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

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Policy Statement

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

FibroSURE multianalyte assays are considered investigational for monitoring of patients with chronic liver disease.

Other multianalyte assays with algorithmic analyses are considered investigational for the evaluation or monitoring of patients with chronic liver disease.

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

Transient elastography (FibroScan) imaging is considered investigational for monitoring of patients with chronic liver disease.

The use of other noninvasive imaging is considered investigational for the evaluation or monitoring of patients with chronic liver disease including but not limited to any of the following:

I. Magnetic resonance elastography
II. Acoustic radiation force impulse imaging (ARFI; e.g., Acuson S2000)
III. Real-time tissue elastography

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

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.

Coding

The following Category 1 CPT code replaced CPT MAAA code 0001M and is specific for the FibroSURE™ test performed by LabCorp:

- 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

The following CPT multianalyte assays with algorithmic analyses (MAAA) codes are specific for the FibroSURE™ tests performed by LabCorp:

- ASH FibroSURE™, LabCorp
  - 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)

- NASH FibroSURE™, LabCorp
  - 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)

There is a CPT MAHA code that is specific for the Enhanced Liver Fibrosis™ (ELFTM) Test, which was produced by Siemens Healthcare Laboratory:

- **0014M**: 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-related clinical events within 5 years

LiverFAST

There is a CPT Proprietary Laboratory Analyses (PLA) code specific for the LiverFAST test, which was produced by Fibronostics:

- **0166U***: Liver disease, 10 biochemical assays (a2-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

*Note: This test is for adult patients with non-alcoholic fatty liver disease from asymptomatic early stage through non-malignant late stage. The test utilizes a combination of serum biomarkers and patient demographics that is intended to aid in the staging of fibrosis, inflammatory activity, and steatosis of liver disease. This test is not intended for use as a stand-alone test, but to be used in conjunction with other laboratory, radiological and clinical findings.

FIBROSpect

There are no specific CPT codes that represent FIBROSpect as a whole. At this time, it may be reported using the unlisted chemistry procedure code 84999, or with the codes for each component test. There is no specific CPT code for the use of the associated proprietary algorithm for FIBROSpect. The following CPT codes are examples of possible coding:

- **Hyaluronic acid**
  - **83520**: Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified

- **Tissue inhibitor of metalloproteinase (TIMP-1)**
  - **83520**: Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified

- **Alpha-2-macroglobulin**
  - **83883**: Nephelometry, each analyte not elsewhere specified

Elastography

The following CPT code is specific for liver elastography without imaging:

- **91200**: Liver elastography, mechanically induced shear wave (e.g., vibration), without imaging, with interpretation and report

The following CPT codes that specifically describe ultrasound elastography will replace category III CPT code 0346T and will be used in conjunction with other ultrasound tests:

- **76981**: Ultrasound, elastography; parenchyma (e.g., organ). This code is for the entire organ
- **76982**: Ultrasound, elastography; first target lesion
- **76983**: Ultrasound, elastography; each additional target lesion (List separately in addition to code for primary procedure). This code an add-on to the primary procedure 76982

The following CPT code may be billed for Magnetic Resonance Elastography (MRE):

- **76391**: Magnetic resonance (e.g., vibration) elastography

This policy does not address standard imaging with ultrasound or magnetic resonance imaging.
Effective August 1, 2021, there are two new Category III codes that were created for reporting quantitative magnetic resonance for analysis of tissue composition. Per the manufacturer, this technology uses software to analyze tissue physiology (most commonly in chronic liver disease) and generates diagnostic information, (i.e., parametric maps and summary statistics):

- **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)

### 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, transient elastography, acoustic radiation force impulse imaging, and real-time transient elastography.

### Related Policies

- N/A

### Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

### 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)(K123622).

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

FDA product code: IYO.

In November 2018, the FDA granted a Breakthrough Device designation for the ADVIA Centaur Enhanced Liver Fibrosis (ELF™) Test (Siemens Healthcare). As of November 25, 2019, the ELF Test is available in the U.S., however, the test has not been cleared or approved for use by the FDA.

### Rationale

**Background**

**Biopsy for Chronic Liver Disease**

The diagnosis of non-neoplastic liver disease is often 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. The degree of inflammation and fibrosis may be assessed by different scoring schemes. Most of these scoring schemes grade inflammation from 0 (no or minimal inflammation) to 4 (severe) and fibrosis from 0 (no fibrosis) to 4 (cirrhosis). There are several limitations to liver biopsy, including its invasive nature, small tissue sample size, and subjective grading system. Regarding small tissue sample size, liver fibrosis can be patchy and thus missed on a biopsy sample, which includes only 0.002% of the liver tissue. A noninvasive alternative to liver biopsy would be particularly helpful, both to initially assess patients and then to monitor response to therapy. The implications of using liver biopsy as a reference standard are discussed in the Rationale.

**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 a histologic scoring system; the most commonly used for HCV is the Metavir system, which scores the presence and degree of inflammatory activity and fibrosis. The fibrosis is graded from F0 to F4, with a Metavir score of F0 signifying no fibrosis and F4 signifying cirrhosis (which is defined as the presence throughout the liver of fibrous septa that subdivide the liver parenchyma into nodules, representing the final and irreversible form of the disease). The stage of fibrosis is the most important single predictor of morbidity and mortality in patients with hepatitis C. Biopsies for HCV are also evaluated according to the degree of inflammation present, referred to as the grade or activity level. For example, the Metavir system includes scores for necroinflammatory activity ranging from A0 to A3 (A0 = no activity, A1 = minimal activity, A2 = moderate activity, 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. As with HCV, identification of liver fibrosis is needed to determine timing and management of treatment, and liver biopsy is the criterion standard for staging fibrosis. The grading of fibrosis in HBV also uses the Metavir system.

**Alcoholic Liver Disease**

Alcoholic liver disease (ALD) is the leading cause of liver disease in most Western countries. Histologic features of ALD usually include steatosis, alcoholic steatohepatitis, hepatocyte necrosis, Mallory bodies (tangled proteins seen in degenerating hepatocytes), a large polymorphonuclear inflammatory infiltrate, and, with continued alcohol abuse, fibrosis, and possibly cirrhosis. The grading of fibrosis is similar to the scoring system used in HCV. The commonly used Laënnec scoring system uses grades 0 to 4, with 4 being cirrhosis.
Nonalcoholic Fatty Liver Disease
Nonalcoholic fatty liver disease (NAFLD) is defined as a condition that pathologically resembles ALD, but occurs in patients who are not heavy users of alcohol. Moreover, NAFLD may be associated with a variety of conditions, including obesity, diabetes, and dyslipidemia. The characteristic feature of NAFLD is steatosis. At the benign end of the disease spectrum, there is usually no appreciable inflammation, hepatocyte death, or fibrosis. In contrast, nonalcoholic steatohepatitis (NASH), which shows overlapping histologic features with ALD, is an intermediate form of liver damage, and liver biopsy may show steatosis, Mallory bodies, focal inflammation, and degenerating hepatocytes. NASH can progress to fibrosis and cirrhosis. A variety of histologic scoring systems have been used to evaluate NAFLD. The NAFLD Activity Score system for NASH includes scores for steatosis (0 to 3), lobular inflammation (0 to 3), and ballooning (0 to 2). Cases with scores of 5 or greater are considered NASH, while cases with scores of 3 and 4 are considered borderline (probable or possible) NASH. The grading of fibrosis is similar to the scoring system used in hepatitis C. The commonly used Laënnec scoring system uses grades 0 to 4, with 4 being cirrhosis.

