established or validated cutoffs for fibrosis stages across the diseases for most tests. For FibroTest, established cutoffs exist, but were used inconsistently across studies. Test failures or reference standard(s) were frequently not captured in analyses. Most populations included in the studies were from tertiary care settings that have more advanced disease than the general population, which would overestimate the prevalence of the disease and diagnostic accuracy. These issues likely cause overestimates of sensitivities and specificities. The quality of the studies was generally rated as poor, with only 1.6% receiving a high-quality rating.

Houot et al (2016) reported on a systematic review funded by BioPredictive, the manufacturer of FibroTest.[21,] This review included 71 studies published between January 2002 to February 2014 with over 12,000 participants with HCV and HBV comparing the diagnostic accuracy of FibroTest, FibroScan, APRI, and fibrosis-4 (FIB-4) index. Included studies directly compared the tests and calculated median differences in the AUROC curve using Bayesian methods. There was no evaluation of the methodologic quality of the included studies. The Bayesian difference in AUROC curve for significant fibrosis (stage ≥F2) between FibroTest and FibroScan was based on 15 studies and estimated to be 0.06 (95% credible interval [CrI], 0.02 to 0.09) favoring FibroTest. The difference in AUROC curve for cirrhosis for FibroTest versus FibroScan was based on 13 studies and estimated to be 0.00 (95% CrI, -0.04 to 0.04). The difference for advanced fibrosis between FibroTest and APRI was based on 21 studies and estimated to be 0.05 (95% CrI, 0.03 to 0.07); for cirrhosis, it was based on 14 studies and estimated to be 0.05 (95% CrI, 0.00 to 0.11), both favoring FibroTest.

MULTIANALYTE ASSAYS: FIBROSURE SERUM PANEL

Clinical Context and Test Purpose

The purpose of noninvasive testing in individuals with CLD is to detect liver fibrosis so that individuals can avoid the potential adverse events of an invasive liver biopsy and receive appropriate treatment. The degree of liver fibrosis is an important factor in determining the appropriate approach for managing individuals with liver disease (e.g., ALD, NAFLD/MASLD, hepatitis).

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with CLD.

Interventions

The test being considered is the FibroSURE serum panel.

Comparators

The following tests and practices are currently being used to diagnose CLD: liver biopsy, noninvasive radiologic methods, and other multianalyte serum assays.

Outcomes

The general outcomes of interest are test validity, morbid events, and treatment-related morbidity. Follow-up over months to years is of interest to the relevant outcomes.

Study Selection Criteria

For the evaluation of the clinical validity of the tests within this review, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard (describe the reference standard).
- Patient/sample clinical characteristics were described.

- Patient/sample selection criteria were described.

ALCOHOL -ASSOCIATED LIVER DISEASE AND ALCOHOLIC STEATOHEPATITIS

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
The diagnostic value of FibroSURE (FibroTest in Europe) has also been evaluated for the prediction of liver fibrosis in patients with ALD and NAFLD.[22,23,] Thabut et al (2006) reported the development of a panel of biomarkers (ASH FibroSURE [ASH Test]) for the diagnosis of alcoholic steatohepatitis (ASH) in patients with chronic ALD.[24,] Biomarkers were initially assessed in a training group of 70 patients, and a panel was constructed using a combination of the 6 biochemical components of the FibroTest-ActiTest plus AST). The algorithm was subsequently studied in 2 validation groups (1 prospective study for severe ALD, 1 retrospective study for nonsevere ALD) that included 155 patients and 299 controls. The severity of ASH (none, mild, moderate, severe) was blindly assessed from biopsy samples. In the validation groups, there were 28 (18%) cases of discordance between the diagnosis of ASH predicted by the ASH Test and biopsy; 10 (36%) were considered false-negatives of the ASH Test, and 11 were suspected failures of biopsy. Seven cases were indeterminate by biopsy. The AUROC curves were 0.88 and 0.89 in the validation groups. The median ASH Test value was 0.005 in controls, 0.05 in patients without or with mild ASH, 0.64 in the moderate ASH grade, and 0.84 in severe ASH grade 3. Using a cutoff value of 0.50, the ASH Test had a sensitivity of 80% and specificity of 84%, with PPVs and NPVs of 72% and 89%, respectively. Several authors had an interest in the commercialization of this test, and no independent studies on the diagnostic accuracy of ASH FibroSURE (ASH Test) were identified. In addition, it is not clear if the algorithm used in this study is the same as that used in the currently commercially available test, which includes 10 biochemicals.

FibroTest has been studied in patients with ALD. In the Crossan et al (2015) systematic review, 1 study described the diagnostic accuracy of the FibroTest for significant fibrosis (stage ≥ F2) or cirrhosis in ALD.[20,] With a high cutoff for positivity (0.7), the sensitivity and specificity for advanced fibrosis were 55% (95% CI, 47% to 63%) and 93% (95% CI, 85% to 97%) and for cirrhosis were 91% (95% CI, 82% to 96%) and 87% (95% CI, 81% to 91%), respectively. With a low cutoff for positivity (0.3), the sensitivity and specificity for advanced fibrosis were 84% (95% CI, 77% to 89%) and 65% (95% CI, 55% to 75%), respectively. The sensitivity and specificity for cirrhosis were 100% (95% CI, 95% to 100%) and 50% (95% CI, 42% to 58%), respectively.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No studies were identified that assessed clinical outcomes following the use of the ASH FibroSURE (ASH Test) in ALD and ASH.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) FORMERLY NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
Crossan et al (2015) published a systematic review which included 4 studies in the pooled estimate of the diagnostic accuracy of FibroSure/FibroTest for advanced fibrosis (stage ≥ 3) in NAFLD (MASLD).[20,] The summary sensitivities and specificities were 40% (95% CI, 24% to 58%) and 96% (95% CI, 91% to 98%), respectively. Only 1 study included reported accuracy for cirrhosis, with sensitivity and specificity of 74% (95% CI, 54%, to 87%) and 92% (95% CI, 88% to 95%), respectively.

A systematic review conducted to support the AASLD Practice Guidelines (2024) did not identify any studies that examined the relationship between changes in FibroSure/FibroTest and histological improvement in fibrosis among patients with MASLD or MASH.[3,]

Poynard et al (2006) reported the development of a panel of biomarkers (NASH FibroSURE [NASH Test]) for the prediction of nonalcoholic steatohepatitis (NASH) in patients with NAFLD.[25,] Biomarkers were initially assessed with a training group of 160 patients, and a panel was constructed using a combination of 13 of 14 parameters of the currently available test. The algorithm was subsequently studied in a validation group of 97 patients and 383 controls. Patients in the validation group were from a prospective multicenter study with hepatic steatosis at biopsy and suspicion of NAFLD. Histologic diagnoses used Kleiner et al's scoring system, with 3 classes for NASH (NASH, borderline NASH, no NASH). The main endpoint was steatohepatitis, defined as a histologic NASH score of 5 or greater. The AUROC curve for the validation group was 0.79 for the diagnosis of NASH, 0.69 for the diagnosis of borderline NASH, and 0.83 for the diagnosis of no NASH. Results showed a sensitivity of 33% and specificity of 94% for NASH, with a PPV and NPV of 66% and 81%, respectively. For borderline NASH or NASH, sensitivity was 88%, specificity 50%, PPV 74%, and NPV 72%. Clinically significant discordance (2 class difference) was observed in 8 (8%) patients. None of the 383 controls were considered to have NASH by NASH FibroSURE (NASH Test). Authors proposed that this test would be suitable for mass screening for NAFLD in patients with obesity and diabetes.

An independent study by Lassailly et al (2011) attempted to prospectively validate the NASH Test (along with the FibroTest, SteatoTest, and ActiTest) in a cohort of 288 patients treated with bariatric surgery.[24,] Included were patients with severe or morbid obesity (body mass index, >35 kg/m^2), at least 1 comorbidity for at least 5 years, and resistance to medical treatment. Excluded were patients with current excessive drinking, long-term consumption of hepatotoxic drugs, and positive screening for chronic liver diseases including hepatitis. Histology and biochemical measurements were centralized and blinded to other characteristics. The NASH Test provided a 3-category score for no NASH (0.25), possible NASH (0.50), and NASH (0.75). The prevalence of NASH was 6.9%, while the prevalence of NASH or possible NASH was 27%. The concordance rate between the histologic NASH score and the NASH Test was 43.1%, with a weak κ reliability test (0.14). In 183 patients categorized as possible NASH by the NASH Test, 124 (68%) were classified as no NASH by biopsy. In 15 patients categorized as NASH by the NASH Test, 7 (47%) were no NASH and 4 (27%) were possible NASH by biopsy. The NPV of the NASH Test for possible NASH or NASH was 47.5%. Authors suggested that the power of this study to validate agreement between the NASH Test and biopsy was low, due to the low prevalence of NASH. However, the results showed poor concordance between the NASH Test and biopsy, particularly for intermediate values.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No studies were identified that assessed clinical outcomes following the use of the NASH FibroSURE (NASH Test) in NAFLD and NASH.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

HEPATITIS C VIRUS

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
Following the initial research into FibroSURE (patients with liver fibrosis who had undergone biopsy)[26,], the next step in the development of this test was a further evaluation of the algorithm in a cross-section of patients, including patients with HCV participating in large clinical trials before and after the initiation of antiviral therapy. A study by Poynard et al (2003) focused

on patients with HCV participating in a randomized study of pegylated interferon and ribavirin.[27,] From the 1530 participants, 352 patients with stored serum samples and liver biopsies at study entry and at 24-week follow-up were selected. The HCV FibroSURE score was calculated and then compared with the Metavir liver biopsy score. At a cutoff of 0.30, the HCV FibroSURE score had 90% sensitivity and 88% positive predictive value (PPV) for the diagnosis of Metavir F2 to F4 fibrosis; the specificity was 36%, and the negative predictive value (NPV) was 40%.

Poynard et al (2004) also evaluated discordant results in 537 patients who underwent liver biopsy and the HCV FibroSURE and ActiTest on the same day; discordance was attributed to either the limitations in the biopsy or serum markers.[28,] In this study, cutoff values were used for individual Metavir scores (ie, F0 to F4) and for combinations of Metavir scores (ie, F0 to F1, F1 to F2). The definition of a significant discordance between FibroTest and ActiTest and biopsy scores was at least 2 stages or grades in the Metavir system. Discordance was observed in 29% of patients. Risk factors for failure of the HCV FibroSURE scoring system were as follows: the presence of hemolysis, inflammation, possible Gilbert syndrome, acute hepatitis, drugs inducing cholestasis, or an increase in transaminases. Discordance was attributable to markers in 2.4% of patients, to the biopsy in 18%, and unattributed in 8.2% of patients. As noted in 2 reviews, the bulk of the research on HCV FibroSURE was conducted by researchers with an interest in the commercialization of the algorithm.[29,30,]

In the Crossan et al (2015) systematic review, FibroTest was the most widely validated commercial serum test.[20,] Seventeen studies were included in the pooled estimate of the diagnostic accuracy of FibroTest for significant fibrosis (stage ≥F2) in HCV. With varying cutoffs for positivity between 0.32 and 0.53, the summary sensitivity in HCV was 68% (95% confidence interval [CI], 58% to 77%) and specificity was 72% (95% CI, 70% to 77%). Eight studies were included for cirrhosis (stage F4) in HCV. The cutoffs for positivity ranged from 0.56 to 0.74 and the summary sensitivity and specificity were 60% (95% CI, 43% to 76%) and 86% (95% CI, 81% to 91%), respectively. Uninterpretable results were rare for tests based on serum markers.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs). The primary benefit of the FibroSURE (FibroTest in Europe) for HCV is the ability to avoid liver biopsy in patients without significant fibrosis. There are currently no such published studies to demonstrate the effect on patient outcomes.

