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FEP Medical Policy Manual

FEP 2.04.41 Noninvasive Techniques for the Evaluation and Monitoring of Patients With Chronic Liver Disease

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Related Policies:

None

Noninvasive Techniques for the Evaluation and Monitoring of Patients With Chronic Liver Disease

Description

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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.

Multianalyte Assays

A variety of noninvasive laboratory tests are being evaluated as alternatives to liver biopsy. Biochemical tests can be broadly categorized into indirect and direct markers of liver fibrosis. Indirect markers include liver function tests such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), the ALT/AST ratio (also referred to as the AAR), platelet count, and prothrombin index. There has been a growing understanding of the underlying pathophysiology of fibrosis, leading to a direct measurement of the factors involved. For example, the central event in the pathophysiology of fibrosis is the activation of the hepatic stellate cell. Normally, stellate cells are quiescent, but are activated in the setting of liver injury, producing a variety of extracellular matrix (ECM) proteins. In normal livers, the rate of ECM production equals its degradation, but with fibrosis, production exceeds degradation. Metalloproteinases are involved in intracellular degradation of ECM, and a profibrogenic state exists when there is either a down-regulation of metalloproteinases or an increase in tissue inhibitors of metalloproteinases. Both metalloproteinases and tissue inhibitors of

metalloproteinases can be measured in the serum, which directly reflects the fibrotic activity. Other direct measures of ECM deposition include hyaluronic acid or α_2-macroglobulin.

While many studies have been done on these individual markers, or on groups of markers in different populations of patients with liver disease, there has been interest in analyzing multiple markers using mathematical algorithms to generate a score that categorizes patients according to the biopsy score. It is proposed that these algorithms can be used as alternatives to liver biopsy in patients with liver disease. The following proprietary, algorithm-based tests are commercially available in the U.S.

There are 3 different FibroSURE tests available depending on the indication for use: HCV FibroSURE, ASH FibroSURE, and NASH FibroSURE.

HCV FibroSURE

The HCV FibroSURE uses a combination of 6 serum biochemical indirect markers of liver function plus age and sex in a patented algorithm to generate a measure of fibrosis and necroinflammatory activity in the liver that corresponds to the Metavir scoring system for stage (ie, fibrosis) and grade (ie, necroinflammatory activity). The measures are combined using a linear regression equation to produce a score between 0 and 1, with higher values corresponding to more severe disease. The biochemical markers include the readily available measurements of α_2-macroglobulin, haptoglobin, bilirubin, γ-glutamyl transpeptidase, ALT, and apolipoprotein AI. Developed in France, 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.

ASH FibroSURE

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; the test is proposed to provide surrogate markers for liver fibrosis, hepatic steatosis, and ASH. The biochemical markers include α_2-macroglobulin, haptoglobin, apolipoprotein AI, bilirubin, γ-glutamyl transpeptidase, ALT, AST, total cholesterol, triglycerides, and fasting glucose. The test has been available in Europe under the name AshTest™ (BioPredictive); the test is exclusively offered by LabCorp in the U.S. as ASH FibroSURE.

NASH FibroSURE

NASH FibroSURE (NASH Test) uses a proprietary algorithm of the same 10 biochemical markers 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 biochemical markers include α_2-macroglobulin, haptoglobin, apolipoprotein AI, bilirubin, γ-glutamyl transpeptidase, ALT, AST, total cholesterol, triglycerides, and fasting glucose. 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

FIBROSpect II uses a combination of 3 markers that directly measure fibrogenesis of the liver, analyzed with a patented algorithm. The markers include hyaluronic acid, tissue inhibitor of metalloproteinase 1, and α_2-macroglobulin. FIBROSpect II is offered exclusively by Prometheus Laboratories. The measures are combined using a logistic regression algorithm to generate a FIBROSpect II index score, ranging from 1 to 100 (or sometimes reported between 0 and 1), with higher scores indicating more severe disease.