Noninvasive Alternatives to Liver Biopsy
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 α2-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.

FibroSURE
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 necro-inflammatory activity in the liver that corresponds to the Metavir scoring system for stage (i.e., fibrosis) and grade (i.e., 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 α2-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 alcoholic steatohepatitis. The biochemical markers include $\alpha_2$-macroglobulin, haptoglobin, apolipoprotein AI, bilirubin, $\gamma$-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 $\alpha_2$-macroglobulin, haptoglobin, apolipoprotein AI, bilirubin, $\gamma$-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 $\alpha_2$-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.

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 (e.g., FibroScan), magnetic resonance elastography, acoustic radiation force impulse (ARFI) imaging (e.g., Acuson S2000), and real-time tissue elastography (e.g., 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.

ARFI 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.

**Literature Review**

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. 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. 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, most available reviews did not use any correction for the imperfect reference.

A systematic review by Crossan et al (2015) was performed for the National Institute for Health Research. 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 hepatitis C virus (HCV), hepatitis B virus (HBV), nonalcoholic fatty liver disease (NAFLD), and alcoholic liver disease (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%; acoustic radiation force impulse (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. 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% credibility interval [CrI], 0.02 to 0.09) favoring FibroTest. The difference in AUROC curve for cirrhosis for FibroTest vs 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.

Clinical Context and Test Purpose
The purpose of noninvasive testing in individuals with chronic liver disease is to detect liver fibrosis so that patients 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 patients with liver disease (e.g., hepatitis, ALD, NAFLD).

The question addressed in this portion of the evidence review is: Does the use of the FibroSURE multianalyte serum assay, multianalyte serum assays (other than FibroSURE), transient elastography, and other noninvasive imaging for detecting liver fibrosis improve the net health outcome in patients with chronic liver disease?

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 the FibroSURE serum panel, multianalyte serum assays (other than FibroSURE), transient elastography, and other noninvasive imaging.

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.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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.

Multianalyte Serum Assays: FibroSURE (FibroTest)
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).

Following the initial research into FibroSURE (patients with liver fibrosis who had undergone biopsy)², 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.¹⁰ 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.¹¹ In this study, cutoff values were used for individual Metavir scores (i.e., F0 to F4) and for combinations of Metavir scores (i.e., 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.¹²¹³

In the Crossan et al (2015) systematic review, FibroTest was the most widely validated commercial serum test.² Seven 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; and several trials (ION-1,-3; VALENCE; ASTRAL-2, -3, -4) have established the efficacy of HCV treatments. 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 the HCV FibroSURE could be used as an interval test in patients receiving therapy to determine whether an additional liver biopsy was necessary.

**Alcoholic 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).

The diagnostic value of FibroSURE (FibroTest in Europe) has also been evaluated for the prediction of liver fibrosis in patients with ALD and NAFLD. 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. 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 aspartate aminotransferase (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. 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.

Nonalcoholic Fatty Liver Disease and Nonalcoholic 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).

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. 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 ActiTtest) in a cohort of 288 patients treated with bariatric surgery. Included were patients with severe or morbid obesity (body mass index, >35 kg/m²), 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 NASHTest 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 NASHTest was 43.1%, with a weak κ reliability test (0.14). In 183 patients categorized as possible NASH by the NASHTest, 124 (68%) were classified as no NASH by biopsy. In 15 patients categorized as NASH by the NASHTest, 7 (47%) were no NASH and 4 (27%) were possible NASH by biopsy. The NPV of the NASHTest for possible NASH or NASH was 47.5%. Authors suggested that the power of this study to validate agreement between the NASHTest and biopsy was low, due to the low prevalence of NASH. However, the results showed poor concordance between the NASHTest and biopsy, particularly for intermediate values.

In the Crossan et al (2015) systematic review, 4 studies were included in the pooled estimate of the diagnostic accuracy of FibroTest for advanced fibrosis (stage ≥ 3) in NAFLD. 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.

**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 (NASHTest) in NAFLD and NASH.

**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).

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. 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. 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<0.001). The only independent factor for discordance on multivariate analysis was a Metavir stage F3 or F4 on liver biopsy (p<0.001).

Salkic et al (2014) conducted a meta-analysis of studies on the diagnostic accuracy of FibroTest in chronic HBV. Included in the meta-analysis were 16 studies (N=2494) on liver fibrosis diagnosis and 13 studies (1754 patients) 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. 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.

In the Crossan et al (2015) systematic review, 6 studies were included in the pooled estimate of the diagnostic accuracy of FibroTest for significant fibrosis (stage ≥ F2) in HBV. 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 (e.g., HBV FibroSURE) may be needed for this assessment in patients with hepatitis B.

Section Summary: FibroSURE (FibroTest)
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). FibroSURE has been studied in populations with viral hepatitis, NAFLD, and 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 RCTs that showed the efficacy of HCV treatments, which in turn demonstrated the test can identify patients who would benefit from therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Multianalyte Serum Assays: Other Than FibroSURE
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).

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. 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. 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%).

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.

Subsection Summary: FIBROSpect II
FIBROSpect II has been studied in populations with HCV. Cutoffs for positivity varied across studies and were not well validated. The methodologic quality of the validation studies was generally poor. There is no direct evidence that FIBROSpect II improves health outcomes.

Other Multianalyte Scoring Systems
Other scoring systems have been developed. For example, the APRI requires only the serum level of AST and the number of platelets and utilizes a simple nonproprietary formula that can be calculated at the bedside to produce a score for the prediction of fibrosis. Using an optimized cutoff value derived from a training set and validation set of patients with HCV, authors have reported that the NPV for fibrosis was 86% and that the PPV was 88%. In Crossan et al (2015), APRI was frequently evaluated and has been tested in HCV, HBV, NAFLD, and ALD. The summary diagnostic accuracies are in Table 1.