The FibroTest has been used as an alternative to biopsy for the purposes of establishing trial eligibility in terms of fibrosis or cirrhosis; several trials with FibroTest (ION-1,-3; VALENCE; ASTRAL-2, -3, -4) have established the efficacy of HCV treatments.[31,32,33,34,35,36,] For example, in

the ASTRAL-2 and -3 trials, cirrhosis could be defined by a liver biopsy; a FibroScan or a FibroTest score of more than 0.75; or an APRI of more than 2.

These tests also need to be adequately compared with other noninvasive tests of fibrosis to determine their comparative efficacy. In particular, the proprietary, algorithmic tests should demonstrate superiority to other readily available, nonproprietary scoring systems to demonstrate that the tests improve health outcomes.

The FibroSURE test also has a potential effect on patient outcomes as a means to follow response to therapy. In this case, evidence needs to demonstrate that the use of the test for response to therapy impacts decision making and that these changes in management decisions lead to improved outcomes. It is not clear whether HCV FibroSURE could be used as an interval test in patients receiving therapy to determine whether an additional liver biopsy is necessary.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

HEPATITIS B VIRUS

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
While most multianalyte assay studies that have identified fibrosis have been conducted in patients with HCV, studies are also being conducted in patients with chronic HBV.[37,38,] In a study, Park et al (2013) compared liver biopsy with the FibroTest results obtained on the same day from 330 patients who had chronic HBV.[39,] Discordance was found in 30 (9.1%) patients for whom the FibroTest underestimated fibrosis in 25 patients and overestimated it in 5 patients. Those with Metavir liver fibrosis stage F3 or F4 (15.4%) had a significantly higher discordance rate than those with stages F1 or F2 (3.0%; $p<.001$). The only independent factor for discordance on multivariate analysis was a Metavir stage F3 or F4 on liver biopsy ($p<.001$).

Salkic et al (2014) conducted a meta-analysis of studies on the diagnostic accuracy of FibroTest in chronic HBV.[40,] Included in the meta-analysis were 16 studies (n=2494) on liver fibrosis diagnosis and 13 studies (n=1754) on cirrhosis diagnosis. There was strong evidence of heterogeneity in the 16 fibrosis studies and evidence of heterogeneity in the cirrhosis studies. For significant liver fibrosis (Metavir F2 to F4) diagnosis using all of the fibrosis studies, the AUROC curve was 0.84 (95% CI, 0.78 to 0.88). At the recommended FibroTest threshold of 0.48 for a significant liver fibrosis diagnosis, the sensitivity was 60.9%, specificity was 79.9%, and the diagnostic odds ratio (OR) was 6.2. For liver cirrhosis (Metavir F4) diagnosis using all of the cirrhosis studies, the AUROC curve was 0.87 (95% CI, 0.85 to 0.9). At the recommended FibroTest threshold of 0.74 for cirrhosis diagnosis, the sensitivity was 61.5%, specificity was 90.8%, and the diagnostic OR was 15.7. While the results demonstrated FibroTest may be useful in excluding a diagnosis of cirrhosis in patients with chronic HBV, the ability to detect significant fibrosis and cirrhosis and exclude significant fibrosis is suboptimal.

Xu et al (2014) reported on a systematic review and meta-analysis of studies assessing biomarkers to detect fibrosis in HBV.[41,] Included in the analysis of FibroTest were 11 studies (N=1640). In these 11 studies, AUROC curves ranged from 0.69 to 0.90. Heterogeneity in the studies was statistically significant.

Crossan et al (2015) published a systematic review which included 6 studies in the pooled estimate of the diagnostic accuracy of FibroTest for significant fibrosis (stage ≥F2) in HBV.[20,] The cutoffs for positivity ranged from 0.40 to 0.48, and the summary sensitivities and specificities were 66% (95% CI, 57% to 75%) and 80% (95% CI, 72% to 86%), respectively. The accuracy for diagnosing cirrhosis in HBV was based on 4 studies with cutoffs for positivity ranging from 0.58 to 0.74; sensitivities and specificities were 74% (95% CI, 25% to 96%) and 90% (95% CI, 83% to 94%), respectively.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

There are no studies evaluating the effect of this test on outcomes for patients with HBV. Of note, some researchers have suggested that different markers (eg, HBV FibroSURE) may be needed for this assessment in patients with hepatitis B.[42,]

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: FibroSURE Serum Panel
For individuals who have CLD who receive FibroSURE serum panels, the evidence includes systematic reviews of more than 30 observational studies (>5000 patients). FibroSURE has been studied in populations with ALD, NAFLD, and viral hepatitis. There are established cutoffs, although they were not consistently used in validation studies. Given these limitations and the imperfect reference standard, it is difficult to interpret performance characteristics. However, for the purposes of deciding whether a patient has severe fibrosis or cirrhosis, FibroSURE results provide data sufficiently useful to determine therapy. Specifically, FibroSURE has been used as an alternative to biopsy to establish eligibility regarding the presence of fibrosis or cirrhosis in several RCTs that showed the efficacy of HCV treatments, which in turn demonstrated that the test can identify patients who would benefit from therapy.

MULTIANALYTE SERUM ASSAYS OTHER THAN FIBROSURE

Clinical Context and Test Purpose
The purpose of noninvasive testing in individuals with chronic liver disease is to detect liver fibrosis so that individuals can avoid the potential adverse events of an invasive liver biopsy and receive appropriate treatment. The degree of liver fibrosis is an important factor in determining the appropriate approach for managing individuals with liver disease (e.g., hepatitis, ALD, NAFLD).

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with chronic liver disease.

Interventions
The tests being considered are multianalyte serum assays (other than FibroSURE).

Comparators
The following tests and practices are currently being used to diagnose chronic liver disease: liver biopsy, noninvasive radiologic methods, and other multianalyte serum assays.

Outcomes
The general outcomes of interest are test validity, morbid events, and treatment-related morbidity. Follow-up over months to years is of interest to the relevant outcomes.

Study Selection Criteria
For the evaluation of the clinical validity of the tests within this review, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard (describe the reference standard).
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

FIBROSPECT II

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
Patel et al (2004) investigated the use of serum markers in an initial training set of 294 patients with HCV and further validated the resulting algorithm in a validation set of 402 patients.[43,] The algorithm was designed to distinguish between no or mild fibrosis (F0 to F1) and moderate-to-severe fibrosis (F2 to F4). With the prevalence of F2 to F4 disease of 52% and a cutoff value of 0.36, the PPVs and NPVs were 74.3% and 75.8%, respectively.

The published studies for this combination of markers continue to focus on test characteristics such as sensitivity, specificity, and accuracy.[44,45,46,] In Crossan et al (2015), the summary

diagnostic accuracy for detecting significant fibrosis (stage ≥F2) in 5 studies of HCV with FibroSpect II, with cutoffs ranging from 42 to 72, was 78% (95% CI, 49% to 93%) and the summary specificity was 71% (95% CI, 59% to 80%).[20,]

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

The issues of effect on patient outcomes are similar to those discussed for the FibroSURE (FibroTest in Europe). No studies were identified in the published literature in which the results of the FIBROSpect test were actively used in the management of the patient.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of FIBROSpect has not been established, a chain of evidence supporting the clinical utility of this test for this population cannot be constructed.

OTHER MULTIANALYTE SCORING SYSTEMS

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

REVIEW OF EVIDENCE

NONALCOHOLIC FATTY LIVER DISEASE/METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (NAFLD/MASLD)

Enhanced Liver Fibrosis
The Enhanced Liver Fibrosis (ELF) score is based on a proprietary algorithm that combines three specific biomarkers (Table 2). By contrast, non-proprietary scoring systems discussed below use a simplified nonproprietary formula that can be calculated to produce a score for the prediction of fibrosis.

Several systematic reviews have assessed the diagnostic accuracy of ELF in patients across various CLD etiologies. A meta-analysis by Vali et al (2020) of 11 studies using ELF tests in NAFLD for F3-4 noted a high sensitivity (0.93) but limited specificity (0.34) at the lower recommended threshold of 7.7 (Table 2); higher thresholds and F3-4 prevalence of at least 30% were required for increasing ELF positive predictive value to >0.8 for advanced fibrosis.[47,]

A systematic review, conducted in support of the American Association for the Study of Liver Diseases (AASLD) Practice Guidelines (2024),[3,] reported conflicting data on the diagnostic accuracy of ELF compared with nonproprietary blood-based tests such as FIB-4 and NFS for the detection of fibrosis in NAFLD. The AASLD noted that in community-based and other low prevalence cohorts, blood-based noninvasive tests are useful for excluding advanced fibrosis with high NPV but require additional noninvasive tests to improve their PPV.[3,]

OWLiver panel
The OWLiver panel is a serum-based non-invasive test used for the diagnosis of MASH and fibrosis (Table 2). Iruzubieta et al (2024) conducted a multicenter cross-sectional study that included 124 biopsy-proven MASLD in adult patients with overweight/obesity and type 2 diabetes.[48,] TE, FIB-4, NFS, FibroScan-AST, and the OWLiver panel were performed. Sensitivity, specificity, PPV, NPV and AUC were calculated. These four noninvasive tests were assessed individually and in sequential/parallel combinations. Thirty-five (28%) patients had early MASH and 66 (53%) had MASH with significant fibrosis ("at-risk" MASH). The OWLiver panel (OWLiver-MASH and MASEF® algorithm) correctly classified 86% as MASH, showing an accuracy, sensitivity, specificity, PPV, and NPV of 0.77, 0.86, 0.35, 0.85, and 0.36, respectively. Class III obesity, diabetes control, or gender did not impact on the performance of the OWLiver panel ($p > .1$). Tests for at-risk MASH showed an AUC >0.70 except for NFS. The MASEF algorithm showed the highest accuracy and NPV for at-risk MASH (AUC 0.77 [0.68–0.85], NPV 72%) and advanced fibrosis (AUC 0.80 [0.71-0.88], NPV 92%). Combinations of tests for the identification of at-risk MASH did not provide any additional benefit over using MASEF algorithm alone. Further studies involving larger patient groups is required to confirm these results and determine their relevance across broader/heterogenous study populations.

Nonproprietary scoring systems have also been developed, including FIB-4, NAFLD fibrosis score (NFS), APRI, AST/ALT ratio, combined body mass index, AST/ALT ratio and diabetes status (BARD) (see Appendix)

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs. The primary benefit of the multivariate serum assays is the ability to avoid liver biopsy.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Other Multianalyte Scoring Systems
For individuals who have CLD who receive multianalyte serum assays for liver function assessment, such as the ELF test and OWLiver panel, the evidence includes observational studies and systematic reviews. The ELF test shows high sensitivity but lower specificity for detecting advanced fibrosis in NAFLD, especially at lower thresholds. Its PPV improves with higher thresholds and greater disease prevalence. A systematic review conducted in support of the AASLD Practice Guidelines (2025) reported conflicting data on the diagnostic accuracy of ELF compared with nonproprietary blood-based tests such as FIB-4 and NFS for the detection of fibrosis in NAFLD. The AASLD noted that in community-based and other low prevalence cohorts, blood-based noninvasive tests are useful for excluding advanced fibrosis with high NPV but require additional noninvasive tests to improve their PPV. A multicenter cross-sectional study demonstrated high accuracy of the OWLiver panel for diagnosing MASH and advanced fibrosis in patients with obesity and type 2 diabetes, with consistent results across obesity levels and diabetes control. Further studies comparing the OWLiver panel to nonproprietary tests in larger and more diverse patient populations is necessary to confirm these findings.

NONINVASIVE IMAGING: TRANSIENT ELASTOGRAPHY

Clinical Context and Test Purpose
The purpose of noninvasive testing in individuals with CLD is to detect liver fibrosis so that individuals can avoid the potential adverse events of an invasive liver biopsy and receive appropriate treatment. The degree of liver fibrosis is an important factor in determining the appropriate approach for managing individuals with liver disease (eg, hepatitis, ALD, NAFLD/MASLD).