Enhanced Liver Fibrosis Test

The Enhanced Liver Fibrosis (ELF) test uses a proprietary algorithm to produce a score based on 3 serum biomarkers involved in matrix biology: hyaluronic acid, Procollagen III amino terminal peptide and tissue inhibitor of metalloproteinase 1. The manufacturer recommends the following cutoffs for interpretation for risk of development of cirrhosis or liver-related events in patients with NASH: <9.80 (lower risk) and ≥11.30 (higher risk).

Noninvasive Imaging Technologies

Noninvasive imaging technologies to detect liver fibrosis or cirrhosis among patients with chronic liver disease are being evaluated as alternatives to liver biopsy. The noninvasive imaging technologies include transient elastography (eg, FibroScan), magnetic resonance elastography, acoustic radiation force impulse (ARFI) imaging (eg, Acuson S2000), multiparametric magnetic resonance imaging (MRI), and real-time tissue elastography (eg, HI VISION Preirus). Noninvasive imaging tests have been used in combination with multianalyte serum tests such as FibroTest or FibroSURE with FibroScan.

Transient Elastography

Transient elastography (FibroScan) 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. Transient elastography does not perform as well in patients with ascites, higher body mass index, or narrow intercostal margins. Although FibroScan may be used to measure fibrosis (unlike liver biopsy), it does not provide information on necroinflammatory activity and steatosis, nor is it accurate during acute hepatitis or hepatitis exacerbations.

Acoustic Radiation Force Impulse Imaging

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 technologies include Virtual Touch Quantification and Siemens Acuson S2000 system. ARFI elastography can be performed at the same time as a liver sonographic evaluation, even in patients with a significant amount of ascites.

Magnetic Resonance Elastography

Magnetic resonance elastography 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. Magnetic resonance elastography has several advantages over ultrasound elastography, including: (1) the ability to analyze larger liver volumes; (2) the ability to analyze liver volumes of obese patients or patients with ascites; and (3) the ability to precisely analyze viscoelasticity using a 3-dimensional displacement vector.

Real-Time Tissue Elastography

Real-time tissue elastography 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. Hitachi manufactures real-time tissue elastography devices, including the HI VISION Preirus. The challenge is 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 complex. Various subjective and quantitative methods have been developed to evaluate the results. Real-time tissue elastography can be performed in patients with ascites or inflammation. This technology does not perform as well in severely obese individuals.

Multiparametric Magnetic Resonance Imaging

Multiparametric MRI 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® uses a clinical algorithm that accounts for an iron-corrected T1 value, based on the T2* relaxation time, and proton density fat-fraction to assess the presence of fat, inflammation, and fibrosis.

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.

POLICY STATEMENT

A single FibroSURE multianalyte assay may be considered **medically necessary** for the evaluation of individuals with chronic liver disease.

FibroSURE multianalyte assays are considered **not medically necessary** for monitoring of individuals with chronic liver disease.

Other multianalyte assays with algorithmic analyses are considered **not medically necessary** for the evaluation or monitoring of individuals with chronic liver disease.

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

Transient elastography (FibroScan) imaging is considered **not medically necessary** for monitoring of individuals with chronic liver disease.

The use of other noninvasive imaging, including but not limited to magnetic resonance elastography, multiparametric magnetic resonance imaging, acoustic radiation force impulse imaging (eg, Acuson S2000), or real-time tissue elastography, is considered **not medically necessary** for the evaluation or monitoring of individuals with chronic liver disease.

POLICY GUIDELINES

Multianalyte assays with algorithmic analyses 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.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Both FibroSURE and FIBROSpect are offered exclusively by reference laboratories, where the global charge will reflect the cost of the underlying laboratory analysis, and then, in addition, the charge associated with the use of the proprietary algorithm to analyze the data.

State or federal mandates (eg, Federal Employee Program) may dictate that certain U.S. Food and Drug Administration approved devices, drugs, or biologics may not be considered investigational, and thus these devices may be assessed only by their medical necessity.

FDA REGULATORY STATUS

In 2008 Acuson S2000™ Virtual Touch (Siemens AG), which provides ARFI imaging, was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process (K072786).

