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

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 CPT MAAA codes are specific for the 3 FibroSURE™ tests performed by LabCorp:

- **HCV FibroSURE™, LabCorp**
  - **0001M**: Infectious disease, HCV, 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

- **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 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
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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

The following CPT code is a specific for elastography:

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

This policy does not address standard imaging with ultrasound or magnetic resonance imaging.

### Description

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

### 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 November 2008, Acuson S2000™ Virtual Touch (Siemens AG, Erlanger, Germany), which provides acoustic radiation force impulse imaging, was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process (K072786).

In August 2009, AIXPLORER® Ultrasound System (SuperSonic Imagine, Aix en Provence, France), which provides shear wave elastography, was cleared for marketing by the FDA through the 510(k) process (K091970).
In June 2010, Hitachi HI VISION Preirus Diagnostic Ultrasound Scanner (Hitachi Medical Systems America, Twinsburg, OH), which provides real-time tissue elastography, was cleared for marketing by the FDA through the 510(k) process (K093466).

In April 2013, FibroScan® (EchoSense SA, Paris, France), which uses transient elastography, was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process (K123806).

FDA product code: IYO

**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 can 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 to 4 (0 = no or minimal inflammation, 4 = severe) and fibrosis from 0 to 4 (0 = no fibrosis, 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 as a monitoring tool to assess response to therapy. The implications of using liver biopsy as a reference standard are discussed in the Literature Review.

**Hepatitis C Virus**

Infection with hepatitis C virus (HCV) can lead to permanent liver damage. Before noninvasive tests were available, liver biopsy is 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 one for hepatitis C is the Metavir scoring 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 and represents the final and irreversible form of disease). The stage of fibrosis is the most important single predictor of morbidity and mortality in patients with hepatitis C. Biopsies for hepatitis C 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 will develop 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 (ASH), 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 hepatitis C. 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. It 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 (NAS) system for NASH includes scores for steatosis (0-3), lobular inflammation (0-3), and ballooning (0-2). 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. In recent years, there has been growing understanding of the underlying pathophysiology of fibrosis, leading to direct measurement of the factors involved. For example, the central event in the pathophysiology of fibrosis is 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, in the setting of 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 (TIMP). Both metalloproteinases and TIMP can be measured in the serum, which directly reflects fibrotic activity. Other direct measures of ECM deposition include hyaluronic acid or $\alpha_2$-macroglobulin.

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

**FibroSURE and FibroTest**

**Hepatitis C Virus FibroSURE**

HCV FibroSURE (FibroTest) uses a combination of 6 serum biochemical indirect markers of liver function plus age and sex in a patented algorithm to generate a measure of fibrosis and necroinflammatory activity in the liver that correspond 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 $\alpha_2$-macroglobulin, haptoglobin, bilirubin, $\gamma$-glutamyl transpeptidase (GGT), ALT, and a polipoprotein AI. Developed in France, the test has been clinically available in Europe.
under the name FibroTest since 2003 and is exclusively offered by LabCorp in the United States as HCV FibroSURE.

**Alcoholic Steatohepatitis 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 and is proposed to provide surrogate markers for liver fibrosis, hepatic steatosis, and ASH. The biochemical markers include α2-macroglobulin, haptoglobin, apolipoprotein AI, bilirubin, GGT, ALT, AST, total cholesterol, triglycerides, and fasting glucose. The test has been available in Europe under the name ASH Test and is exclusively offered by LabCorp in the United States as ASH FibroSURE.

**Nonalcoholic Steatohepatitis 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 α2-macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, GGT, ALT, AST, total cholesterol, triglycerides, and fasting glucose. The test has been available in Europe under the name NASH Test and is exclusively offered by LabCorp in the United States 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, TIMP-1, and α2-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 also being evaluated as alternatives to liver biopsy. The noninvasive imaging technologies include transient elastography (e.g., FibroScan), magnetic resonance elastography (MRE), acoustic radiation force impulse imaging (ARFI; e.g., Acuson S2000), and real-time tissue elastography (RTE; 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 (US) tracks the wave, measuring its speed in kilopascals, which correlates with liver stiffness. Increases in liver fibrosis also increase liver stiffness and resistance of liver blood flow. Transient elastography does not perform as well in patients with ascites, higher body mass index, or narrow intercostal margins. Although FibroScan may be used to measure fibrosis, unlike liver biopsy, it does not provide information on necroinflammatory activity and steatosis, nor is it accurate during acute hepatitis or hepatitis exacerbations.