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with CLD.

Interventions
The test being considered is transient elastography (TE).

Comparators
The following tests and practices are currently being used to diagnose chronic liver disease: liver biopsy, other noninvasive radiologic methods, and multianalyte serum assays.

Outcomes
The general outcomes of interest are test validity, morbid events, and treatment-related morbidity. Follow-up over months to years is of interest to the relevant outcomes.

Study Selection Criteria
For the evaluation of the clinical validity of the tests within this review, studies that meet the following eligibility criteria were considered:
- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard (describe the reference standard).

- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
There is extensive literature on the use of transient elastography (eg, FibroScan) to gauge liver fibrosis and cirrhosis. Summaries of systematic reviews are shown in Tables 5 and 6.

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)
Duarte-Rojo et al (2025) conducted a systematic review to assess the evidence on the accuracy of TE, shear wave elastography (ARFI imaging), and MRE to stage liver fibrosis.[49,] This review was undertaken to support the AASLD guidelines on noninvasive imaging technologies for staging liver fibrosis in CLD. A comprehensive search was performed for studies (published through April 2022) assessing these methods for the identification of significant fibrosis (F2-4), advanced fibrosis (F3-4), or cirrhosis (F4), using histopathology as the standard of reference by liver disease etiology in adults or children. Two-hundred and forty (240) studies (N=61,193 patients) were included in this systematic review. Fifty-four studies (22%) reported the accuracy of TE for staging fibrosis in patients with NAFLD. For significant fibrosis (F2-4), a TE-liver stiffness measurement (LSM) cutoff value of 7 kPa yielded a sensitivity of 76% and a specificity of 73%, whereas for advanced fibrosis (F3-4), a cutoff of 10 kPa had a sensitivity of 82% and a specificity of 79% (see Table 3 for cut-off thresholds). To detect cirrhosis (F4), a TE-LSM cutoff of 13 kPa had a sensitivity of 90% and a specificity of 89%.

Mixed Etiologies
Brener (2015) performed a health technology assessment summarizing many of the systematic reviews below.[50,] The assessment focused on reviews of the diagnostic accuracy and effect on patient outcomes of TE for liver fibrosis in patients with HCV, HBV, NAFLD, ALD, or cholestatic diseases. Fourteen systematic reviews of TE with biopsy reference standard shown below were included in the Brener assessment, summarizing more than 150 primary studies.[51,52,53,54,55,56,57,58,59,60,61,62,63,64,] There was variation in the underlying cause of liver disease and the cutoff values of TE stiffness used to define Metavir stages in the systematic reviews. There did not appear to be a substantial difference in diagnostic accuracy for one disease over any other. The reviews demonstrated that TE has good diagnostic accuracy compared with biopsy for the assessment of liver fibrosis and steatosis.

Crossan et al (2015) found that FibroScan was the noninvasive liver test most assessed in validation studies across liver diseases (37 studies in HCV, 13 in HBV, 8 in NAFLD, 6 in ALD).[20,] Cutoffs for positivity for fibrosis staging varied between diseases and were frequently not prespecified or validated: HCV, 5.2 to 10.1 kPa in the 37 studies for Metavir stages ≥F2; HBV, 6.3 to 8.9 kPa in 13 studies for stages ≥F2; NAFLD, 7.5 to 10.4 kPa in 8 studies for stages ≥F3; ALD, 11.0 to 12.5 kPa in 4 studies for stages ≥F3. Summary sensitivities and specificities by disease are shown in Table 5. The overall sensitivity and specificity for cirrhosis including all diseases (65 studies; cutoffs range, 9.2 to 26.5 kPa) were 89% (95% CI, 86% to 91%) and 89% (95% CI, 87% to 91%), respectively. The rate of uninterpretable results, when reported,

with FibroScan (due to <10 valid measurements; success rate, <60%; interquartile range, >30%) was 8.5% in HCV and 9.6% in NAFLD.

Table 4. Transient Elastography Systematic Review Characteristics

Study	Dates	Studies	N	Population
Bota et al (2013)[51,]	To May 2012	13	1163	Chronic hepatitis
Cai et al (2021)[65,]	To Mar 2019	62	NR	ALD, NAFLD
Chon et al (2012)[52,]	2002 to Mar 2011	18	2772	HBV
Crossan et al (2015)[20,]	1998 to Apr 2012	66	NR	HCV, HBV, NAFLD, ALD
Friedrich-Rust et al (2008)[53,]	2002 to Apr 2007	50	11,275	All causes of liver disease
Geng et al (2016)[66,]	To Jan 2015	57	10,569	Multiple causes of liver disease
Jiang et al (2018)[67,]	To Dec 2017	11	1735	NAFLD
Kwok et al (2014)[54,]	To Jun 2013	22	1047	NAFLD
Li et al (2016)[68,]	Jan 2003 to Nov 2014	27	4386	HBV
Njei et al (2016)[69,]	To Jan 2016	6	756	HCV/HIV coinfection
Pavlov et al (2015)[70,]	To Aug 2014	14	834	ALD
Poynard et al (2011)[56,]	Feb 2001 to Dec 2010	18	2714	HBV
Shaheen et al (2007)[57,]	Jan 1997 to Oct 2006	12	1981	HCV
Shi et al (2014)[58,]	To May 2013	9	1771	All causes of steatosis
Steadman et al (2013)[59,]	2001 to Jun 2011	64	6028	HCV, HBV, NAFLD, CLD, liver transplant
Stebbing et al (2010)[60,]	NR, prior to Feb 2009	22	4625	All causes of liver disease
Talwalkar et al (2007)[61,]	To Jan 2027	9	2083	All causes of liver disease
Tsochatzis et al (2011)[62,]	To May 2009	40	7661	All causes of liver disease
Tsochatzis et al (2014)[63,]	1998 to Apr 2012	302	NR	HCV, HBV, ALD, NAFLD
Xu et al (2015)[71,]	To Dec 2013	19	3113	HBV
Xue-Ying (2020)[64,]	Jan 2008 to Dec 2018	81	32,694	HBV

ALD: alcoholic liver disease; CLD: chronic liver disease; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; NAFLD: nonalcoholic fatty liver disease; NR: not reported.

Table 5. Transient Elastography Systematic Reviews Diagnostic Accuracy Results

		Significant Fibrosis (ie, Metavir Stages F2 to F4)		Cirrhosis (ie, Metavir Stage F4)	
Study	**Population**	**Studies/ Sample Size**	**AUROC (95% CI) Sensitivity (95% CI) Specificity (95% CI)**	**Studies/ Sample Size**	**AUROC (95% CI) Sensitivity (95% CI) Specificity (95% CI)**
Bota et al (2013)[51]	Multiple diseases	10/1016	0.87 (0.83 to 0.89) 78% (72% to 83%) 84% (75% to 90%)	13/1163	0.93 (0.91 to 0.95) 89% (80% to 94%) 87% (82% to 91%)
	HCV			4/NR	NR 92% (78% to 97%) 86% (82% to 90%)
Cai et al (2021)[65]	ALD/NAFLD	40/2569	0.86 (0.83 to 0.89) 77% (73% to 81%) 82% (78% to 86%)	34/914	0.95 (0.92 to 0.96) 91% (87% to 94%) 86% (83% to 89%)
Chon et al (2012)[52]	Chronic HBV	12/2000	0.86 (0.86 to 0.86) 74.3% (NR) 78.3% (NR)	16/2614	0.93 (0.93 to 0.93) 84.6% (NR) 81.5% (NR)
Crossan et al(2015)[20]	HCV	37/NR	NR 79% (74% to 84%) 83% (77% to 88%)	36/NR	NR 89% (84% to 92%) 91% (89% to 93%)
	HBV	13/NR	NR 71% (62% to 78%) 84% (74% to 91%)	19/NR	NR 86% (79% to 91%) 85% (78% to 89%)
	NAFLD			4/NR	NR 96% (83% to 99%) 89% (85% to 92%)
	ALD	1/NR	NR 81% (70% to 88%) 92% (76% to 98%)	4/NR	NR 87% (64% to 96%) 82% (67% to 91%)
Friedrich-Rust (2008)[53]	Multiple diseases	25/3685	0.84 (0.82 to 0.86) NR NR	25/4557	0.94 (0.93 to 0.95) NR NR
	HCV	NR	0.84 (0.80 to 0.86) NR NR		
Geng et al(2016)[66]	Multiple diseases				0.93 (NR) 81% (79% to 83%) 88% (87% to 89%)
Jiang et al (2018)[67]	NAFLD	10/NR	0.85 (0.82 to 0.88) 77% (70% to 84%) 80% (74% to 84%)	11/NR	0.96 (0.93 to 0.97) 90% (73% to 97%) 91% (87% to 94%)

		Significant Fibrosis (ie, Metavir Stages F2 to F4)		**Cirrhosis (ie, Metavir Stage F4)**	
Kwok et al(2014)[54,]	NAFLD	7/800	0.83 (0.79 to 0.87) 0.79 (0.72 to 0.84) 0.75 (0.71 to 0.79)	57/10,569	0.96 (0.94 to 0.99) 92% (82% to 97%) 92% (86% to 98%)
Li et al (2016)[68,]	HBV	19/NR	0.88 (0.85 to 0.91) 81% (76% to 85%) 82% (71% to 87%)	24/NR	0.93 (0.91 to 0.95) 86% (82% to 90%) 88% (84% to 90%)
Njei et al (2016)[69,]	HCV/HIV	6/756	NR 97% (82% to 91%) 64% (45% to 79%)	6/756	NR 90% (74% to 91%) 87% (80% to 92%)
Pavlov et al(2015)[70,]	ALD	7/338	NR 94% (86% to 97%) 89% (76% to 95%)	7/330	NR 95% (87% to 98%) 71% (56% to 82%)
Poynard et al(2011)[56,]	HBV	4/NR	0.84 (0.78 to 0.89) NR NR	NR	0.93 (0.87 to 0.99) NR NR
Shaheen et al(2007)[57,]	HCV	4/NR	0.84 (0.78 to 0.89) NR NR	NR	0.93 (0.87 to 0.99) NR NR
Shi et al(2014)[58,]	No summary statistics reported. Concluded that transient elastography controlled attenuation parameter has good sensitivity and specificity for diagnosing steatosis, but it has limited utility.				
Steadman et al(2013)[59,]	Multiple diseases	45/NR	0.88 (0.84 to 0.90) 80% (76% to 83%) 81% (77% to 85%)	49/NR	0.94 (0.91 to 0.96) 86% (82% to 89%) 89% (87% to 91%)
	HBV	5/710	0.81 (0.78 to 0.84) 77% (68% to 84%) 72% (55% to 85%)	8/1092	0.86 (0.82 to 0.89) 67% (57% to 75%) 87% (83% to 91%)
	HCV	13/2732	0.89 (0.86 to 0.91) 76% (61% to 86%) 86% (77% to 92%)	12/2887	0.94 (0.92 to 0.96) 85% (77% to 91%) 91% (87% to 93%)
	NAFLD	5/630	0.78 (0.74 to 0.82) 77% (70% to 83%)	4/469	0.96 (0.94 to 0.97) 92% (77% to 98%) 95% (88% to 98%)