### Table 1. Diagnostic Accuracy for APRI

<table>
<thead>
<tr>
<th>Disease</th>
<th>Metavir Stage</th>
<th>Cutoff</th>
<th>Studies</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV ≥ F2 (significant)</td>
<td>Low: 0.4-0.7</td>
<td>47</td>
<td>82 (77 to 86)</td>
<td>57 (49 to 65)</td>
<td></td>
</tr>
<tr>
<td>HCV ≥ F2 (significant)</td>
<td>High: 1.5</td>
<td>36</td>
<td>39 (32 to 47)</td>
<td>92 (89 to 95)</td>
<td></td>
</tr>
<tr>
<td>HCV F4 (cirrhosis)</td>
<td>Low: 0.75-1</td>
<td>24</td>
<td>77 (73 to 81)</td>
<td>78 (74 to 81)</td>
<td></td>
</tr>
<tr>
<td>HCV F4 (cirrhosis)</td>
<td>High: 2</td>
<td>19</td>
<td>48 (41 to 56)</td>
<td>94 (91 to 95)</td>
<td></td>
</tr>
<tr>
<td>HBV ≥ F2 (significant)</td>
<td>Low: 0.4-0.6</td>
<td>8</td>
<td>80 (68 to 88)</td>
<td>65 (52 to 77)</td>
<td></td>
</tr>
<tr>
<td>HBV ≥ F2 (significant)</td>
<td>High: 1.5</td>
<td>6</td>
<td>37 (22 to 55)</td>
<td>93 (85 to 97)</td>
<td></td>
</tr>
<tr>
<td>HBV F4 (cirrhosis)</td>
<td>Low: 1</td>
<td>4</td>
<td>58 (49 to 66)</td>
<td>76 (70 to 81)</td>
<td></td>
</tr>
<tr>
<td>HBV F4 (cirrhosis)</td>
<td>High: 2</td>
<td>3</td>
<td>24 (18 to 52)</td>
<td>91 (83 to 96)</td>
<td></td>
</tr>
<tr>
<td>NAFLD ≥ F3 (significant)</td>
<td>0.5 to 1.0</td>
<td>4</td>
<td>40 (7 to 86)</td>
<td>82 (78 to 60)</td>
<td></td>
</tr>
<tr>
<td>NAFLD F4 (cirrhosis)</td>
<td>0.54 and NA</td>
<td>2</td>
<td>78 (11 to 99)</td>
<td>71 (30 to 93)</td>
<td></td>
</tr>
<tr>
<td>ALD ≥ F2 (significant)</td>
<td>Low: 0.5</td>
<td>2</td>
<td>72 (60 to 82)</td>
<td>46 (33 to 60)</td>
<td></td>
</tr>
<tr>
<td>ALD ≥ F2 (significant)</td>
<td>High: 1.5</td>
<td>2</td>
<td>54 (42 to 66)</td>
<td>78 (64 to 88)</td>
<td></td>
</tr>
<tr>
<td>ALD F4 (cirrhosis)</td>
<td>High: 2.0</td>
<td>1</td>
<td>40 (22 to 61)</td>
<td>62 (41 to 79)</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Crossan et al (2015). ALD: alcoholic liver disease; APRI: aspartate aminotransferase-platelet ratio index; CI: confidence interval; HBV: hepatitis B virus; HCV: hepatitis C virus; NA: not available; NAFLD: nonalcoholic fatty liver disease.
Giannini et al (2006) reported that the use of the AST/ALT ratio and platelet counts in a
diagnostic algorithm would have avoided liver biopsy in 69% of their patients and would have
correctly identified the absence or presence of significant fibrosis in 80.5% of these cases. In
Crossan et al (2015), the cutoffs for the positivity of AST/ALT ratio for diagnosis of significant fibrosis
(stage ≥ F2) varied from 0.6 to 1 in 7 studies. Summary sensitivity and specificity were 44% (95%
CI, 27% to 63%) and 71% (95% CI, 62% to 78%), respectively. Thirteen studies used a cutoff of 1 to
evaluate the diagnostic accuracy of cirrhosis with the AST/ALT ratio, and summary sensitivity and
specificity were 49% (95% CI, 39% to 59%) and 87% (95% CI, 75% to 94%), respectively.

A number of studies have compared HCV FibroSURE (FibroTest) and other noninvasive tests of
fibrosis with biopsy using receiver operating characteristic (ROC) analysis. For example, Bourliere
et al (2006) reported on the validation of FibroSURE (FibroTest) and found that, based on ROC
analysis, FibroSURE (FibroTest) was superior to APRI for identifying significant fibrosis, with AUROC
curves of 0.81 and 0.71, respectively. A prospective multicenter study by Zarksi et al (2012)
compared 9 of the best-evaluated blood tests in 436 patients with HCV and found similar
performance for HCV FibroSURE (FibroTest), FibroMeter, and HepaScore (ROC curve, 0.84, 0.86,
0.84, respectively). These 3 tests were significantly superior to the 6 other tests, with 70% to 73%
of patients considered well classified according to a dichotomized score (F0/F1 vs ≥ F2). The
number of “theoretically avoided liver biopsies” for the diagnosis of significant fibrosis was
calculated to be 35.6% for HCV FibroSURE (FibroTest). To improve diagnostic accuracy,
the sequential algorithm for fibrosis evaluation, combines the APRI and FibroSURE. Crossan et al (2015)
reported that the algorithm has been assessed in 4 studies of HCV for diagnosing both significant fibrosis (stage ≥ F2) and cirrhosis. Summary sensitivity and specificity for significant fibrosis were estimated to be 100% (95% CI, 100% to 100%) and 81% (95% CI, 80% to 83%), respectively. The summary sensitivity and specificity for cirrhosis
were 74% (95% CI, 42% to 92%) and 93% (95% CI, 91% to 94%), respectively.

Rosenberg et al (2004) developed a scoring system based on an algorithm combining
hyaluronic acid, amino-terminal propeptide of type III collagen, and tissue inhibitors of
metalloproteinase 1. This test is manufactured by Siemens Healthcare as the Enhanced Liver
Fibrosis (ELF) Test. The ELF Test is available in the U.S., however, the test has not been cleared or
approved for use by the U.S. Food and Drug Administration. The algorithm was developed in a
test set of 400 patients with a wide variety of chronic liver diseases and then validated in another
521 patients. The algorithm was designed to discriminate between no or mild fibrosis and
moderate-to-severe fibrosis. The NPV for fibrosis was 92%.

The FIB-4 index was developed in a cohort of patients with HCV and is similar to APRI in that it
uses a simple nonproprietary formula to produce a score for the prediction of fibrosis,
incorporating patient age, AST level, ALT level, and platelet count. In the original cohort studied
by Sterling et al (2006), a low cut-off score of <1.45 had NPV of 90% for advanced fibrosis
whereas a high cut-off score >3.25 had a 97% specificity and PPV of 65% for advanced fibrosis.
Overall, 70% of patients were stratified <1.45 or >3.25 and represented potential cases that could
have avoided liver biopsy with a corresponding diagnostic accuracy of 86%. In a comparative
study by Vallet-Pichard et al (2007) in patients with HCV utilizing the same cut-off values, an NPV
of 94.7% with a sensitivity of 74.3% and a specificity of 80.1% and a PPV of 82.1% with a specificity
of 98.2% and sensitivity of 37.6% were reported. When the diagnostic performance of FIB-4 was
compared against FibroTest (FibroSure in the U.S.), the exclusion of severe fibrosis and the
detection of severe fibrosis were found to agree between the tests in 92.1% and 76.0% of cases,
respectively. In work by Angulo et al (2013) in patients with NAFLD for prediction of advanced
fibrosis (F3 to F4), adjusted cut-offs of 1.30 and 2.67 were used. The corresponding NPV at 1.30
was 83% and PPV at 2.67 was 80%. A liver biopsy was appropriately avoided in 54% of cases.