**Acoustic Radiation Force Impulse Imaging**
ARFI uses an US 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
MRE uses a driver to generate 60-Hz mechanical waves on the patient’s chest. The magnetic resonance equipment creates elastograms by processing the acquired images of propagating shear waves in the liver using an inversion algorithm. These elastograms represent the shear stiffness as a pixel value in kilopascals. MRE has several advantages over US elastography, including: (1) analyzing larger liver volumes; (2) analyzing liver volumes of obese patients or patients with ascites; and (3) precise analysis of viscoelasticity using a 3-dimensional displacement vector.

Real-Time Tissue Elastography
RTE is a type of strain elastography that uses a combined autocorrelation method to measure tissue strain caused by manual compression or a person’s heartbeat. The relative tissue strain is displayed on conventional color B mode US images in real time. Hitachi manufacturers the RTE devices, including one called 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. RTE can be performed in patients with ascites or inflammation. This technology does not perform as well in severely obese individuals.

Literature Review
Validation of the clinical use of any diagnostic test focuses on 3 main principles: (1) technical performance of the test; (2) diagnostic accuracy of the test (e.g., sensitivity, specificity, and positive and negative predictive values in relevant populations of patients and compared with the criterion standard); and (3) effect on patient outcomes of the test (i.e., how the results of the diagnostic test will be used to improve management of the patient).

Liver Biopsy is an Imperfect Reference Standard
As mentioned in the Background, liver biopsy is an imperfect reference standard. There is a high rate of sampling error in biopsy, which can lead to underdiagnosis of liver disease.1 This will bias estimates of performance characteristics of the noninvasive tests to which it is compared and must be considered in appraising the body of evidence. Mehta et al estimated that, under the best scenario where sensitivity and specificity of liver biopsy are 90% and the prevalence of significant disease (Metavir ≥ F2) is 40%, even a perfect alternative marker would have calculated area under the receiver operating characteristic (AUROC) curve of 0.90.3 Therefore, 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.

Although options exist for performing systematic reviews with imperfect reference standards,4 the majority of available reviews on this topic did not use any correction for the imperfect reference.

Systematic Reviews Including Multiple Noninvasive Tests
Due to the large number of primary studies published on this topic, this evidence review focuses on systematic reviews when available. The validation of multiple noninvasive tests will be assessed individually in the following sections. In this section, systematic reviews that compare several noninvasive tests will be discussed.

In a 2013 systematic review, Chou and Wasson evaluated the accuracy of a wide variety of blood tests in determining fibrosis and/or cirrhosis.5 Both “simple” tests (e.g., platelet count) and more complex scoring systems (e.g., the FibroTest and FibroIndex) were included. A total of 172 studies were identified that compared the diagnostic accuracy of blood tests with liver biopsy. Blood tests associated with AUROC curves of 0.70 or greater (range, 0.70-0.86) were considered
fair to good for identifying fibrosis, and AUROC curves of 0.80 or greater (range, 0.80-0.91) were considered good to excellent for identifying cirrhosis. Tests for identifying clinically significant fibrosis with AUROC curves of 0.70 to 0.86 included platelet count, age-platelet index, aspartate aminotransferase-platelet ratio index (APRI), FibroIndex, FibroTest, and Forns index with median positive likelihood ratios of 5 to 10 at commonly used cutoffs. Tests for identifying cirrhosis with AUROC curves of 0.80 to 0.91 included platelet count, age-platelet index, APRI, and HepaScore also with median positive likelihood ratios of 5 to 10. Most tests did not have high negative predictive values (NPV) for fibrosis, and negative likelihood ratios were found in the moderately useful range (0.10-0.20) at commonly used cutoffs, only with FibroIndex and FibroTest. This suboptimal NPV suggests that these tests perform better in identifying fibrosis than in ruling it out. Additionally, differences were small between the FibroTest or APRI and other blood tests, suggesting routinely available blood tests and simple calculations are not outperformed by additional blood tests and more complex algorithms in identifying fibrosis.