		Significant Fibrosis (ie, Metavir Stages F2 to F4)		Cirrhosis (ie, Metavir Stage F4)	
			75% (70% to 79%)		
Stebbing et al(2010)[60],	Multiple diseases	17/3066	NR 72% (71% to 72%) 82% (82% to 83%)	17/4052	NR 84% (84% to 85%) 95% (94% to 95%)
Talwalkar et al(2007)[61],	Multiple diseases	7/>1100	0.87 (0.83 to 0.91) 70% (67% to 73%) 84% (80% to 88%)	9/2083	0.96 (0.94 to 0.98) 87% (84% to 90%) 91% (89% to 92%)
Tsochatzis et al(2011)[62],	Multiple diseases	31/5919	NR 79% (74% to 82%) 78% (72% to 83%)	30/6530	NR 83% (79% to 86%) 89% (87% to 91%)
	HCV	14/NR	NR 78% (71% to 84%) 80% (71% to 86%)	11/NR	NR 83% (77% to 88%) 90% (87% to 93%)
	HBV	4/NR	NR 84% (67% to 93%) 78% (68% to 85%)	6/NR	NR 80% (61% to 91%) 86% (82% to 94%)
Tsochatzis et al(2014)[63],	HCV	37/NR	0.87 (0.83 to 0.90) 79% (74% to 84%) 83% (77% to 88%)	36/NR	0.96 (0.94 to 0.97) 89% (84% to 92%) 91% (89% to 93%)
	HBV	13/NR	0.83 (0.76 to 0.90) 71% (62% to 78%) 84% (74% to 91%)	13/NR	0.92 (0.89 to 0.96) 86% (79% to 91%) 85% (78% to 89%)
	NAFLD			4/NR	0.96 (0.94 to 0.99) 96% (83% to 99%) 89% (85% to 92%)

		Significant Fibrosis (ie, Metavir Stages F2 to F4)		Cirrhosis (ie, Metavir Stage F4)	
	ALD			6/NR	0.90 (0.87 to 0.94) 86% (76% to 92%) 83% (74% to 89%)
Xu et al(2015)[71,]	HBV	14/2318	0.82 (0.78 to 0.86) NR NR	18/2996	0.91 (0.89 to 0.93) NR NR
Xue-Ying (2020)[64,]	HBV	29/5035	0.83 (0.80 to 0.86) 72% (68% to 76%) 82% (77% to 86%)	NR/NR	NR NR NR

ALD: alcoholic liver disease; AUROC: area under the receiver operating characteristic curve; CI: confidence interval; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; NAFLD: nonalcoholic fatty liver disease; NR: not reported.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

There are currently no published studies that directly demonstrate the effect of TE (e.g., FibroScan) on patient outcomes.

FibroScan is used extensively in practice to make management decisions. In addition, FibroScan was used as an alternative to biopsy to diagnose fibrosis or cirrhosis to establish trial eligibility in several trials (ION-1,-3; VALENCE; ASTRAL-2, -3, -4) that confirmed the efficacy of HCV treatments.[31,32,33,34,35,36,] For example, in the VALENCE trial, cirrhosis could be defined by liver biopsy or a confirmatory FibroTest or FibroScan result at 12.5 kPa or greater. In VALENCE, FibroScan was used to determine cirrhosis in 74% of the participants. In a retrospective, multicenter analysis of 7256 chronic HCV patients by Abdel Alem et al (2019), both transient elastography and FIB-4 were found to be predictors of treatment failure to sofosbuvir-based treatment regimens with an NPV of 95%.[72,]

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Transient Elastography
For individuals who have chronic liver disease who receive TE (e.g., FibroScan), the evidence includes many systematic reviews of more than 50 observational studies (>10,000 patients). TE has been studied in populations with viral hepatitis, NAFLD/MASLD, and ALD. There are varying cutoffs for positivity. Failures of the test are not uncommon, particularly for those with high body mass index, but these failures often went undetected in analyses of the validation studies. Given these limitations and the imperfect reference standard, it can be difficult to interpret performance characteristics. However, for the purposes of deciding whether a patient has severe fibrosis or cirrhosis, the FibroScan results provide data sufficiently useful to determine therapy. In fact, FibroScan has been used as an alternative to biopsy to establish eligibility regarding the presence of fibrosis or cirrhosis in the participants of several RCTs. These trials showed the efficacy of HCV treatments, which in turn demonstrated that the test can identify patients who would benefit from therapy.

NONINVASIVE IMAGING: MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING

Clinical Context and Test Purpose
The purpose of noninvasive testing in individuals with CLD is to detect liver fibrosis so that individuals can avoid the potential adverse events of an invasive liver biopsy and receive appropriate treatment. The degree of liver fibrosis is an important factor in determining the appropriate approach for managing individuals with liver disease (eg, hepatitis, ALD, NAFLD/MASLD).

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with CLD.

Interventions
The test being considered is multiparametric MRI (e.g., LiverMultiScan).

Comparators
The following tests and practices are currently being used to diagnose chronic liver disease: liver biopsy, other noninvasive radiologic methods, and multianalyte serum assays.

Outcomes
The general outcomes of interest are test validity, morbid events, and treatment-related morbidity. Follow-up over months to years is of interest to the relevant outcomes.

Study Selection Criteria
For the evaluation of the clinical validity of the tests within this review, studies that meet the following eligibility criteria were considered:
- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard (describe the reference standard).
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
Azizi et al (2024) published a systematic review comparing the diagnostic accuracy of MRI proton density fat fraction with liver biopsy.[73,] Tables 7 and 8 summarize study characteristics and results, respectively. Authors concluded that MRI Proton Density Fat Fraction has high diagnostic accuracy, though its accuracy slightly declines as the severity of hepatic steatosis increases.

Table 6. Magnetic Resonance Imaging Systematic Review Characteristics

Study	Dates	Studies	N (Range)	Population	Index tests	Reference Standard
Azizi et al (2024)[73,]	Until January 2024	22	2844 (19 to 497)	Patients with MASLD and hepatic steatosis	MRI-PDFF	Histology

Abbreviations. MASLD: metabolic dysfunction-associated steatotic liver disease; MRI:magnetic resonance imaging; PDFF:proton density fat-fraction.

Table 7. Magnetic Resonance Imaging Systematic Review Results

Index Test	Steatosis		
Azizi et al (2024)[73,]	**AUC** **Sensitivity** **Specificity**		
	Grade ≥1	Grade ≥2	Grade 3
Total studies (n)	17 (2454)	16 (1726)	12 (1469)
Index Test Threshold	5.7	NR	NR
MRI-PDFF	0.97 0.93 0.93	0.91 0.79 0.90	0.91 0.76 0.89

Abbreviations: AUC:area under the curve; MRI:magnetic resonance imaging; NR: not reported; PDFF:proton density fat-fraction.

Tables 8 and 9 summarize studies that have evaluated the diagnostic accuracy of multiparametric MRI, which incorporates assessment of proton density fat-fraction, T_2*, and T_1 mapping to characterize liver fat, iron, fibrosis, and inflammation. Generally, technical failures were less common with MRI than transient elastography.[74,75,76,]

Table 8. Characteristics of Studies Assessing the Diagnostic Accuracy of Multiparametric Magnetic Resonance Imaging

Study	Population	Design	Index Test(s)	Reference Standard	Timing of Reference and Index Tests
Beyer et al (2021)[74,]	N=580 patients with suspected NAFLD/NASH	Retrospective evaluation of patients from 2 clinical trials	MRI PDFF (LMS-IDEAL)* CAP (FibroScan)	Liver biopsy	Not reported
Imajo et al (2021)[75,]	N=145 patients with suspected NASH	Prospective, observational	MRI liver fat* MRI cT_1 measurements* MRI cT_1 + PDFF* MRE VCTE-LSM (FibroScan) CAP (FibroScan) 2D-SWE	Liver biopsy	All performed at first clinical visit
McDonald et al (2018)[76,]	N=149 patients with known or suspected liver disease	Prospective, validation cohort	MRI cT_1* ELF test TE (FibroScan)	Liver biopsy	Liver biopsy performed within 2 weeks of noninvasive assessments

*Measurements obtained with LiverMultiscan protocol.
2D-SWE: 2-dimensional shear-wave elastography; CAP: controlled attenuation parameter; ELF: Enhanced Liver Fibrosis; LMS-IDEAL: LiverMultiScan-Iterative Decomposition of water and fat with Echo Asymmetry and Least-squares estimation; MRE: magnetic resonance elastography; MRI: magnetic resonance imaging; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; PDFF: proton density fat-fraction; TE: transient elastography; VCTE-LSM: vibration-controlled transient elastography-liver stiffness measure.

Table 9. Results of Studies Assessing the Diagnostic Accuracy of Multiparametric Magnetic Resonance Imaging

		Significant Fibrosis			Steatosis				Advanced NASH (NAS ≥4 and ≥F2)	
Study	Population	Test	AUROC (95% CI) Sensitivity Specificity		Test	AUROC (95% CI) Sensitivity Specificity			Test	AUROC (95% CI) Sensitivity Specificity
						Grade ≥1	Grade ≥2	Grade ≥3		
Beyer et al (2021)[74,]	Suspected NAFLD/NASH	-	-		MRI PDFF (LMS-IDEAL)*	1.0 (0.99 to 1.00)	0.77 (0.73 to 0.82)	0.81 (0.76 to 0.87)	-	-

		Significant Fibrosis			**Steatosis**				**Advanced NASH (NAS ≥4 and ≥F2)**	
						99% 100%	72% 72%	68% 81%		
		-	-		CAP (FibroScan)	0.95 (0.91 to 0.99) 89% 100%	0.60 (0.55 to 0.65) 78% 41%	0.63 (0.57 to 0.70) 61% 59%	-	-
			Stage ≥2							
Imajo et al (2021)[75,]	Suspected NASH	MRE	0.92 (0.87 to 0.97) NR NR		MRI liver fat*	0.92 (0.87 to 0.98) NR NR	0.86 (0.80 to 0.93) NR NR	-	MRI cT_1*	0.74 (0.66 to 0.82) NR NR
		VCTE-LSM	0.88 (0.81 to 0.95) NR NR		CAP (FibroScan)	0.75 (0.58 to 0.92) NR NR	0.68 (0.59 to 0.78) NR NR	-	MRI liver fat*	0.71 (0.63 to 0.80) NR NR
		2D-SWE	0.87 (0.76 to 0.99) NR NR						MRE	0.66 (0.57 to 0.75) NR NR
		MRI cT_1*	0.62 (0.49 to 0.74) NR NR						VCTE-LSM	0.64 (0.54 to 0.74) NR NR
			Stage ≥3	Stage ≥5						
McDonald et al (2018)[76,]	Known or suspected liver disease (unselected)	MRI cT_1*	0.72 (0.63 to 0.80) 88% 51%	0.72 (0.64 to 0.81) 71% 64%						

		Significant Fibrosis			**Steatosis**				**Advanced NASH (NAS ≥4 and ≥F2)**	
		ELF test	0.70 (0.61 to 0.78) 49% 77%	0.68 (0.57 to 0.79) 19% 91%						
		TE	0.84 (0.76 to 0.91) NR NR	0.86 (0.79 to 0.93) NR NR						

*Measurements obtained with LiverMultiscan protocol.
2D-SWE: 2-dimensional shear-wave elastography; AUROC: area under the receiver operating characteristic curve; CAP: controlled attenuation parameter; CI: confidence interval; ELF: Enhanced Liver Fibrosis; LMS-IDEAL: LiverMultiScan-Iterative Decomposition of water and fat with Echo Asymmetry and Least-squares estimation; MRE: magnetic resonance elastography; MRI: magnetic resonance imaging; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; NR: not reported; PDFF: proton density fat-fraction; TE: transient elastography; VCTE-LSM: vibration-controlled transient elastography-liver stiffness measure.