In 2009, AIXPLORER Ultrasound System (SuperSonic Imagine), which provides shear wave elastography, was cleared for marketing by the FDA through the 510(k) process (K091970).

In 2010, Hitachi HI VISION™ Preirus™ Diagnostic Ultrasound Scantier (Hitachi Medical Systems America), which provides real-time tissue elastography, was cleared for marketing by the FDA through the 510(k) process (K093466).

In 2013, FibroScan (EchoSens), which uses transient elastography, was cleared for marketing by the FDA through the 510(k) process (K123806).

In June 2015, LiverMultiScan (Perspectum), which is a magnetic resonance diagnostic device software application, was cleared for marketing by the FDA through the 510(k) process (K143020).

In February 2017, ElastQ Imaging shear wave elastography (Royal Phillips) was cleared for marketing by the FDA through the 510(k) process (K163120).

In August 2021, ADVIA Centaur Enhanced Liver Fibrosis (ELF^{TM}) test (Siemens Healthcare) was cleared for marketing by the FDA through the 513(f)(2) De Novo review pathway (DEN190056). In 2018, the device had been granted a Breakthrough Device designation for predicting disease progression in patients with advanced fibrosis due to NAFLD.

In July 2023, the Enhanced Liver Fibrosis (ELF™) Test was granted a Breakthrough Device Designation to aid in the identification of advanced fibrosis (≥F3) and cirrhosis (F4) in patients with NAFLD.

FDA product codes: IYO, LNH, QQB.

RATIONALE

Summary of Evidence

Multianalyte Serum Assays

For individuals who have chronic liver disease who receive FibroSURE serum panels, the evidence includes systematic reviews of more than 30 observational studies (>5000 patients). Relevant outcomes are test validity, morbid events, and treatment-related morbidity. FibroSURE has been studied in populations with viral hepatitis, nonalcoholic fatty liver disease (NALFD)/metabolic dysfunction-associated steatotic liver disease (MASLD), and alcoholic liver disease (ALD). 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 randomized controlled trials (RCTs) that showed the efficacy of hepatitis C virus (HCV) treatments, which in turn demonstrated that the test can identify patients who would benefit from therapy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have chronic liver disease who receive multianalyte serum assays for liver function assessment other than FibroSURE, the evidence includes a number of observational studies and systematic reviews of those studies. Relevant outcomes are test validity, morbid events, and treatment-related morbidity. Studies have frequently included varying cutoffs, some of which were standardized and others not validated. Cutoff thresholds have often been modified over time, may be specific to certain patient populations, and in some cases, guideline recommendations differ from cutoffs designated by manufacturers and those utilized in studies. Authors of one meta-analysis concluded that when compared to biopsy, the following noninvasive scoring systems demonstrated better diagnostic accuracy for predicting liver fibrosis severity in individuals with MASLD: fibrosis-4 index (FIB-4) for any fibrosis, FibroMeter for significant fibrosis, Enhanced Liver Fibrosis (ELF) for advanced fibrosis, and FIB-4 for cirrhosis. A comparison of transient elastography to various serum-based tests found that the former was superior in detecting fibrosis, and a meta-analysis of 4 studies found higher multianalyte scores associated with an increased risk of mortality relative to lower scores, but the evidence is limited by the small number of included studies and high heterogeneity and imprecision for some estimates. Given these limitations and the imperfect reference standard, it is difficult to interpret performance characteristics. There is no direct evidence that other multianalyte serum assays 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Noninvasive Imaging