The systematic review by Crossan et al (2015) was performed for the Health Technology Assessment (HTA) program of the National Institute for Health Research. The first objective of the review was to determine the diagnostic accuracy of different noninvasive liver tests compared to 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). Three hundred two publications and presentations from 1998 to April 2012 were included. 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. APRI was also widely assessed in HBV and HCV but not in NAFLD or ALD. Estimates of diagnostic accuracy from Crossan for each test by disease are discussed in more detail in the following sections. Briefly, for diagnosing significant fibrosis (stage ≥ F2) in HCV, the summary sensitivities and specificities were: FibroScan, 79% and 83%; FibroTest, 68% and 72%; APRI (low cutoff), 82% and 57%; ARFI, 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%; 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. Failures of the test or reference standard were frequently not captured in analyses. The populations included in the studies were generally from tertiary care settings who 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.

In 2016, Houot et al reported on a systematic review funded by BioPredictive, the manufacturer of FibroTest. Reviewers 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 FIB4 index. Reviewers included studies that directly compared the tests and calculated median differences in the AUROC using Bayesian methods. There was no evaluation of the methodologic quality of the included studies. The Bayesian difference in AUROC curve for significant fibrosis (stage ≥ F2) between FibroTest and FibroScan was based on 15 studies and estimated to be 0.06 (95% credible interval [CrI], 0.02 to 0.09) favoring FibroTest. The difference in AUROC curve for cirrhosis for FibroTest versus FibroScan was based on 13 studies and estimated to be 0.00 (95% CrI, 0.04 to 0.04). The difference for advanced fibrosis between FibroTest and APRI was based on 21 studies and estimated to be 0.05 (95% CrI, 0.03 to 0.07); for cirrhosis, it was based on 14 studies and estimated to be 0.05 (95% CrI, 0.00 to 0.11), both favoring FibroTest.
Noninvasive Techniques for the Evaluation and Monitoring of Patients With Chronic Liver Disease

Multianalyte Assays
FibroSURE and FibroTest

Hepatitis C Virus
Technical Performance
Measurement of the serum levels of liver function tests (i.e., α2-macroglobulin, haptoglobin, γ-glutamyl transpeptidase [GGT], total bilirubin, apolipoprotein AI) are readily available biochemical tests. However, measurement of serum factors that directly measure fibrogenesis are relatively novel, and not readily available. Studies to formally validate the parameters used to calculate the HCV FibroSURE scores reported acceptable levels of intra laboratory and intrapatient variability.8,9

Diagnostic Accuracy
Initial research into the HCV FibroSURE algorithm involved testing an initial panel of 11 serum markers in 339 patients with liver fibrosis who had undergone liver biopsy. From the original group of 11 markers, 5 were selected as the most informative, based on logistic regression, neural connection, and receiver operating characteristic (ROC) curves. Markers included α2-macroglobulin, haptoglobin, γ-globulin, apolipoprotein AI, GGT, and total bilirubin.10 Using an algorithm-derived scoring system ranging from 0 to 1.0, authors reported that a score of less than 0.10 was associated with a NPV of 100% (i.e., absence of fibrosis, as judged by liver biopsy scores of Metavir F2-F4). A score greater than 0.60 was associated with a 90% positive predictive value (PPV) of fibrosis (i.e., Metavir F2-F4). Authors concluded that liver biopsy might be deferred in patients with a score less than 0.10.

The next step in the development of this test was 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. One study focused on patients with HCV who were participating in a randomized study of pegylated interferon and ribavirin.11 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% PPV for the diagnosis of Metavir F2-F4. The specificity was 36%, and the NPV was 40%.