Jayaswal et al (2020) compared the prognostic value of MRI cT1 measurements, transient elastography, and multianalyte serum assays in a cohort of 197 patients with compensated chronic liver disease.[77,] Patients who were referred for a clinically indicated liver biopsy, or with a known diagnosis of liver cirrhosis, were eligible. At baseline, patients underwent multiparametric MRI scans, transient elastography, and blood tests. Additionally, all patients received a liver biopsy and had their fibrosis rated on the Ishak scale; results of the biopsies informed clinical care. The most common underlying disease states were NAFLD (n=85, 43%), viral hepatitis (n=50, 25%), and ALD (n=22, 11%). The primary endpoint was a composite of ascites, variceal bleeding, hepatic encephalopathy, hepatocellular carcinoma, liver transplantation and mortality. Binary cutoff values were predefined. Patients were followed for a median of 43 months. Over this period, 14 new clinical events were recorded, including 11 deaths. The prognostic value of the noninvasive testing is summarized in Table 10. Technical failures were also reported (eg, poor quality scan); reliable measurements were obtained in 182 of 197 (92%) patients for multiparametric MRI and in 121 of 160 (76%) patients for transient elastography (transient elastography was additionally not attempted in 37 patients). The study was limited by having variable follow-up periods and the effect of patients being censored at different time points was not taken into account, so sensitivities, specificities, PPVs, and NPVs should be interpreted cautiously. The CI for the survival analysis was wide likely due to the relatively small number of new clinical events observed.

Table 10. Survival Analysis and Performance in Identifying Development of a New Clinical Event[a]

Test, Binary Cutoff	Cox Regression Analysis, HR (95% CI)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Liver cT_1 >825 ms	9.91 (1.287 to 76.24)	92.3	47.3	11.9	98.8
Transient elastography >8 kPa	7.79 (0.974 to 62.3)	88.9	51.8	12.9	98.3
FIB-4 >1.45	4.11 (0.91 to 18.56)	84.6	47.7	10.9	97.6
APRI >1	2.645 (0.886 to 7.9)	46.2	79.2	14.3	95.1
AST/ALT >1	6.093 (1.673 to 22.19)	76.9	65.6	14.3	97.4
Ishak >F4 (liver biopsy)	12.64 (2.8 to 57.08)	84.6	73.9	20.4	98.4

[a]Composite of ascites, variceal bleeding, hepatic encephalopathy, HCC, liver transplantation, and mortality
ALT: alanine aminotransferase; APRI: AST-to-platelet ratio; AST: aspartate aminotransferase; CI: confidence interval; FIB-4: fibrosis-4 index; HR: hazard ratio; kPa: kilopascal.

Pavlides et al (2016) evaluated whether data obtained from multiparametric MRI was predictive of all-cause mortality and liver-related clinical events.[78,] Patients who were referred for a clinically indicated liver biopsy, or with a diagnosis of liver cirrhosis on MRI scan, were eligible. Liver-related clinical events were defined as liver-related death, hepatocellular carcinoma, and new hepatic decompensation (ie, clinically evident ascites, variceal bleeding, and hepatic encephalopathy). Patients received multiparametric MRI and liver cT_1 values were mapped into a Liver Inflammation and Fibrosis (LIF) score. One hundred twenty three patients were recruited to the study; 6 were excluded due to claustrophobia or incomplete MRI data. Of the 117 patients who had complete MRI data, follow-up data were available for 112; the study reported outcomes on these 112 patients. The most common underlying disease states were NAFLD (35%), viral hepatitis (30%), and ALD (10%). Over a median follow-up time of 27 months, 10 patients had a liver-related clinical event and 6 patients died. No patients who had a LIF <2 (no or mild liver disease) developed a clinical event. Ten of 56 (18%) patients with a LIF ≥2 (moderate or severe liver disease) experienced a clinical event. A study limitation is the use of LIF scores, which are no longer used in clinical practice. The authors further described the study as a small proof of principle study.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs. The primary benefit of multiparametric MRI for chronic liver disease is the ability to avoid liver biopsy in patients without significant fibrosis. There are currently no such published studies to demonstrate the effect on patient outcomes.

Multiparametric MRI has been used as an alternative to biopsy for measuring fibrosis or cirrhosis in clinical trials. Phase 2 clinical trials have used multiparametric MRI to measure therapeutic efficacy of an investigational treatments for NASH[79,] and NAFLD.[80,]

The utility of multiparametric MRI to provide clinically useful information on the presence and extent of liver fibrosis and inflammation has been evaluated in smaller prospective studies. Specifically, it has been evaluated in the setting of biochemical remission in liver diseases where noninvasive testing for continued disease activity could further aid in direct management of patients as a prognostic marker of future liver-related complications. Quantitative multiparametric MRI has been used to measure disease burden after treatment in patients with chronic HCV[81,] and autoimmune hepatitis.[82,83,84,85,]

Currently, there is not evidence that demonstrates that the use of the test for response to therapy impacts decision making and that these changes in management decisions lead to improved outcomes.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Multiparametric Magnetic Resonance Imaging
For individuals who have chronic liver disease who receive multiparametric MRI, the evidence includes several prospective and retrospective observational studies. Multiparametric MRI (eg, LiverMultiScan) has been studied in mixed populations, including NAFLD/MASLD, viral hepatitis, and ALD. Quantitative MRI provides various measures assessing both liver fat content and fibrosis and inflammation. Various cutoffs have been utilized for positivity. Generally, multiparametric MRI performed similarly to transient elastography, and fewer technical failures of multiparametric MRI were reported. Given these limitations and the imperfect reference standard, it can be difficult to interpret performance characteristics. The prognostic ability of quantitative MRI to predict liver-related clinical events has been evaluated in 2 studies; both reported positive correlations with wide CIs. Larger cohorts with a longer follow-up time would be useful to further derive the prognostic ability. Additionally, multiparametric MRI has been used to measure the presence of fibrosis or cirrhosis in the patients who have achieved biochemical remission after treatment in small prospective studies.

OTHER NONINVASIVE IMAGING

Clinical Context and Test Purpose
The purpose of noninvasive testing in individuals with CLD is to detect liver fibrosis so that individuals can avoid the potential adverse events of an invasive liver biopsy and receive

appropriate treatment. The degree of liver fibrosis is an important factor in determining the appropriate approach for managing individuals with liver disease (e.g., hepatitis, ALD, NAFLD/MASLD).

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with chronic liver disease.

Interventions
The tests being considered are other noninvasive imaging, including MRE, ARFI , and RTE (see Table 3).

Comparators
The following tests and practices are currently being used to diagnose chronic liver disease: liver biopsy, other noninvasive radiologic methods, and multianalyte serum assays.

Outcomes
The general outcomes of interest are test validity, morbid events, and treatment-related morbidity. Follow-up over months to years is of interest to the relevant outcomes.

Study Selection Criteria
For the evaluation of the clinical validity of the tests within this review, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard (describe the reference standard).
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

ACOUSTIC RADIATION FORCE IMPULSE IMAGING

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

REVIEW OF EVIDENCE

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)
Duarte-Rojo et al (2025) conducted a systematic review to assess the evidence on the accuracy of transient elastography (TE), shear wave elastography (ARFI imaging), and magnetic resonance elastography to stage liver fibrosis.[49,] This review was undertaken to support the AASLD guidelines on noninvasive imaging technologies for staging liver fibrosis in CLD. A comprehensive search was performed for studies (published through April 2022) assessing these methods for the identification of significant fibrosis (F2-4), advanced fibrosis (F3-4), or cirrhosis (F4), using histopathology as the standard of reference by liver disease etiology in adults or children. Two-hundred and forty (240) studies (N=61,193 patients) were included in

this systematic review. Regarding pSWE (see Table 3), 8 studies reported its accuracy to stage fibrosis in NAFLD. For significant fibrosis (F2-4), a pSWE-LSM cutoff value of 1.2 m/s showed a sensitivity of 85%–90% and a specificity of 36%–90%, whereas for advanced fibrosis (F3-4), the 1.5 m/s threshold had a sensitivity of 70% and a specificity of 92%. To detect cirrhosis (F4), pSWE-LSM at a cutoff of 2 m/s had a sensitivity of 75%–90% and a specificity of 67%–90%. Regarding 2D-SWE, 11 studies reported its accuracy to stage fibrosis in NAFLD. For significant fibrosis (F2-4), using a 2D-SWE-LSM cutoff value of 7.4 kPa, the sensitivity was 85% and the specificity was 79%, whereas for advanced fibrosis (F3-4), the 8.4 kPa threshold had a sensitivity of 90% and a specificity of 79%. To detect cirrhosis (F4), 2D-SWE-LSM at a cutoff value of 10 kPa had a sensitivity of 83%–92% and a specificity of 76%–90%.

Mixed Etiologies

Tables 11 and 12 summarize the characteristics and results of systematic reviews that have assessed the diagnostic accuracy of ARFI imaging.

Table 11. Characteristics of Systematic Reviews Assessing Acoustic Radiation Force Impulse Imaging

Study	Dates	Studies	N	Population
Bota et al (2013)[51,]	To May 2012	6	518	Chronic hepatitis
Crossan et al (2015)[20,]	1998 to Apr 2012	4	NR	HCV
Guo et al (2015)[86,]	To Jun 2013	15	2128	Multiple diseases
Hu et al (2017)[87,]	To Jul 2014	7	723	NAFLD
Lin et al (2020)[88,]	To Apr 2019	29	NR	Non-viral liver disease
Jiang et al (2018)[67,]	To Dec 2017	9	982	NAFLD
Liu et al (2015)[89,]	To Apr 2016	23	2691	Chronic HBV or HCV
Nierhoff et al (2013)[90,]	2007 to Feb 2012	36	3951	Multiple diseases

HBV: hepatitis B virus; HCV: hepatitis C virus; NAFLD: nonalcoholic fatty liver disease; NR: not reported.

Table 12. Results of Systematic Reviews Assessing the Diagnostic Accuracy of Acoustic Radiation Force Impulse Imaging

		Significant Fibrosis(ie, Metavir Stages F2 to F4)		Cirrhosis (ie, Metavir Stage F4)	
Study	**Population**	**Studies/ Sample Size**	**AUROC (95% CI) Sensitivity (95% CI) Specificity (95% CI)**	**Studies/ Sample Size**	**AUROC (95% CI) Sensitivity (95% CI) Specificity (95% CI)**
Bota et al (2013)[51,]	Chronic hepatitis	6/518	0.88 (0.83 to 0.93) NR NR		0.92 (0.87 to 0.98) NR NR
Crossan et al (2015)[20,]	HCV	4/NR	NR 85% (69% to 94%) 89% (72% to 97%)		

		Significant Fibrosis(ie, Metavir Stages F2 to F4)		Cirrhosis (ie, Metavir Stage F4)	
Guo et al (2015)[86,]	Multiple diseases	13/NR	NR 76% (73% to 78%) 80% (77% to 83%)	14/NR	NR 88% (84% to 91%) 80% (81% to 84%)
Hu et al (2017)[87,]	HBV, HCV	15/NR	88% (85% to 91%) 75% (69% to 78%) 85% (81% to 89%)		
Jiang et al (2018)[67,]	NAFLD	6/NR	0.86 (0.83 to 0.89) 70% (59% to 79%) 84% (79% to 88%)	7/NR	0.95 (0.93 to 0.97) 89% (60% to 98%) 91% (82% to 95%)
Liu et al (2015)[89,]	NAFLD	7/723	NR 80% (76% to 84%) 85% (81% to 89%)		
Lin et al (2020)[88,]	Non-viral liver disease	23/NR	0.87 (0.83 to 0.89) 79% (73% to 83%) 81% (75% to 86%)	14/NR	0.94 (0.92 to 0.96) 89% (79% to 95%) 89% (85% to 92%)
Nierhoff et al (2013)[90,]	Multiple diseases	26/NR	0.83 (0.80 to 0.86) NR NR	27/NR	0.91 (0.89 to 0.93) NR NR

AUROC: area under the receiver operating characteristic curve; CI: confidence interval; HBV: hepatitis B virus; HCV: hepatitis C virus; NAFLD: nonalcoholic fatty liver disease; NR: not reported.