Sanyal et al (2019) reported on findings of 2, phase 2b, placebo-controlled trials of simtuzumab
in NASH in patients with bridging fibrosis (F3; n=217) or compensated cirrhosis (F4; n=258) that
assessed patients with liver biopsy and serum biomarker tests, including ELF, APRI,
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FibroSure/FibroTest, and the FIB-4 index. Laboratory screening was conducted at baseline and at every 3 months during the course of the trials. The trials were terminated after 96 weeks due to simtuzumab inefficacy, at which point data from treatment groups were combined for analysis. In patients with bridging fibrosis, increased risk of progression to cirrhosis was observed with higher baseline levels of all serum fibrosis tests (p<0.001). Change in the ELF score over time was also associated with progression to cirrhosis (p<0.001). For a cut-off score of 9.76, progression to cirrhosis had a reported hazard ratio of 4.12 (95% CI, 2.14 to 7.93; p<0.001). For patients with compensated cirrhosis, higher levels of baseline biomarker tests were also associated with liver-related clinical events in 19% of patients, such as ascites, hepatic encephalopathy, newly diagnosed varices, esophageal variceal bleed, increase in Child-Pugh and/or model for end-stage liver disease (MELD) score, or death (p<0.001 to 0.006). While the manufacturer of the test differentiates moderate from severe fibrosis with a cut-off ELF score of 9.8, current National Institute for Health and Care Excellence guidelines for NAFLD recommend reserving a diagnosis of advanced fibrosis to NAFLD patients with an ELF score of 10.51 or greater, limiting the clinical significance of these findings. Furthermore, serum fibrosis test results were not directly used in patient management in the simtuzumab trials.

Yan et al (2020) evaluated the diagnostic value of total bile acid-to-cholesterol ratio (TBA/TC) as a serum marker for cirrhosis and fibrosis in chronic HBV-infected patients without cholestasis. This was a cross-sectional study including 667 patients. In a multivariate analysis, TBA/TC was found to be independently correlated with cirrhosis in the study population (OR, 1.102, 95% CI, 1.085 to 1.166). ROC curve analyses yielded similar AUCs for TBA/TC, APRI, and FIB-4 at 0.87, 0.84, and 0.80, respectively. For diagnosing cirrhosis, the specificity and PPV of TBA/TC (83.33%, 91.10%) were higher than those of APRI (73.61%, 87.20%). The AUC of TBA/TC that distinguished significant liver cirrhosis was 2.70. In another multivariate analysis, TBA/TC was also independently correlated with significant fibrosis (OR, 1.040, 95% CI, 1.001 to 1.078). The AUC of TBA/TC that distinguished significant liver fibrosis was 0.70. Among 32 patients who also had a liver biopsy performed, TBA/TC was significantly higher in both fibrosis and cirrhosis as well as significantly correlated with fibrosis stage (p<0.001 for all).

Section Summary: Multianalyte Serum Assays Other Than FibroSURE

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. Studies have frequently included varying cutoffs, some of which were standardized and others not validated. Cut-off thresholds have often been modified over time, may be specific to certain patient populations, and in some cases, guideline recommendations differ from cut-offs designated by manufacturers and those utilized in studies. Other multianalyte serum tests (e.g., APRI, fibrosis-4) lack data on clinical validity and utility. There does not appear to be evidence of incremental benefit over clinical assessment using the individual laboratory assay components. 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 the effects of the technology on health outcomes.

Noninvasive Imaging: Transient 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).

There is extensive literature on the use of transient elastography (e.g., FibroScan) to gauge liver fibrosis and cirrhosis. Summaries of systematic reviews are shown in Tables 2 and 3. Brener (2015) performed a health technology assessment summarizing many of the systematic reviews below. The assessment focused on reviews of the diagnostic accuracy and effect on patient outcomes of transient elastography for liver fibrosis in patients with HCV, HBV, NAFLD, ALD, or cholestatic diseases. Fourteen systematic reviews of transient elastography with biopsy reference
standard shown below were included in the Brener assessment, summarizing more than 150 primary studies. There was variation in the underlying cause of liver disease and the cutoff values of transient elastography stiffness used to define Metavir stages in the systematic reviews. There did not appear to be a substantial difference in diagnostic accuracy for 1 disease over any other. The reviews demonstrated that transient elastography 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). Cutoffs for positivity for fibrosis staging varied between diseases and were frequently not prespecified or validated: HCV, 5.2 to 10.1 kilopascal (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 in 4 studies for stages ≥ F3. Summary sensitivities and specificities by the disease are shown in Table 3. 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 2. Transient Elastography Systematic Review Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Studies</th>
<th>N</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bota et al (2013)</td>
<td>To May 2012</td>
<td>13</td>
<td>1163</td>
<td>Chronic hepatitis</td>
</tr>
<tr>
<td>Friedrich-Rust et al</td>
<td>2002 to Apr 2007</td>
<td>50</td>
<td>11,275</td>
<td>All causes of liver disease</td>
</tr>
<tr>
<td>Crossan et al (2015)</td>
<td>To Oct 2010</td>
<td>8</td>
<td>518</td>
<td>All causes of liver disease</td>
</tr>
<tr>
<td>Geng et al (2016)</td>
<td>To Jan 2015</td>
<td>57</td>
<td>10,569</td>
<td>Multiple causes of liver disease</td>
</tr>
<tr>
<td>Njie et al (2016)</td>
<td>To Jan 2016</td>
<td>6</td>
<td>765</td>
<td>HCV/HIV coinfection</td>
</tr>
<tr>
<td>Shi et al (2014)</td>
<td>To May 2013</td>
<td>9</td>
<td>1771</td>
<td>All causes of steatosis</td>
</tr>
<tr>
<td>Steadman et al (2013)</td>
<td>2001 to Jun 2011</td>
<td>64</td>
<td>6028</td>
<td>HCV, HBV, NAFLD, CLD, liver transplant</td>
</tr>
<tr>
<td>Stebbing et al (2010)</td>
<td>NR, prior to Feb 2009</td>
<td>22</td>
<td>4625</td>
<td>All causes of liver disease</td>
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<tr>
<td>Talwalkar et al (2007)</td>
<td>To Jan 2027</td>
<td>9</td>
<td>2083</td>
<td>All causes of liver disease</td>
</tr>
<tr>
<td>Tsochatzis et al (2011)</td>
<td>To May 2009</td>
<td>40</td>
<td>7661</td>
<td>All causes of liver disease</td>
</tr>
<tr>
<td>Xu et al (2015)</td>
<td>To Dec 2013</td>
<td>19</td>
<td>3113</td>
<td>HBV</td>
</tr>
<tr>
<td>Xue-Ying (2020)</td>
<td>Jan 2008 to Dec 2018</td>
<td>81</td>
<td>32,694</td>
<td>HBV</td>
</tr>
</tbody>
</table>