Poynard et al 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.12 In this study, cutoff values were used for individual Metavir scores (i.e., F0-F4) and for combinations of Metavir scores (i.e., F0-F1, F1-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 HCV FibroSURE scoring system were 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 and to the biopsy in 18% and nonattributed 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.13,14

One Australian study attempted to independently replicate the results of FibroSURE in 125 patients with hepatitis C.15 Using the cutoff of less than 0.1 to identify lack of bridging fibrosis (i.e., Metavir stages F0-F1) and greater than 0.6 to identify fibrosis (i.e., Metavir stages F2-F4), the NPV for a score of less than 0.1 was 89%, and the PPV of a score greater than 0.6 was 78%.

In 2012, Poynard et al assessed the relative accuracy of FibroTest and FibroScan using a method to estimate performance characteristics when no perfect reference standard exists.16 The study included 1893 subjects retrospectively extracted from 4 prospective cohorts: 3 cohorts with HCV
(n=1289) and 1 cohort of healthy volunteers (n=604). Four different tests (FibroTest, FibroScan, alanine aminotransferase [ALT], liver biopsy) were performed on all patients with HCV. Latent class models with random effects were used to combine the test results to construct a reference standard. When compared to biopsy as the reference standard, the sensitivity and specificity for the diagnosis of advanced fibrosis were 85% and 66% for FibroTest and 93% and 48% for FibroScan. However, when compared to the latent class reference standard, the specificity and sensitivity for the diagnosis of advanced fibrosis were 93% and 70% for FibroTest and 96% and 45% for FibroScan.

In the Crossan (2015) systematic review, FibroTest was the most widely validated commercial serum test.6 Seventeen studies were included in the pooled estimate of the diagnostic accuracy of FibroTest for significant fibrosis (stage ≥ F2) in HCV. With varying cutoffs for positivity between 0.32 and 0.53, the summary sensitivity in HCV was 68% (95% confidence interval [CI], 58% to 77%) and specificity was 72% (95% CI, 70% to 77%). Eight studies were included for cirrhosis (stage F4) in HCV. The cutoffs for positivity ranged from 0.56 to 0.74 and the summary sensitivity and specificity were 60% (95% CI, 43% to 76%) and 86% (95% CI, 81% to 91%), respectively. Uninterpretable results were rare for tests based on serum markers.

**Effect on Patient Outcomes**

The effect on patient outcomes of a test depends on a demonstration that the test can be used to improve patient management. The primary benefit of the FibroSURE (FibroTest) for HCV is the ability to avoid liver biopsy in patients without significant fibrosis. Thus, empiric data are needed that demonstrate that the FibroSURE test impacts clinician decision making on whether a biopsy should be performed and that the net effect is to reduce the overall number of biopsies while achieving similar clinical outcomes. There are currently no such published studies to demonstrate effect on patient outcomes. However, FibroTest has been used as an alternative to biopsy to establish trial eligibility in terms of fibrosis or cirrhosis in several trials (ION-1, -3; VALENCE; ASTRAL-2, -3, -4) that established efficacy of HCV treatments.17-22 For example, in the ASTRAL-2 and -3 trials, cirrhosis could be defined by liver biopsy, FibroScan, or FibroTest score of more than 0.75 and 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 test also has potential effect on patient outcomes as a means to follow response to therapy. In this case, evidence needs to demonstrate that 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**

**Technical Performance**

As above (see the Technical Performance: Hepatitis C Virus section).

**Diagnostic Accuracy**

The diagnostic value of FibroSURE (FibroTest) has also been evaluated for the prediction of liver fibrosis in patients with ALD and NAFLD.23,24 In 2006, Thabut et al reported the development of a panel of biomarkers (ASH FibroSURE [ASH Test]) for the diagnosis of alcoholic steatohepatitis (ASH) in patients with chronic ALD.25 Biomarkers were initially assessed with a training group consisting 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 to be false negatives of the ASH Test, and 11 were suspected to be 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 sensitivity of 80% and specificity of 84% with PPVs and NPVs of 72% and 89%, respectively.