The previously introduced 5-year observational study by Kluppel et al (2023) compared the prognostic value of ARFI elastography, the FIB-4 score, and liver biopsy.[91,] AFRI was significantly better than FIB-4 at predicting liver-related death within 5 years (p=.02), but it did not differ significantly from biopsy (p=.83). For predicting liver decompensation or variceal bleeding, AFRI outperformed both biopsy (p=.02) and FIB-4 (p=.003). However, there was no significant difference between AFRI and biopsy (p=.33) or FIB-4 (p=.14) in predicting hepatocellular carcinoma.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

There are currently no published studies that directly demonstrate the effect of ARFI imaging on patient outcomes.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of ARFI imaging has not been established, a chain of evidence supporting the clinical utility of this test for this population cannot be constructed.

MAGNETIC RESONANCE ELASTOGRAPHY

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

REVIEW OF EVIDENCE

Metabolic Dysfunction-Associated Steatotic Liver Disease
Duarte-Rojo et al (2025) conducted a systematic review to assess the evidence on the accuracy of transient elastography (TE), shear wave elastography (ARFI imaging), and magnetic resonance elastography to stage liver fibrosis.[49,] This review was undertaken to support the AASLD guidelines on noninvasive imaging technologies for staging liver fibrosis in CLD. A comprehensive search was performed for studies (published through April 2022) assessing these methods for the identification of significant fibrosis (F2-4), advanced fibrosis (F3-4), or cirrhosis (F4), using histopathology as the standard of reference by liver disease etiology in adults or children. Two-hundred and forty (240) studies (N=61,193 patients) were included in this systematic review.

Twelve studies reported MRE accuracy to stage fibrosis in NAFLD. For significant fibrosis (F2-4), an MRE-LSM cutoff value of 3.4 kPa yielded a sensitivity of 78% and a specificity of 90%, whereas for advanced fibrosis (F3-4), with a cutoff of 3.7 kPa, the sensitivity was 82%–93% and the specificity was 90%–95%. To detect cirrhosis (F4), an MRE-LSM cutoff value of 6.7 kPa had a sensitivity of 91% and a specificity of 95%.

Mixed Etiologies
Tables 13 and 14 summarize the characteristics and results of systematic reviews that have assessed the diagnostic accuracy of MRE. MRE has been studied primarily in hepatitis and NAFLD.

Table 13. Characteristics of Systematic Reviews Assessing Magnetic Resonance Elastography

Study	Dates	Studies	N	Population
Crossan et al (2015)[20,]	1998 to Apr 2012	3	NR	CLD
Guo et al (2015)[86,]	To Jun 2013	11	982	Multiple diseases
Singh et al (2015)[92,]	2003 to Sep 2013	12	697	Chronic hepatitis
Singh et al (2016)[93,]	To Oct 2014	9	232	NAFLD
Xiao et al (2017)[94,]	To 2016	5	628	NAFLD

CLD: Chronic liver disease; NAFLD: nonalcoholic fatty liver disease; NR: not reported.

Table 14. Results of Systematic Reviews Assessing the Diagnostic Accuracy of Magnetic Resonance Elastography

		Significant Fibrosis (ie, Stages F2 to F4)		Cirrhosis (ie, Stage F4)	
Study	**Population**	**Studies/ Sample Size**	**AUROC (95% CI) Sensitivity (95% CI) Specificity (95% CI)**	**Studies/ Sample Size**	**AUROC (95% CI) Sensitivity (95% CI) Specificity (95% CI)**
Crossan et al (2015)[20,]	CLD	3/NR	NR 94% (13% to 100%) 92% (72% to 98%)		
Guo et al (2015)[86,]	Multiple diseases	9/NR	NR 87% (84% to 90%) 94% (91% to 97%)		NR 93% (88% to 96%) 91% (88% to 93%)
Singh et al (2015)[92,]	Chronic hepatitis	12/697	0.84 (0.76 to 0.92) 73% (NR) 79% (NR)	12/697	0.92 (0.90 to 0.94) 91% (NR) 81% (NR)
Singh et al (2016)[93,]	NAFLD	9/232	0.87 (0.82 to 0.93) 79% (76% to 90%) 81% (72% to 91%)	9/232	0.91 (0.76 to 0.95) 88% (82% to 100%) 87% (77% to 97%)
Xiao et al (2017)[94,]	NAFLD	3/384	0.88 (0.83 to 0.92) 73.2% (65.7% to 87.3%) 90.7% (85.0% to 95.7%)	3/384	0.92 (0.80 to 1.00) 86.6% (80.0% to 90.9%) 93.4% (91.4% to 94.5%)

CLD: Chronic liver disease; AUROC: area under the receiver operating characteristic curve; CI: confidence interval; NAFLD: nonalcoholic fatty liver disease; NR: not reported.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

There are currently no published studies that directly demonstrate the effect of MRE on patient outcomes.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of MRE has not been established, a chain of evidence supporting the clinical utility of this test for this population cannot be constructed.

REAL-TIME TISSUE ELASTOGRAPHY

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
Kobayashi et al (2015) published the results of a meta-analysis assessing RTE for staging liver fibrosis.[95,] The authors selected 15 studies (N=1626) published through December 2013, including patients with multiple liver diseases and healthy adults. A bivariate random-effects model was used to estimate summary sensitivity and specificity. The summary AUROC, sensitivity, and specificity were 0.69 , 79% (95% CI, 75% to 83%), and 76% (95% CI, 68% to 82%) for detection of significant fibrosis (stage ≥F2), and 0.72 , 74% (95% CI, 63% to 82%), and 84% (95% CI, 79% to 88%) for detection of cirrhosis, respectively. Reviewers found evidence of heterogeneity due to differences in study populations, scoring methods, and cutoffs for positivity. They also found evidence of publication bias based on funnel plot asymmetry.

Hong et al (2014) reported on the results of a meta-analysis evaluating RTE for staging fibrosis in multiple diseases.[96,] Thirteen studies (N=1,347) published between April 2000 and April 2014 that used a liver biopsy or transient elastography as the reference standard were included. Different quantitative methods were used to measure liver stiffness in the included studies: Liver Fibrosis Index (LFI), Elasticity Index, elastic ratio 1 (ER1), and elastic ratio 2. For predicting significant fibrosis (stage ≥F2), the pooled sensitivities for LFI and ER1 were 78% (95% CI, 70% to 84%) and 86% (95% CI, 80% to 90%), respectively. The specificities were 63% (95% CI, 46% to 78%) and 89% (95% CI, 83% to 94%) and the AUROCs were 0.79 (95% CI, 0.75 to 0.82) and 0.94 (95% CI, 0.92 to 0.96), respectively. For predicting cirrhosis (stage F4), the pooled sensitivities of LFI, ER1, and elastic ratio 2 were 79% (95% CI, 61% to 91%), 96% (95% CI, 87% to 99%), and 79% (95% CI, 61% to 91%), respectively. The specificities were 88% (95% CI, 81% to 93%) for LFI, 89% (95% CI, 83% to 93%) for ER1, and 88% (95% CI, 81% to 93%) for elastic ratio 2, and the AUROCs were 0.85 (95% CI, 0.81 to 0.87), 0.93 (95% CI, 0.94 to 0.98), and 0.92 (95% CI, not reported), respectively. Pooled estimates for Elasticity Index were not performed due to insufficient data.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

There are currently no published studies that directly demonstrate the effect of RTE on patient outcomes.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of RTE has not been established, a chain of evidence supporting the clinical utility of this test for this population cannot be constructed.

Section Summary: Noninvasive Radiological Methods Other Than Transient Elastography

The use of ARFI imaging has been evaluated in viral hepatitis and NAFLD. ARFI imaging has potential advantages over FibroScan. ARFI can be implemented on a standard ultrasound machine, may be more applicable for assessing complications such as ascites, and may be more applicable in obese patients. ARFI imaging appears to have similar diagnostic accuracy to FibroScan, but there are fewer data available on performance characteristics. Validation studies have used varying cutoffs for positivity.

Magnetic resonance elastography (MRE) has a high success rate and is highly reproducible. The diagnostic accuracy also appears to be high. In particular, MRE has high diagnostic accuracy for the detection of fibrosis in NAFLD, independent of BMI and degree of inflammation. However, further validation is needed to determine standard cutoffs and confirm performance characteristics because CI for estimates are wide. MRE is also not widely available. RTE has been evaluated in multiple diseases with varying scoring methods and cutoffs. Although data are limited, the accuracy of RTE appears to be similar to FibroScan for the evaluation of significant liver fibrosis, but less accurate for the evaluation of cirrhosis. There was evidence of publication bias in the systematic review and the diagnostic accuracy may be overestimated.

A systematic review conducted to inform the AASLD Practice Guidelines (2024) reported that liver-stiffness measurement from shear wave elastography/ARFI and MRE (in addition to TE) shows acceptable to outstanding accuracy for the detection of liver fibrosis across various liver disease etiologies. Accuracy increased from F2-4 to F3-4 and was the highest for F4. Given these limitations and the imperfect reference standard, it is difficult to interpret performance characteristics. There is no direct evidence that other noninvasive radiologic methods improve health outcomes; further, it is not possible to construct a chain of evidence for clinical utility due to the lack of sufficient evidence on clinical validity.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) FORMERLY NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

American Gastroenterological Association et al
In 2018, the practice guidelines on the diagnosis and management of nonalcoholic fatty liver disease (NAFLD), developed by the American Gastroenterological Association (AGA), the American Association for the Study of Liver Diseases (AASLD), and the American College of Gastroenterology, stated that "NFS [NAFLD fibrosis score] or FIB-4 [Fibrosis-4] index are clinically useful tools for identifying NAFLD patients with a higher likelihood of having bridging fibrosis (stage 3) or cirrhosis (stage 4)."[97,] This guideline also cited vibration-controlled transient elastography (VCTE) and magnetic resonance elastography (MRE) as "clinically useful tools for identifying advanced fibrosis in patients with NAFLD."

A 2022 consensus-based clinical care pathway was published by the AGA on risk stratification and management of NAFLD, including some recommendations regarding the use of non-invasive testing for individuals with chronic liver disease[98,] Among individuals with increased risk of NAFLD or nonalcoholic steatohepatitis (NASH)-related fibrosis (i.e., individuals with type-2 diabetes, ≥2 metabolic risk factors, or an incidental finding of hepatic steatosis or elevated aminotransferases), assessment with a nonproprietary fibrosis scoring system such as FIB-4 is recommended, although aspartate transaminase to platelet ratio index can be used in lieu of FIB-4 scoring. Depending on the fibrosis score, imaging-based testing for liver stiffness may be warranted with transient elastography (FibroScan), although bidimensional shear wave elastography or point shear wave elastography are also imaging options included in the clinical care pathway.

In 2023, the AGA published an expert review on the role of noninvasive tests [NITs] in the evaluation and management of NAFLD.[99,] The following practice advice statements were made.

- "A Fibrosis 4 Index score [FIB-4] <1.3 is associated with strong negative predictive value for advanced hepatic fibrosis and may be useful for exclusion of advanced hepatic fibrosis in patients with NAFLD
- A combination of 2 or more NITs combining serum biomarkers and/or imaging-based biomarkers is preferred for staging and risk stratification of patients with NAFLD whose Fibrosis 4 Index score [FIB-4] is >1.3
- Use of NITs in accordance with manufacturer's specifications can minimize risk of discordant results and adverse events
- NITs should be interpreted with context and consideration of pertinent clinical data...to optimize positive predictive value in the identification of patients with advanced fibrosis
- Liver biopsy should be considered for patients with NIT results that are indeterminate or discordant; conflict with other clinical, laboratory, or radiologic findings; or when alternative etiologies for liver disease are suspected

- Serial longitudinal monitoring using NITs for assessment of disease progression or regression may inform clinical management
- Patients with NAFLD and NITs results suggestive of advanced fibrosis or cirrhosis should be considered for surveillance of liver complications...Patients with NAFLD and NITs suggestive of advanced hepatic fibrosis should be monitored with serial liver stiffness measurement; vibration controlled transient elastography; or magnetic resonance elastography, given its correlation with clinically significant portal hypertension and clinical decompensation."