For individuals who have chronic liver disease who receive transient elastography, the evidence includes many systematic reviews of more than 50 observational studies (>10,000 patients). Relevant outcomes are test validity, morbid events, and treatment-related morbidity. Transient elastography (FibroScan) has been studied in populations with viral hepatitis, NALFD, 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. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have chronic liver disease who receive multiparametric magnetic resonance imaging (MRI), the evidence includes several prospective and retrospective observational studies. Multiparametric MRI (eg, LiverMultiScan) has been studied in mixed populations, including NAFLD, viral hepatitis, and ALD. Quantitative MRI provides various measures to assess liver fat content, fibrosis and inflammation. Various cutoffs have been utilized for positivity. Given these limitations and the imperfect reference standard, it can be difficult to interpret performance characteristics. Otherwise, multiparametric MRI performed similarly to transient elastography, and fewer technical failures of multiparametric MRI were reported. The prognostic ability of quantitative MRI to predict liver-related clinical events has been evaluated in 2 studies. Both studies reported positive correlations, but the CI was wide. Larger cohorts with a longer follow-up time would be useful to further derive the prognostic characteristic of the test. Multiparametric MRI has been used to measure the presence of fibrosis or cirrhosis in patients who have achieved biochemical remission after treatment in small prospective studies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have chronic liver disease who receive noninvasive radiologic methods other than transient elastography for liver fibrosis measurement, the evidence includes systematic reviews of observational studies and a comparative study with 5-year follow up. Relevant outcomes are test validity, morbid events, and treatment-related morbidity. Other radiologic methods (eg, magnetic resonance elastography [MRE], real-time transient elastography [RTE], acoustic radiation force impulse imaging [ARFI] imaging) may have similar performance for detecting significant fibrosis or cirrhosis. In the comparative study, ARFI elastography was found to be at least as effective as liver histology in predicting liver-related survival, and

was superior to both histology and the FIB-4 score in predicting certain liver-related complications. Studies have frequently included varying cutoffs not prespecified or validated. 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

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.

Nonalcoholic Fatty Liver Disease

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)."[101,] 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[102,] 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.[103,] 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

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.[104,]

- 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

A 2024 publication from the AASLD describes the impact of new nomenclature on the AASLD practice guidance on NAFLD and hepatic steatosis described above.[105,] 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)[106,]:

- 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.[107,108,]Recommendations are provided in Table 16 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 1. AASLD Recommendations for Blood- and Imaging-based Noninvasive Liver Disease Assessment.[108,107,]

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 assesment; TE-CAP: US: ultrasound;

National Institute for Health and Care Excellence

In 2016, the NICE published guidance on the assessment and management of NAFLD.[54,] 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.

American Gastroenterological Association Institute

In 2017, the American Gastroenterological Association Institute published guidelines on the role of elastography in chronic liver disease. The guidelines indicate that, in adults with NAFLD, VCTE has superior diagnostic sensitivity and specificity for diagnosing cirrhosis when compared to the aspartate aminotransferase platelet ratio index (APRI) or FIB-4 tests (very low quality of evidence).[109,] Moreover, the guidelines state that, in adults with NAFLD, magnetic resonance-guided elastography has little or no increased diagnostic accuracy for identifying cirrhosis compared with VCTE in patients who have cirrhosis, and has higher diagnostic accuracy than VCTE in patients who do not have cirrhosis (very low quality of evidence).

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.[107,108,] 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]"[110,]

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.[111,] Specific recommendations for a preferred noninvasive testing strategy are not provided.

American Gastroenterological Association Institute

In 2017, guidelines published by the American College of Gastroenterology Institute on the role of elastography in chronic liver disease indicated that, in adults with chronic hepatitis B virus and chronic HCV, VCTE has superior diagnostic performance for diagnosing cirrhosis when compared to the APRI and FIB-4 tests (moderate quality of evidence for HCV, low quality of evidence for hepatitis B virus).[109,] In addition, the guidelines state that, in adults with HCV, magnetic resonance-guided elastography has little or no increased diagnostic accuracy for identifying cirrhosis compared with VCTE in patients who have cirrhosis, and has lower diagnostic accuracy than VCTE in patients who do not have cirrhosis (very low quality of evidence).

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.[112,] 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 2. 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.[107,108,] 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.[113,] 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.[114,] This statement does not give preference to a specific noninvasive test.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2023	New policy	Policy updated with literature review through September 12, 2022; references added. Minor editorial refinements to policy statements; intent unchanged. FEP new benefit, new policy.
June 2025	Replace policy	Policy updated with literature review through September 27, 2024; references added. Policy statements unchanged.