Several authors have 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 (2015) systematic review, 1 study was identified that described diagnostic accuracy of 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%) and for cirrhosis were 100% (95% CI, 95% to 100%) and 50% (95% CI, 42% to 58%), respectively.

**Effect on Patient Outcomes**
No studies were identified that assessed clinical outcomes following use of ASH FibroSURE (ASH Test).

**Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis**

**Technical Performance**
As above (see the Technical Performance: Hepatitis C Virus section).

**Diagnostic Accuracy**
In 2006, Poynard et al 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 consisting 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 end point was steatohepatitis, defined as a histologic NASH score (NAS) 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 sensitivity of 33% and specificity of 94% for NASH, with PPVs and NPVs of 66% and 81%, respectively. For borderline NASH or NASH, there was a sensitivity of 88%, specificity of 50%, PPV of 74%, and NPV of 72%. Clinically significant discordance (2 class difference) was observed in 8 (8%) patients. None of the 383 controls was 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 from France attempted to prospectively validate the NASH Test (along with the FibroTest, SteatoTest, and ActiTest) in a cohort of 288 patients treated with bariatric surgery. Included were patients with severe or morbid obesity (body mass index [BMI], >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 NASH test provided a 3-category score for no NASH (0.25), possible NASH (0.50), and NASH (0.75). The prevalence of NASH was 6.9% while the prevalence of NASH or possible NASH was 27%. The concordance rate between histologic NAS and the NASH Test was 43.1%, with a weak \( \kappa \) reliability test (0.14). In 183 patients categorized as possible NASH by the NASH Test, 124 (68%) were classified as no NASH by biopsy. In 15 patients categorized as NASH by the NASH Test, 7 (47%) were no NASH and 4 (27%) were possible NASH by biopsy. The NPV of the NASH Test for possible NASH or NASH was 47.5%. Authors suggested that the power of this study to validate agreement between the NASH Test and biopsy was low, due to the low prevalence of NASH. However, the results showed poor concordance between the NASH Test and biopsy, particularly for intermediate values.

In the Crossan (2015) systematic review, 4 studies were included in the pooled estimate of the diagnostic accuracy of FibroTest for advanced fibrosis (stage \( \geq 3 \)) in NAFLD. The summary sensitivities and specificities were 40% (95% CI, 24% to 58%) and 96% (95% CI, 91% to 98%). 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.

**Effect on Patient Outcomes**

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

**Hepatitis B Virus**

**Technical Performance**

As above (see the Technical Performance: Hepatitis C Virus section).

**Diagnostic Accuracy**

While most multianalyte assay studies that have identified fibrosis have been in patients with HCV, studies are also being conducted in patients with chronic HBV. In a 2013 study, Park et al compared liver biopsy and the FibroTest results obtained on the same day from 330 patients with 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 stages F3 or F4 (15.4%) had a significantly higher discordance rate than with stages F1 or F2 (3.0%; \( p < 0.001 \)). The only independent factor for discordance on multivariate analysis was a Metavir stages F3 or F4 on liver biopsy (\( p < 0.001 \)).

In 2014 Salkic et al conducted a meta-analysis of studies on the diagnostic accuracy of FibroTest in chronic HBV. Included in the meta-analysis were 16 studies (2494 patients) 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-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 odds ratio 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. In 2014 Xu et al reported on a systematic review and meta-analysis of studies on biomarkers to detect fibrosis in HBV. Included in the analysis on FibroTest were 11 studies (total N=1640 patients). In these 11 studies, AUROC curves ranged from 0.69 to 0.90. Heterogeneity in the studies was statistically significant.

In the Crossan (2015) systematic review, 6 studies were included in the pooled estimate of the diagnostic accuracy of FibroTest for significant fibrosis (stage \( \geq F2 \)) 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 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%).