American Association for the Study of Liver Diseases (AASLD)
A 2023 updated practice guidance focused on the clinical assessment and management NAFLD and hepatic steatosis issued by the AASLD included the following guidance statements on the use of noninvasive techniques for diagnosis and management of NAFLD and hepatic steatosis.[7,]

- All patients with hepatic steatosis or clinically suspected NAFLD based on the presence of obesity and metabolic risk factors should undergo primary risk assessment with FIB-4
- In patients with pre-DM [diabetes mellitus], T2DM, or 2 or more metabolic risk factors (or imaging evidence of hepatic steatosis), primary risk assessment with FIB-4 should be repeated every 1–2 years
- Although standard ultrasound can detect hepatic steatosis, it is not recommended as a tool to identify hepatic steatosis due to low sensitivity across the NAFLD spectrum
- CAP [controlled attenuation parameter] as a point-of-care technique may be used to identify steatosis. MRI-PDFF [proton density fat fraction] can additionally quantify steatosis
- If FIB-4 is ≥ 1.3, VCTE, MRE, or ELF [Enhanced Liver Fibrosis] may be used to exclude advanced fibrosis
- Improvement in ALT or reduction in liver fat content by imaging in response to an intervention can be used as a surrogate for histological improvement in disease activity

The 2023 guidance recommend that patients with hepatic steatosis or NAFLD/MASLD based on the presence of obesity and metabolic risk factors should undergo primary risk assessment with FIB-4 index as this is considered the most valid noninvasive test.[7,] Patients with FIb-4 scores less than 1.3 are unlikely to have advanced fibrosis. High-risk individuals, such as those with type 2 diabetes, medically complicated obesity, family history of cirrhosis, or more than mild alcohol consumption, should be screened for advanced fibrosis. VCTE or ultrasound-based methods such as ARFI are favored over MRE, as initial secondary assessments due to cost considerations. The ELF test is approved for prognostication when advanced fibrosis is suspected, although it can be ordered for secondary risk assessment, particularly because the availability of elastography may be limited in some settings.

A 2024 publication from the AASLD describes the impact of new nomenclature on the AASLD practice guidance on NAFLD and hepatic steatosis described above.[2,] Briefly, available data suggest a near complete overlap (99%) between the metabolic dysfunction-associated steatotic liver disease (MASLD)-defined population and the historical NAFLD-defined population. Therefore, all recommendations on the clinical assessment and management of NAFLD AND NASH can be applied to patients with MASLD and metabolic-dysfunction associated steatohepatitis (MASH). Additionally, data from biomarker validation studies among patients

with NAFLD and NASH are applicable to patients with MASLD and MASH, respectively, until further guidance

A 2022 joint clinical practice guideline issued by the American Association of Clinical Endocrinology and AASLD included the following recommendations on the use of noninvasive techniques for diagnosis of NAFLD with clinically significant fibrosis (stage F2 to F4)[100,]:

- Clinicians should use liver fibrosis prediction calculations to assess the risk of NAFLD with liver fibrosis. The preferred noninvasive initial test is the FIB-4 (Grade B, Level 2 evidence)
- High-risk individuals with indeterminate or high FIB-4 score for further workup with an transient elastography or enhanced liver fibrosis test, as available (Grade B, Level 2 evidence)
- Clinicians should prefer the use of transient elastography as best validated to identify advanced disease and predict liver-related outcomes. Alternative imaging approaches may be considered, including shear wave elastography (less well validated) and/or magnetic resonance elastography (most accurate but with a high cost and limited availability; best if ordered by liver specialist for selected cases) (Grade B, Level 2 evidence).

In 2024, the AASLD published 2 guidelines focused on blood-based and imaging-based noninvasive liver disease assessment (NILDA) of hepatic fibrosis and steatosis.[3,4,] Recommendations are provided in Table 15 and include guidance for individuals with various etiologies of chronic liver disease, including hepatocellular (hepatitis C virus [HCV], HCV/HIV, hepatitis B virus [HBV], HCV/HBV, HBV/HIV, NAFLD, alcohol-associated liver disease [ALD]) and cholestatic disorders (primary sclerosing cholangitis [PSC], primary biliary cholangitis [PBC]).

Table 15. AASLD Recommendations for Blood- and Imaging-based Noninvasive Liver Disease Assessment.[4,3,]

Blood-based
• In adult patients with chronic HBV and HCV undergoing fibrosis staging prior to antiviral therapy, AASLD recommends using simple blood-based NILDA such as APRI or FIB-4 as an initial test to detect significant (F2-4), advanced fibrosis (F3-4) or cirrhosis (F4) compared with no test (strong recommendation, moderate quality of evidence) • In adult patients with NAFLD undergoing fibrosis staging, AASLD recommends using simple blood-based NILDA tests such as FIB-4 to detect advanced fibrosis (F3-4) compared to no test (strong recommendation, moderate quality of evidence) • In adult patients with ALD or chronic cholestatic liver disease undergoing fibrosis staging, there is insufficient evidence to recommend using blood-based NILDA for staging • In patients with chronic HCV who require fibrosis staging, AASLD recommends using simple, less costly, and readily available blood-based NILDA such as FIB-4 over complex proprietary tests (strong recommendation, moderate quality of evidence) • In patients with NAFLD who require fibrosis staging, AASLD recommends the use of simple, less costly, and readily available blood-based NILDA tests such as FIB-4 or NAFLD fibrosis score over complex proprietary tests for the detection of advanced fibrosis (F3-4; strong recommendation, moderate quality of evidence)

- In patients with chronic untreated HCV, AASLD suggests a sequential combination of blood-based markers may perform better than a single biomarker for F2-4 or F4 (ungraded statement)
- In patients with NAFLD, AASLD suggests the sequential combination of blood-based NILDA may be considered for diagnosis of advanced fibrosis (F3-4) over using a single test alone (ungraded statement)
- AASLD suggests against the use of blood-based NILDA tests to follow progression, stability, or regression in histologic stage (as determined by biopsy) in chronic liver disease (ungraded statement).

Imaging-based

- In adults with chronic HCV, chronic HBV, and NAFLD, AASLD recommends using imaging-based NILDA tests to detect significant fibrosis (F2-4), advanced fibrosis (F3-4), and cirrhosis (F4) (strong recommendation, moderate quality of evidence)
- In adults with ALD or chronic cholestatic liver disease, AASLD suggests using imaging-based NILDA tests to detect advanced fibrosis (F3-4) and cirrhosis (F4) (conditional recommendation, low quality of evidence)
- In adults with CLD, AASLD recommends utilizing either US-based elastography methods or MRE to stage fibrosis. Depending on local availability and expertise, it is reasonable to perform MRE as an investigation when concomitant cross-sectional imaging is needed or for patients in whom the accuracy of US-based elastography might be compromised (ungraded statement)
- In adults with CLD, AASLD suggests imaging-based NILDA be incorporated into the initial fibrosis staging process because it is more accurate than blood-based NILDA (conditional recommendation, low quality of evidence)
- In adults with CLD undergoing initial fibrosis staging, AASLD suggests combining blood-based and imaging-based NILDA, particularly for the detection of significant fibrosis (F2-4) and advanced fibrosis (F3-4 (conditional recommendation, low quality of evidence)
- AASLD suggests against the use of imaging-based NILDA as a standalone test to assess regression or progression of liver fibrosis (ungraded statement)
- AASLD suggests interpreting a longitudinal decrease or increase in liver stiffness within an individualized clinical context that considers the effect of NILDA modifiers and other supportive evidence of improving or worsening clinical course (ungraded statement)
- In patients with treated HBV and HCV, AASLD suggests using the LSM obtained prior to the start of antiviral therapy as the most accurate longitudinal NILDA parameter for the effect of prognostication, given the limited amount of evidence associating LSM with clinical outcomes once viral suppression or eradication is achieved (ungraded statement)
- In adults, TE-CAP has good diagnostic accuracy to grade steatosis and can be used in clinical practice (ungraded statement)
- In adults, imaging-based NILDA, specifically TE-CAP and MRI-PDFF or MRS, are superior to blood-based NILDA tests and should be used in the assessment of hepatic steatosis where available (ungraded statement)
- In the pediatric population, there is insufficient evidence to recommend a single imaging-based NILDA over another to assess liver fibrosis or steatosis (ungraded statement)
- Recognizing that liver histology is an imperfect reference standard, prior to considering a liver biopsy to assess fibrosis staging in patients with CLD, AASLD recommends using blood and imaging-based NILDA as the initial tests to detect significant (F2-4) to advanced fibrosis (F3-4) and cirrhosis (F4) (ungraded statement)

Abbreviations: AASLD:American Association for the Study of Liver Diseases; ALD:alcohol-associated liver disease; APRI:acoustic radiation force impulse; CLD:chronic liver disease; FIB-4: Fibrosis-4 Index; HBV:hepatitis C virus; HCV:hepatitis C virus; LSM:liver stiffness measurement; MRE:magnetic resonance elastography; MRI-PDFF: magnetic resonance imagine proton density fat fraction; MRS: magnetic resonance spectroscopy; NILDA: noninvasive liver disease assessment; TE-CAP: US: ultrasound;

National Institute for Health and Care Excellence
In 2016, the NICE published guidance on the assessment and management of NAFLD.[101,] The guidance did not reference elastography. The guidance recommended the enhanced liver fibrosis test to test for advanced liver fibrosis, utilizing a cutoff enhanced liver fibrosis score of 10.51.

HEPATITIS B AND C VIRUSES

American Association for the Study of Liver Diseases
In 2024, the AASLD published 2 guidelines focused on blood-based and imaging-based NILDA of hepatic fibrosis and steatosis.[3,4,] Recommendations regarding the use of these noninvasive assessments for patients with HBV and HCV are found in Table 16.

American Association for the Study of Liver Diseases and Infectious Diseases Society of America
In 2020, the American Association for the Study of Liver Diseases and Infectious Diseases Society of America guidelines for testing, managing, and treating hepatitis C virus (HCV) recommended that, for counseling and pretreatment assessment purposes, the following should be completed:

"Evaluation for advanced fibrosis using noninvasive markers and/or elastography, and rarely liver biopsy, is recommended for all persons with HCV infection to facilitate decision making regarding HCV treatment strategy and determine the need for initiating additional measures for the management of cirrhosis (eg, hepatocellular carcinoma screening) Rating: Class I, Level A [evidence and/or general agreement; data derived from multiple randomized trials, or meta-analyses]"[102,]

The guidelines noted that there are several NITs to stage the degree of fibrosis in patients with HCV. Tests included indirect serum biomarkers, direct serum biomarkers, and VCTE. The guidelines asserted that no single method is recognized to have high accuracy alone and careful interpretation of these tests is required.

A 2023 update of this guideline includes noninvasive liver markers such as HCV FibroSure, FIB-4, and FibroScan in their simplified treatment algorithm for HCV.[103,] Specific recommendations for a preferred noninvasive testing strategy are not provided.

National Institute for Health and Care Excellence
In 2017, the NICE published updated guidance on the management and treatment of patients with hepatitis B virus.[104,] The guidance recommends offering transient elastography as the initial test in adults diagnosed with chronic hepatitis B, to inform the antiviral treatment decision (Table 17).