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

### Table 3. Transient Elastography Systematic Reviews Diagnostic Accuracy Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>AUROC (95% CI)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bota et al (2013)</td>
<td>Multiple diseases</td>
<td>0.87 (0.83 to 0.89)</td>
<td>78% (72% to 83%)</td>
<td>84% (75% to 90%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13/1163</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poynard et al (2011)</td>
<td></td>
<td>0.93 (0.91 to 0.95)</td>
<td>89% (80% to 94%)</td>
<td>87% (82% to 91%)</td>
</tr>
</tbody>
</table>

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### Significant Fibrosis

(i.e., Metavir Stages F2-F4)

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>AUROC (95% CI)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chon et al (2012)&lt;sup&gt;60&lt;/sup&gt;</td>
<td>HCV</td>
<td>4/NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Crossan et al(2015)&lt;sup&gt;72&lt;/sup&gt;</td>
<td>Chronic HBV</td>
<td>0.86 (0.86 to 0.86)</td>
<td>74.3% (NR)</td>
<td>83% (77% to 88%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16/2614</td>
<td>0.93 (0.93 to 0.93)</td>
<td>84.6% (NR)</td>
</tr>
<tr>
<td></td>
<td>HCV</td>
<td>37/NR</td>
<td>NR</td>
<td>89% (84% to 92%)</td>
</tr>
<tr>
<td></td>
<td>HBV</td>
<td>13/NR</td>
<td>NR</td>
<td>86% (79% to 91%)</td>
</tr>
<tr>
<td></td>
<td>NAFLD</td>
<td>4/NR</td>
<td>NR</td>
<td>96% (83% to 99%)</td>
</tr>
<tr>
<td>Friedrich-Rust (2008)&lt;sup&gt;51&lt;/sup&gt;</td>
<td>ALD</td>
<td>1/NR</td>
<td>NR</td>
<td>87% (64% to 96%)</td>
</tr>
<tr>
<td>Friedrich-Rust et al(2012)&lt;sup&gt;65&lt;/sup&gt;</td>
<td>Multiple</td>
<td>0.84 (0.82 to 0.86)</td>
<td>79% (74% to 84%)</td>
<td></td>
</tr>
<tr>
<td>Geng et al(2016)&lt;sup&gt;44&lt;/sup&gt;</td>
<td>NAFLD</td>
<td>10/NR</td>
<td>NR</td>
<td>86% (82% to 90%)</td>
</tr>
<tr>
<td>Jiang et al (2018)&lt;sup&gt;65&lt;/sup&gt;</td>
<td>NAFLD</td>
<td>0.85 (0.82 to 0.88)</td>
<td>77% (70% to 84%)</td>
<td></td>
</tr>
<tr>
<td>Kwok et al(2014)&lt;sup&gt;52&lt;/sup&gt;</td>
<td>NAFLD</td>
<td>0.83 (0.79 to 0.87)</td>
<td>79% (72% to 84%)</td>
<td></td>
</tr>
<tr>
<td>Li et al (2016)&lt;sup&gt;46&lt;/sup&gt;</td>
<td>HBV</td>
<td>0.88 (0.85 to 0.91)</td>
<td>81% (76% to 85%)</td>
<td></td>
</tr>
<tr>
<td>Njei et al (2016)&lt;sup&gt;47&lt;/sup&gt;</td>
<td>HCV/HIV</td>
<td>0.84 (0.78 to 0.89)</td>
<td>84% (74% to 91%)</td>
<td></td>
</tr>
<tr>
<td>Pavlov et al(2015)&lt;sup&gt;45&lt;/sup&gt;</td>
<td>ALD</td>
<td>4/NR</td>
<td>NR</td>
<td>93% (0.87 to 0.99)</td>
</tr>
<tr>
<td>Poynard et al(2008)&lt;sup&gt;60&lt;/sup&gt;</td>
<td>HBV</td>
<td>4/NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Poynard et al(2011)&lt;sup&gt;65&lt;/sup&gt;</td>
<td>HBV</td>
<td>0.84 (0.78 to 0.89)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Shaheen et al(2007)&lt;sup&gt;55&lt;/sup&gt;</td>
<td>HCV</td>
<td>4/NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Shi et al(2014)&lt;sup&gt;46&lt;/sup&gt;</td>
<td>NAFLD</td>
<td>4/NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

### Cirrhosis

(i.e., Metavir Stage F4)

<table>
<thead>
<tr>
<th>Study</th>
<th>AUROC (95% CI)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chon et al (2012)&lt;sup&gt;60&lt;/sup&gt;</td>
<td>92% (78% to 97%)</td>
<td>86% (82% to 90%)</td>
<td></td>
</tr>
<tr>
<td>Crossan et al(2015)&lt;sup&gt;72&lt;/sup&gt;</td>
<td>74.3% (NR)</td>
<td>83% (77% to 88%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16/2614</td>
<td>0.93 (0.93 to 0.93)</td>
<td>84.6% (NR)</td>
</tr>
<tr>
<td></td>
<td>36/NR</td>
<td>NR</td>
<td>91% (89% to 93%)</td>
</tr>
<tr>
<td></td>
<td>19/NR</td>
<td>NR</td>
<td>85% (78% to 89%)</td>
</tr>
<tr>
<td></td>
<td>4/NR</td>
<td>NR</td>
<td>96% (83% to 99%)</td>
</tr>
<tr>
<td>Friedrich-Rust (2008)&lt;sup&gt;51&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Friedrich-Rust et al(2012)&lt;sup&gt;65&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Geng et al(2016)&lt;sup&gt;44&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Jiang et al (2018)&lt;sup&gt;65&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kwok et al(2014)&lt;sup&gt;52&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Li et al (2016)&lt;sup&gt;46&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Njei et al (2016)&lt;sup&gt;47&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Pavlov et al(2015)&lt;sup&gt;45&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Poynard et al(2008)&lt;sup&gt;60&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Poynard et al(2011)&lt;sup&gt;65&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Shaheen et al(2007)&lt;sup&gt;55&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Shi et al(2014)&lt;sup&gt;46&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

No summary statistics reported for transient elastography.