**Effect on Patient Outcomes**
There are no studies of the effect on patient outcomes for patients with HBV. Of note, some researchers have noted that different markers (e.g., HBV FibroSURE) may be needed for this assessment in patients with hepatitis B.33

**Section Summary: FibroSURE and FibroTest**
FibroSURE (FibroTest) is the most widely validated of the noninvasive commercial serum tests. It has been studied in populations with viral hepatitis, NAFLD, and ALD. Although there are established cutoffs for positivity for FibroTest, they were not consistently used in validation studies. The methodologic quality of the validation studies was generally poor. There is no direct evidence that FibroSURE (FibroTest) improves health outcomes. However, FibroTest has been allowed as an alternative to biopsy to establish trial eligibility in terms of fibrosis or cirrhosis in several randomized controlled trials (RCTs) that established the efficacy of HCV treatments.

**FIBROSpect II**

**Technical Performance**
As previously noted, the FIBROSpect test consists of measurements of hyaluronic acid, tissue inhibitors of metalloproteinase-1 (TIMP-1), and α2-macroglobulin. In a 2004 review, Lichtinghagen and Bahr noted that the lack of standardization of assays of matrix metalloproteinases and TIMP limited the interpretation of studies.14

**Diagnostic Accuracy**
Patel et al investigated the use of these 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.34 The algorithm was designed to distinguish between no or mild fibrosis (F0-F1) and moderate-to-severe fibrosis (F2-F4). With the prevalence of F2-F4 disease of 52% and a cutoff value of 0.36, the PPVs and NPVs were 74.3% and 75.8%, respectively. Using a FIBROSpect II cutoff score of 0.42, Christensen et al reported a sensitivity of 93%, specificity of 66%, overall accuracy of 76%, and a NPV of 94% for advanced fibrosis in 136 patients with HCV.35

The published studies for this combination of markers continue to focus on test characteristics such as sensitivity, specificity, and accuracy.36-38 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%).6

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

**Section 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 uses a simple nonproprietary formula that can be calculated at the bedside to produce a score for the prediction of fibrosis.39 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>
<thead>
<tr>
<th>Disease</th>
<th>Metavir Fibrosis Stage</th>
<th>Cutoff</th>
<th>Studies</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV</td>
<td>≥ F2 (significant)</td>
<td>Low: 0.4 to 0.7</td>
<td>47</td>
<td>82% (77% to 86%)</td>
<td>57% (49% to 65%)</td>
</tr>
<tr>
<td>HCV</td>
<td>≥ F2 (significant)</td>
<td>High: 1.5</td>
<td>36</td>
<td>39% (32% to 47%)</td>
<td>92% (89% to 95%)</td>
</tr>
<tr>
<td>HCV</td>
<td>F4 (cirrhosis)</td>
<td>Low: 0.75 to 1</td>
<td>24</td>
<td>77% (73% to 81%)</td>
<td>78% (74% to 81%)</td>
</tr>
<tr>
<td>HCV</td>
<td>F4 (cirrhosis)</td>
<td>High: 2</td>
<td>19</td>
<td>48% (41% to 56%)</td>
<td>94% (91% to 95%)</td>
</tr>
<tr>
<td>HBV</td>
<td>≥ F2 (significant)</td>
<td>Low: 0.4 to 0.6</td>
<td>8</td>
<td>80% (68% to 88%)</td>
<td>65% (52% to 77%)</td>
</tr>
<tr>
<td>HBV</td>
<td>≥ F2 (significant)</td>
<td>High: 1.5</td>
<td>6</td>
<td>37% (22% to 55%)</td>
<td>93% (85% to 97%)</td>
</tr>
<tr>
<td>HBV</td>
<td>F4 (cirrhosis)</td>
<td>Low: 1</td>
<td>4</td>
<td>58% (49% to 66%)</td>
<td>76% (70% to 81%)</td>
</tr>
<tr>
<td>HBV</td>
<td>F4 (cirrhosis)</td>
<td>High: 2</td>
<td>3</td>
<td>24% (8% to 52%)</td>
<td>91% (83% to 96%)</td>
</tr>
<tr>
<td>NAFLD</td>
<td>≥ 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>
</tr>
<tr>
<td>NAFLD</td>
<td>F4 (cirrhosis)</td>
<td>0.54 and NA</td>
<td>2</td>
<td>78% (71% to 99%)</td>
<td>71% (30% to 93%)</td>
</tr>
<tr>
<td>ALD</td>
<td>≥ F2 (significant)</td>
<td>Low: 0.5</td>
<td>2</td>
<td>72% (60% to 82%)</td>
<td>46% (33% to 60%)</td>
</tr>
<tr>
<td>ALD</td>
<td>≥ F2 (significant)</td>
<td>High: 1.5</td>
<td>2</td>
<td>54% (42% to 66%)</td>
<td>78% (64% to 88%)</td>
</tr>
<tr>
<td>ALD</td>
<td>F4 (cirrhosis)</td>
<td>High: 2.0</td>
<td>1</td>
<td>40% (22% to 61%)</td>
<td>62% (41% to 79%)</td>
</tr>
</tbody>
</table>