Table 16. Antiviral Treatment Recommendations by Transient Elasticity Score

Transient Elasticity Score	Antiviral Treatment
>11 kPa	Offer antiviral treatment
6 to 10 kPa	Offer liver biopsy to confirm fibrosis level prior to offering antiviral treatment
<6 kPa plus abnormal ALT	Offer liver biopsy to confirm fibrosis level prior to offering antiviral treatment
<6 kPa plus normal ALT	Do not offer antiviral treatment

ALT: alanine aminotransferase; kPa: kilopascal.

Chronic Liver Disease

In 2024, the AASLD published 2 guidelines focused on blood-based and imaging-based NILDA of hepatic fibrosis and steatosis.[3,4,] Recommendations regarding the use of these noninvasive assessments for patients with chronic liver disease, including hepatocellular (HCV, HCV/HIV, HBV, HCV/HBV, HBV/HIV, NAFLD, ALD) and cholestatic disorders (PSC, PBC) are found in Table 16.

American College of Radiology

In 2020, the American College of Radiology appropriateness criteria rated ultrasound shear wave elastography as an 8 (usually appropriate) for the diagnosis of liver fibrosis in patients with chronic liver disease.[105,] The criteria noted that high-quality data can be difficult to obtain in obese patients, and assessments of liver stiffness can be confounded by parenchyma, edema, inflammation, and cholestasis.

U.S. Preventive Services Task Force Recommendations

A 2020 U.S. Preventive Services Task Force Recommendation Statement for HCV screening notes that a diagnostic evaluation for fibrosis stage or cirrhosis with a noninvasive test reduces the risk for harm compared to a liver biopsy.[106,] This statement does not give preference to a specific noninvasive test.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 17.

Table 17. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT06592820[a]	Shear Wave Elastography Registry Study (SW)	300	Mar 2027 recruiting)
NCT06463366	Multi-parametric Magnetic Resonance Imaging for the Precise Diagnosis and Quantitative Study of Liver Steatosis, Inflammation, and Fibrosis in Chronic Liver Disease.	100	Sep 2025 (recruiting)

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT04365855	The Olmsted NAFLD Epidemiology Study (TONES)	800	Jun 2028 (recruiting)
NCT04550481	Role of Lisinopril in Preventing the Progression of Non-Alcoholic Fatty Liver Disease, RELIEF-NAFLD Study	45	Sept 2026 (not recruiting)
Unpublished			
NCT03789825	Screening for Liver Fibrosis. A Population-based Study in European Countries. The "LiverScreen" Project.	30000	Jan 2025
NCT04435054	Screening for NAFLD-related Advanced Fibrosis in High Risk popuLation: Optimization of the Diabetology Pathway Referral Using Combinations of Non-invAsive Biological and elastogRaphy paramEters	1000	Sep 2024

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
76391	Magnetic resonance (e.g., vibration) elastography
76981	Ultrasound, elastography; parenchyma (e.g., organ)
76982	Ultrasound, elastography; first target lesion
76983	Ultrasound, elastography; each additional target lesion (List separately in addition to code for primary procedure)
81517	Liver disease, analysis of 3 biomarkers (hyaluronic acid [HA], procollagen III amino terminal peptide [PIIINP], tissue inhibitor of metalloproteinase 1 [TIMP-1]), using immunoassays, utilizing serum, prognostic algorithm reported as a risk score and risk of liver fibrosis and liver[1]related clinical events within 5 years
81596	Infectious disease, chronic hepatitis C virus (HCV) infection, six biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, and haptoglobin) utilizing serum, prognostic algorithm reported as scores for fibrosis and necroinflammatory activity in liver
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
83883	Nephelometry, each analyte not elsewhere specified
91200	Liver elastography, mechanically induced shear wave (e.g., vibration), without imaging, with interpretation and report
0002M	Liver disease, ten biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, haptoglobin, AST, glucose, total cholesterol and triglycerides) utilizing serum, prognostic algorithm reported as quantitative scores for fibrosis, steatosis and alcoholic steatohepatitis (ASH)
0003M	Liver disease, ten biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, haptoglobin, AST, glucose, total cholesterol and triglycerides) utilizing serum, prognostic algorithm reported as quantitative scores for fibrosis, steatosis and nonalcoholic steatohepatitis (NASH)
0166U	Liver disease, 10 biochemical assays (α2-macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, GGT, ALT, AST, triglycerides, cholesterol, fasting glucose) and biometric and demographic data, utilizing serum, algorithm reported as scores for fibrosis, necroinflammatory activity, and steatosis with a summary interpretation

CPT/HCPCS	
0648T	Quantitative magnetic resonance for analysis of tissue composition (e.g., fat, iron, water content), including multiparametric data acquisition, data preparation and transmission, interpretation and report, obtained without diagnostic MRI examination of the same anatomy (e.g., organ, gland, tissue, target structure) during the same session
0649T	Quantitative magnetic resonance for analysis of tissue composition (e.g., fat, iron, water content), including multiparametric data acquisition, data preparation and transmission, interpretation and report, obtained with diagnostic MRI examination of the same anatomy (e.g., organ, gland, tissue, target structure) (List separately in addition to code for primary procedure)

REVISIONS	
09-16-2016	Policy added to the bcbsks.com web site on 08-17-2016.
01-18-2017	Updated Description section.
	Updated Rationale section.
	Updated References section.
12-20-2017	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Added CPT code 0346T.
	Updated References section.
01-01-2019	In Coding section: ▪ Added new CPT codes: 76391, 76981, 76982, 76983, 81596.
02-01-2019	Policy posted 01-04-2019 with an effective date of 02-01-2019.
	Updated Description section.
	In Policy section: ▪ Added new Item A, "A single FibroSURE multianalyte assay may be considered medically necessary for the initial evaluation of patients with chronic liver disease." ▪ In new Item B (previous Item A), removed "with algorithmic analyses" and "the evaluation or" and added "FibroSURE" to read, "FibroSURE Multianalyte assays are considered experimental / investigational for monitoring of patients with chronic liver disease." ▪ Added new Item C, "Other multianalyte assays with algorithmic analyses are considered experimental / investigational for the initial evaluation or monitoring of patients with chronic liver disease." ▪ In new Item D (previous Item B), removed "ARFI" and added "initial" to read, "The use of noninvasive imaging, including, but not limited to, transient elastography (e.g., FibroScan), magnetic resonance elastography, acoustic radiation force impulse imaging (e.g., Acuson S2000), or real-time tissue elastography, is considered experimental / investigational for the initial evaluation or monitoring of patients with chronic liver disease."
	Updated Rationale section.
	In Coding section: ▪ Removed CPT code: 0346T *(deleted January 1, 2019)*.
	Updated References section.
03-13-2019	Updated Description section.
	In Policy section:

REVISIONS	
	▪ Added new Item D, "Transient elastography (FibroScan) imaging may be considered medically necessary for the initial evaluation of patients with chronic liver disease." ▪ Added new Item E, "Transient elastography (FibroScan) imaging is considered experimental / investigational for monitoring of patients with chronic liver disease." ▪ In Item F (previously Item D), removed "transient elastography (e.g., FibroScan)" to read, "The use of other noninvasive imaging, including, but not limited to, magnetic resonance elastography, acoustic radiation force impulse imaging (e.g., Acuson S2000), or real-time tissue elastography, is considered experimental / investigational for the initial evaluation or monitoring of patients with chronic liver disease."
	Updated Rationale section.
	In Coding section: ▪ Removed CPT code: 0001M.
	Updated References section.
02-25-2021	Updated Description section
	Updated Rationale section
	Updated Reference section
07-01-2021	In Coding section ▪ Added codes 0648T and 0649T (effective 07-01-21)
01-04-2022	Updated Description Section
	Updated Rationale Section
	Updated Codes Section ▪ Added: 0014M, 0166U ▪ Deleted Codes:84999
	Updated References Section
12-29-2022	Updated Description Section
	Updated Policy Section ▪ Section F Added: "multiparametric magnetic resonance imaging" as a noninvasive imaging
	Updated Rationale Section
	Updated Reference Section
01-05-2024	Updated Description Section
	Update Rationale Section
	Updated Coding Section ▪ Removed Deleted Code 0014M (eff. 01-01-2024) ▪ Removed ICD-10 Diagnoses Box ▪ Added New code 81517 (eff. 01-01-2024)
	Updated References Section
12-23-2024	Updated Description Section
	Update Rationale Section
	Updated References Section
11-26-2025	Updated Description Section
	Updated Policy Section ▪ Added: Subtitle A Multianalyte Assays ▪ Section A1 Removed: "a single" and added "fibrosis staging" ▪ Added: Subtitle B Noninvasive Imaging Technologies ▪ Section B3 Removed: (e.g., Acuson S2000),
	Updated Policy Guideline Section Added:

REVISIONS	
	A. Increased fibrosis stage has important prognostic implications in nonalcoholic fatty liver disease (NAFLD) (now metabolic dysfunction-associated steatotic liver disease, MASLD, see Background). B. The American Association for the Study of Liver Diseases (AASLD) has developed an algorithm intended to be used by clinicians in need of a readily available and simple decision support tool for liver disease assessment (see below). The AASLD recommends that fibrosis staging begin with nonproprietary blood-based tests because of their wide availability and performance compared to proprietary tests. Nonproprietary tests include the Fibrosis-4 (FIB-4) Index, and NAFLD/NASH fibrosis score (NFS) which are used as initial blood-based tests to rule-out advanced fibrosis. The fibrosis 4 (FIB-4) Index calculator estimates the likelihood of advanced liver fibrosis (scarring) by combining a patient's age with aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count values. A low FIB-4 score (typically <1.3 or <1.45) suggests a low risk of advanced fibrosis, while a high score (typically >2.67 or >3.25) indicates a high risk and may warrant further assessment, potentially a liver biopsy. C. The NFS score is calculated using a formula that considers the following factors: age, body mass index (BMI), diabetes status, and blood test results (AST/ALT ratio, albumin, platelet count). The NFS is interpreted as follows: 1. Score <-1.455: Low risk of advanced fibrosis 2. Score between -1.455 and 0.676: Indeterminate risk 3. Score >0.676: High risk of advanced fibrosis D. The AASLD Practice Guidelines Committee commissioned a diverse group of experts across multiple disciplines in the field of adult and pediatric liver disease to develop guidelines and guidance statements along with a systematic review covering blood-based noninvasive tests to address specific clinically focused questions. Of these tests, FIB-4 was considered to have superior performance, particularly for the identification of F3-4 stages of fibrosis, which is the spectrum of fibrosis for which the tests were designed. NFS was considered an equivalent to FIB-4 in patients with NAFLD in the assessment of advanced fibrosis. FIB-4 thresholds of ≤1.30 and ≥2.67, and NFS thresholds of ≤-1.455 and ≥0.676, have been proposed as having higher predictive values for F3-4 in NAFLD. The AASLD recommends that in the appropriate clinical setting (i.e., low pre-test probability), both tests should suffice to rule out significant/advanced fibrosis. E. Confirmatory testing (secondary assessment) such as noninvasive imaging technologies should be performed for patients with values between the lower and upper thresholds of these tests. Patients with FIB-4 scores less than 1.3 are unlikely to have advanced fibrosis. High-risk individuals, such as those with type 2 diabetes, medically complicated obesity, family history of cirrhosis, or more than mild alcohol consumption, should be screened for advanced fibrosis. F. The AASLD Practice Guidelines Committee made an ungraded statement that in adults with CLD, either ultrasound-based elastography methods or magnetic resonance elastography (MRE) can be utilized to stage fibrosis. Depending on local availability and expertise, it is reasonable to perform MRE as an investigation when concomitant cross-sectional imaging is needed or for patients in whom the accuracy of US-based elastography might be compromised. Removed: A. Multianalyte assays with algorithmic analyses (MAAAs) use the results from multiple assays of various types in an algorithmic analysis to determine and report a numeric score(s) or probability. The results of individual component assays are not reported separately.

REVISIONS	
	Updated Rationale Section
	Updated Reference Section

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