Concluded that transient elastography controlled attenuation parameter has good sensitivity and specificity for diagnosing steatosis, but it has limited utility.
### Significant Fibrosis (i.e., Metavir Stages F2-F4)

**AUROC (95% CI)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>AUROC (95% CI)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Steadman et al(2013)</strong>&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Multiple diseases</td>
<td>0.88 (0.84 to 0.90)</td>
<td>80% (76% to 83%)</td>
<td>81% (77% to 85%)</td>
</tr>
<tr>
<td></td>
<td>HBV</td>
<td>0.81 (0.78 to 0.84)</td>
<td>77% (68% to 84%)</td>
<td>72% (55% to 85%)</td>
</tr>
<tr>
<td></td>
<td>HCV</td>
<td>0.89 (0.86 to 0.91)</td>
<td>76% (61% to 86%)</td>
<td>86% (77% to 92%)</td>
</tr>
<tr>
<td><strong>Stebbing et al(2010)</strong>&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Multiple diseases</td>
<td>NR</td>
<td>72% (71% to 72%)</td>
<td>82% (82% to 83%)</td>
</tr>
<tr>
<td><strong>Talwalkar et al(2007)</strong>&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Multiple diseases</td>
<td>0.87 (0.83 to 0.91)</td>
<td>70% (67% to 73%)</td>
<td>84% (80% to 88%)</td>
</tr>
<tr>
<td><strong>Tschochatzis et al(2011)</strong>&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Multiple diseases</td>
<td>0.79 (74% to 82%)</td>
<td>78% (72% to 83%)</td>
<td>84% (80% to 88%)</td>
</tr>
<tr>
<td></td>
<td>HCV</td>
<td>NR</td>
<td>78% (71% to 84%)</td>
<td>80% (71% to 86%)</td>
</tr>
<tr>
<td></td>
<td>HBV</td>
<td>NR</td>
<td>84% (67% to 93%)</td>
<td>78% (68% to 85%)</td>
</tr>
<tr>
<td><strong>Tschochatzis et al(2014)</strong>&lt;sup&gt;31&lt;/sup&gt;</td>
<td>HCV</td>
<td>0.87 (0.83 to 0.90)</td>
<td>79% (74% to 84%)</td>
<td>83% (77% to 88%)</td>
</tr>
<tr>
<td></td>
<td>HBV</td>
<td>0.83 (0.76 to 0.90)</td>
<td>71% (62% to 78%)</td>
<td>84% (74% to 91%)</td>
</tr>
<tr>
<td></td>
<td>NAFLD</td>
<td>NR</td>
<td>0.96 (0.94 to 0.97)</td>
<td>0.9 (87% to 93%)</td>
</tr>
<tr>
<td><strong>Xu et al(2015)</strong>&lt;sup&gt;32&lt;/sup&gt;</td>
<td>HBV</td>
<td>0.82 (0.78 to 0.86)</td>
<td>88% (77% to 85%)</td>
<td>8% (77% to 86%)</td>
</tr>
<tr>
<td><strong>Xue-Ying(2020)</strong>&lt;sup&gt;33&lt;/sup&gt;</td>
<td>HBV</td>
<td>0.83 (0.80 to 0.86)</td>
<td>72% (68% to 76%)</td>
<td>82% (77% to 86%)</td>
</tr>
</tbody>
</table>

**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.

ALD: alcoholic liver disease; 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.
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 transient elastography (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. 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%.

Section Summary: Transient Elastography (FibroScan)

For individuals who have chronic liver disease who receive transient elastography (e.g., FibroScan), the evidence includes many systematic reviews of more than 50 observational studies (>10,000 patients). Transient elastography has been studied in populations with viral hepatitis, NAFLD, 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 a meaningful improvement in the net health outcome.

Other Noninvasive Imaging

The following noninvasive imaging types are evaluated in this section: magnetic resonance elastography (MRE), acoustic radiation force impulse (ARFI) imaging (e.g., Acuson S2000), and real-time tissue elastography (RTE; e.g., HI VISION Preirus).

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).

Tables 4 and 5 summarize the characteristics and results of systematic reviews that have assessed the diagnostic accuracy of ARFI imaging.

Table 4. Characteristics of Systematic Reviews Assessing Acoustic Radiation Force Impulse Imaging

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Studies</th>
<th>N</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bota et al (2013)</td>
<td>To May 2012</td>
<td>6</td>
<td>518</td>
<td>Chronic hepatitis</td>
</tr>
<tr>
<td>Hu et al (2017)</td>
<td>To Jul 2014</td>
<td>7</td>
<td>723</td>
<td>NAFLD</td>
</tr>
<tr>
<td>Lin et al (2020)</td>
<td>To Apr 2019</td>
<td>29</td>
<td>NR</td>
<td>Non-viral liver disease</td>
</tr>
<tr>
<td>Liu et al (2018)</td>
<td>To Apr 2016</td>
<td>23</td>
<td>2691</td>
<td>Chronic HBV or HCV</td>
</tr>
</tbody>
</table>
HBV: hepatitis B virus; HCV: hepatitis C virus; NAFLD: nonalcoholic fatty liver disease; NR: not reported.

Table 5. Results of Systematic Reviews Assessing the Diagnostic Accuracy of Acoustic Radiation Force Impulse Imaging

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Significant Fibrosis (i.e., Metavir Stages F2-F4)</th>
<th>Cirrhosis (i.e., Metavir Stage F4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Studies/ Sample Size</td>
<td>AUROC (95% CI)</td>
</tr>
<tr>
<td>Bota et al (2013)</td>
<td>Chronic hepatitis</td>
<td>6/518</td>
<td>0.88 (0.83 to 0.93)</td>
</tr>
<tr>
<td>Crossan et al (2015)</td>
<td>HCV</td>
<td>4/NR</td>
<td>NR</td>
</tr>
<tr>
<td>Guo et al (2015)</td>
<td>Multiple diseases</td>
<td>13/NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hu et al (2017)</td>
<td>HBV, HCV</td>
<td>15/NR</td>
<td>NR</td>
</tr>
<tr>
<td>Jiang et al (2018)</td>
<td>NAFLD</td>
<td>6/NR</td>
<td>0.86 (0.83 to 0.89)</td>
</tr>
<tr>
<td>Liu et al (2015)</td>
<td>NAFLD</td>
<td>7/723</td>
<td>NR</td>
</tr>
<tr>
<td>Lin et al (2020)</td>
<td>Non-viral liver disease</td>
<td>23/NR</td>
<td>0.87 (0.83 to 0.89)</td>
</tr>
<tr>
<td>Nierhoff et al (2013)</td>
<td>Multiple diseases</td>
<td>26/NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

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.

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.

Subsection Summary: Acoustic Radiation Force Impulse Imaging

The use of ARFI imaging has been evaluated in viral hepatitis and NAFLD. Moreover, many have noted that 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**

**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).

Tables 6 and 7 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 6. Characteristics of Systematic Reviews Assessing Magnetic Resonance Elastography**

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Studies</th>
<th>N</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singh et al (2015)</td>
<td>2003 to Sep 2013</td>
<td>12</td>
<td>697</td>
<td>Chronic liver disease</td>
</tr>
<tr>
<td>Xiao et al (2017)</td>
<td>To 2016</td>
<td>5</td>
<td>628</td>
<td>NAFLD</td>
</tr>
</tbody>
</table>

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

**Table 7. Results of Systematic Reviews Assessing the Diagnostic Accuracy of Magnetic Resonance Elastography**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Studies/Sample Size</th>
<th>AUROC (95% CI)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crossan et al (2015)</td>
<td>Chronic liver disease</td>
<td>3/NR</td>
<td>NR</td>
<td>94% (13% to 100%)</td>
<td>92% (72% to 98%)</td>
</tr>
<tr>
<td>Guo et al (2015)</td>
<td>Multiple diseases</td>
<td>9/NR</td>
<td>NR</td>
<td>87% (84% to 90%)</td>
<td>94% (91% to 97%)</td>
</tr>
<tr>
<td>Singh et al (2015)</td>
<td>Chronic hepatitis</td>
<td>12/697</td>
<td>0.84 (0.76 to 0.92)</td>
<td>73% (NR)</td>
<td>9% (NR)</td>
</tr>
<tr>
<td>Singh et al (2016)</td>
<td>NAFLD</td>
<td>9/232</td>
<td>0.87 (0.82 to 0.93)</td>
<td>79% (76% to 90%)</td>
<td>81% (72% to 91%)</td>
</tr>
<tr>
<td>Xiao et al (2017)</td>
<td>NAFLD</td>
<td>3/384</td>
<td>0.88 (0.83 to 0.92)</td>
<td>73.2% (65.7% to 87.3%)</td>
<td>90.7% (85.0% to 95.7%)</td>
</tr>
</tbody>
</table>

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.

Subsection Summary: 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 body mass index and degree of inflammation. However, further validation is needed to determine standard cutoffs and confirm performance characteristics because CIs for estimates are wide. MRE is also not widely available.

Real-Time Tissue Elastography (HI VISION 15 Preirus)
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).

Kobayashi et al (2015) published the results of a meta-analysis assessing RTE for staging liver fibrosis. The authors selected 15 studies (N=1,626) 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 (precision NR), 79% (95% CI, 75% to 83%), and 76% (95% CI, 68% to 82%) for detection of significant fibrosis (stage ≥ F2), and 0.72 (precision NR), 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. Thirteen studies (N=1,347 patients) 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 NR), 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.

Subsection Summary: Real-Time Tissue Elastography
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. However, there was evidence of publication bias in the systematic review and the diagnostic accuracy may be overestimated.

Section Summary: Noninvasive Radiological Methods Other Than Transient Elastography
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. Other radiologic methods (e.g., MRE, RTE, ARFI) may have similar performance for detecting significant fibrosis or cirrhosis. 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 the effects of the technology on health outcomes.

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, and alcoholic liver disease. 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 results have been used as an alternative to biopsy to establish eligibility regarding the presence of fibrosis or cirrhosis in several randomized controlled trials that showed the efficacy of hepatitis C virus treatments, which in turn demonstrated the test can identify patients who would benefit from therapy. The evidence is sufficient to determine that the technology results in a meaningful 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. 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. Cut-off thresholds have often been modified over time, may be specific to certain patient populations, and in some cases, guideline recommendations differ from cut-offs designated by manufacturers and those utilized in studies. Other multianalyte serum tests (e.g.,
aminotransferase to platelet ratio index, fibrosis-4) lack data on clinical validity and utility. There does not appear to be evidence of incremental benefit over clinical assessment using the individual laboratory assay components. 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 the effects of the technology on health outcomes.

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, nonalcoholic fatty liver disease, and alcoholic liver disease. 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 randomized controlled trials. These trials showed the efficacy of hepatitis C virus 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 a meaningful 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. Relevant outcomes are test validity, morbid events, and treatment-related morbidity. Other radiologic methods (e.g., magnetic resonance elastography, real-time transient elastography, acoustic radiation force impulse imaging) may have similar performance for detecting significant fibrosis or cirrhosis. 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 the effects of the technology on health outcomes.

Supplemental Information
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.

In response to requests Blue Cross Blue Shield Association, input was received from 3 physician specialty societies and 3 academic medical centers in 2015. Most reviewers considered noninvasive techniques for the evaluation and monitoring of chronic liver disease to be investigational, both individually and in combination.

Practice Guidelines and Position Statements
Nonalcoholic Fatty Liver Disease

American Gastroenterological Association et al
In 2018, the practice guidelines on the diagnosis and management of NAFLD, developed by the American Gastroenterological Association, the American Association for the Study of Liver
Diseases, 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).”\textsuperscript{81} This guideline also cited VCTE [vibration-controlled transient elastography] and MRE [magnetic resonance elastography] as “clinically useful tools for identifying advanced fibrosis in patients with NAFLD.”

National Institute for Health and Care Excellence
In 2016, the National Institute for Health and Care Excellence (NICE) published guidance on the assessment and management of NAFLD.\textsuperscript{46} The guidance did not reference elastography. The guidance recommended the enhanced liver fibrosis test to test for advanced liver fibrosis, utilizing a cut-off 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).\textsuperscript{36} 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
National Institute for Health and Care Excellence
In 2017, the NICE published updated guidance on the management and treatment of patients with hepatitis B.\textsuperscript{83} The guidance recommends offering transient elastography as the initial test in adults diagnosed with chronic hepatitis B, to inform the antiviral treatment decision (Table 8).

### Table 8. Antiviral Treatment Recommendations by Transient Elasticity Score

<table>
<thead>
<tr>
<th>Transient Elasticity Score</th>
<th>Antiviral Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;11 kPa</td>
<td>Offer antiviral treatment</td>
</tr>
<tr>
<td>6 to 10 kPa</td>
<td>Offer liver biopsy to confirm fibrosis level prior to offering antiviral treatment</td>
</tr>
<tr>
<td>&lt;6 kPa plus abnormal ALT</td>
<td>Offer liver biopsy to confirm fibrosis level prior to offering antiviral treatment</td>
</tr>
<tr>
<td>&lt;6 plus normal ALT</td>
<td>Do not offer antiviral treatment</td>
</tr>
</tbody>
</table>

ALT: alanine aminotransferase; kPa: kilopascal.

The NICE does not have general guidelines for hepatitis C management; however, this organization has published several drug-specific guidance documents that provide evidence-based recommendations for treating chronic hepatitis C in adults.

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 (e.g., hepatocellular carcinoma screening) Rating: Class I, Level A [evidence and/or general agreement; data derived from multiple randomized trials, or meta-analyses]”\textsuperscript{76}

The guidelines noted that there are several noninvasive tests 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.

**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). 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).

**Chronic Liver Disease**

**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. 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.

**European Association for the Study of Liver Disease et al**

In 2015, the European Association for the Study of Liver Disease and the Asociacion Latinoamericana para el Estudio del Higado convened a panel of experts to develop clinical practice guidelines on the use of noninvasive tests to evaluate liver disease severity and prognosis. The publication summarized the advantages and disadvantages of noninvasive techniques (serum biomarkers, imaging techniques). Table 9 summarizes the joint recommendations for serum biomarkers and transient elastography.

**Table 9. Recommendations for Serum Biomarkers and Transient Elastography**

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>QOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Serum biomarkers can be used in clinical practice due to high applicability (&gt;95%) and good reproducibility.&quot;</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>&quot;TE can be considered the non-invasive standard for the measure of LS&quot;</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>&quot;Serum biomarkers are well-validated for chronic viral hepatitis.... They are less well-validated for NAFLD not validated in other chronic kidney diseases.&quot;</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>&quot;For the diagnosis of significant fibrosis a combination of tests with concordance may provide the highest diagnostic accuracy&quot;</td>
<td>High</td>
<td>Weak</td>
</tr>
<tr>
<td>&quot;All HCV patients should be screened to exclude cirrhosis by TE [or] serum biomarkers....&quot;</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>&quot;Non-invasive assessment including serum biomarkers or TE can be used as first-line procedure for the identification of patients at low risk of severe fibrosis/cirrhosis&quot;</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>&quot;Follow-up assessment by either serum biomarkers or TE for progression of liver fibrosis should be used for NAFLD patients at a 3-year interval&quot;</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
</tbody>
</table>

HCV: hepatitis C virus; LS: liver stiffness; NAFLD: nonalcoholic fatty liver disease; QOE: quality of evidence; SOR: strength of recommendation; TE: transient elastography.

**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. 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.
Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 10.

Table 10. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT03938246a</td>
<td>A Phase 2, Multi-Center, Single-Blind, Randomized, Placebo-Controlled Study of TVB 2640 in Subjects With Non-Alcoholic Steatohepatitis</td>
<td>117</td>
<td>Nov 2020 (recruiting)</td>
</tr>
<tr>
<td>NCT0330165a</td>
<td>A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Pemafibrate in Patients With Nonalcoholic Fatty Liver Disease</td>
<td>100</td>
<td>May 2020 (not recruiting)</td>
</tr>
<tr>
<td>NCT03308916a</td>
<td>Screening At-risk Populations for Hepatic Fibrosis With Non-invasive Markers (SIPHON)</td>
<td>4000</td>
<td>Oct 2032 (recruiting)</td>
</tr>
<tr>
<td>NCT02037867</td>
<td>The Stratification of Liver Disease in the Community Using Fibrosis Biomarkers</td>
<td>2000</td>
<td>May 2033 (recruiting)</td>
</tr>
<tr>
<td>NCT04435054</td>
<td>Screening for NAFLD-related Advanced Fibrosis in High Risk Population in Diabetology. (NAFLD-CARE)</td>
<td>1000</td>
<td>Oct 2023 (not yet recruiting)</td>
</tr>
<tr>
<td>NCT04365855</td>
<td>The Olmsted NAFLD Epidemiology Study (TONES)</td>
<td>1000</td>
<td>Jun 2026 (not yet recruiting)</td>
</tr>
<tr>
<td>NCT04550481</td>
<td>Role of Lisinopril in Preventing the Progression of Non-Alcoholic Fatty Liver Disease, RELIEF-NAFLD Study</td>
<td>45</td>
<td>Jun 2022 (not yet recruiting)</td>
</tr>
</tbody>
</table>

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

References


Documentation for Clinical Review

Please provide the following documentation:
- History and physical and/or consultation notes including:
  - Laboratory report including: specific name and test requested
  - Reason for testing

Post Service (in addition to the above, please include the following):
- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>0166U</td>
<td>Liver disease, 10 biochemical assays (a2-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</td>
</tr>
<tr>
<td></td>
<td>0002M</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>0003M</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>0014M</td>
<td>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-related clinical events within 5 years</td>
</tr>
</tbody>
</table>
### Noninvasive Techniques for the Evaluation and Monitoring of Patients With Chronic Liver Disease

#### Type  
**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 (Code effective 8/1/2021)

#### Type  
**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) (Code effective 8/1/2021)

#### Type  
**76391**  
Magnetic resonance (e.g., vibration) elastography

#### Type  
**76981**  
Ultrasound, elastography; parenchyma (e.g., organ)

#### Type  
**76982**  
Ultrasound, elastography; first target lesion

#### Type  
**76983**  
Ultrasound, elastography; each additional target lesion (List separately in addition to code for primary procedure)

#### Type  
**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

#### Type  
**83520**  
Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified

#### Type  
**83883**  
Nephelometry, each analyte not elsewhere specified

#### Type  
**84999**  
Unlisted chemistry procedure

#### Type  
**91200**  
Liver elastography, mechanically induced shear wave (e.g., vibration), without imaging, with interpretation and report

### Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/28/2013</td>
<td>BCBSA Medical Policy adoption</td>
</tr>
<tr>
<td>09/30/2014</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>05/29/2015</td>
<td>Policy title change from Multianalyte Assays with Algorithmic Analysis for the Evaluation and Monitoring of Patients with Chronic Liver Disease Policy revision with position change</td>
</tr>
<tr>
<td>02/01/2016</td>
<td>Coding update</td>
</tr>
<tr>
<td>03/01/2017</td>
<td>Policy revision with position change</td>
</tr>
<tr>
<td>04/01/2017</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>01/01/2018</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>01/01/2019</td>
<td>Policy revision without position change Coding update</td>
</tr>
<tr>
<td>02/01/2020</td>
<td>Annual review. No change to policy statement. Literature review updated.</td>
</tr>
<tr>
<td>04/01/2020</td>
<td>Coding update</td>
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<tr>
<td>01/01/2021</td>
<td>Annual review. No change to policy statement. Literature review updated.</td>
</tr>
<tr>
<td>08/01/2021</td>
<td>Coding update</td>
</tr>
</tbody>
</table>
Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member’s illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member’s health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member’s eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.
### POLICY STATEMENT

<table>
<thead>
<tr>
<th>BEFORE</th>
<th>AFTER</th>
</tr>
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<tbody>
<tr>
<td>Noninvasive Techniques for the Evaluation and Monitoring of Patients</td>
<td>Noninvasive Techniques for the Evaluation and Monitoring of Patients</td>
</tr>
<tr>
<td>With Chronic Liver Disease 2.04.41</td>
<td>With Chronic Liver Disease 2.04.41</td>
</tr>
<tr>
<td><strong>Policy Statement:</strong></td>
<td><strong>Policy Statement:</strong></td>
</tr>
<tr>
<td>A single FibroSURE multianalyte assay may be considered *medically</td>
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</tr>
<tr>
<td>necessary* once for the evaluation of patients with chronic liver</td>
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</tr>
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<td>disease.</td>
<td>disease.</td>
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</table>

FibroSURE multianalyte assays are considered *investigational* for
monitoring of patients with chronic liver disease.

Other multianalyte assays with algorithmic analyses are considered
*investigational* for the evaluation or monitoring of patients with chronic
liver disease.

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

Transient elastography (FibroScan) imaging is considered *investigational*
for monitoring of patients with chronic liver disease.

The use of other noninvasive imaging is considered *investigational* for
the evaluation or monitoring of patients with chronic liver disease
including but not limited to *any* of the following:

I. Magnetic resonance elastography
II. Acoustic radiation force impulse imaging (ARFI; e.g., Acuson S2000)
III. Real-time tissue elastography

FibroSURE multianalyte assays are considered *investigational* for
monitoring of patients with chronic liver disease.

Other multianalyte assays with algorithmic analyses are considered
*investigational* for the evaluation or monitoring of patients with chronic
liver disease.

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

Transient elastography (FibroScan) imaging is considered *investigational*
for monitoring of patients with chronic liver disease.

The use of other noninvasive imaging is considered *investigational* for
the evaluation or monitoring of patients with chronic liver disease
including but not limited to *any* of the following:

I. Magnetic resonance elastography
II. Acoustic radiation force impulse imaging (ARFI; e.g., Acuson S2000)
III. Real-time tissue elastography