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.

Rosenberg et al developed a scoring system based on an algorithm combining hyaluronic acid, amino terminal propeptide of type III collagen, and TIMP-1. 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%.

Giannini et al reported that 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/presence of significant fibrosis in 80.5% of these cases. In Crossan et al (2015), the cutoffs for 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 estimate diagnostic accuracy of cirrhosis with 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 ROC analysis. For example, Bourliere et al reported 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 2012 prospective multicenter study from France compared 9 of the best-evaluated blood tests in 436 patients with hepatitis C 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, algorithms that combine HCV FibroSURE (FibroTest) with other tests (e.g., APRI) are also being evaluated. One of these, the sequential algorithm for fibrosis evaluation (SAFE), combines the APRI and FibroTest. 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.
Noninvasive Imaging
The following noninvasive imaging types are reviewed here: transient elastography (e.g., FibroScan), magnetic resonance elastography (MRE), acoustic radiation force impulse imaging (ARFI; e.g., Acuson S2000), and real-time tissue elastography (RTE; e.g., HI VISION Preirus).

Transient Elastography (FibroScan)
Technical Performance
Fraquelli et al cited high intra- and interobserver agreement for transient elastography results of 96% to 98% and 89% to 98%, respectively.46 In a retrospective study of 38,464 Chinese patients with HBV, HCV, liver cirrhosis, ALD, autoimmune liver disease, and hepatocellular carcinoma, Ji et al (2014) examined clinical and biologic factors associated with TE reliability.47 Trained operators performed 10 transient elastography measurements per patient in the target area. “Unsuccessful” results were those that obtained no values after at least 10 shots. “Unreliable” results were those for which the interquartile range divided by the median was greater than 0.30 or if the median was greater than 7.1 kilopascals (kPa). Approximately 2.5% of examinations were unsuccessful and 0.85% were unreliable. Success and reliability were independently associated with BMI, female sex, age, and size of intercostal spaces. Castera et al (2010) estimated that no valid shots could be obtained in 3% of examinations while 15% of examinations produced unreliable results in a study of 13,369 examinations over a 5-year period.48 Success and reliability were associated with BMI, operator experience, age, female sex, hypertension, type 2 diabetes, and waist circumference.

Diagnostic Accuracy
There is extensive literature on the use of transient elastography to gauge liver fibrosis and cirrhosis, but the body of evidence has a number of limitations.

Summaries of systematic reviews are shown in Tables 2 and 3. Brener et al (2015) performed an HTA summarizing many of the systematic reviews below.49 The HTA 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 HTA, summarizing more than 150 primary studies.50-63 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 to 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).6 Cutoffs for positivity for fibrosis staging varied between diseases and were frequently not prespecified or validated: HCV, 5.2 to 10.1 kPa in the 37 studies for Metavir stages ≥ F2; HBV, 6.3 to 8.9 kPa in 13 studies for stages ≥ F2; NAFLD, 7.5 to 10.4 kPa in 8 studies for stages ≥ F3; ALD, 11.0 to 12.5 in 4 studies for stages ≥ F3. Summary sensitivities and specificities by disease are shown in Table 2. The overall sensitivity and specificity for cirrhosis including all diseases (65 studies; cutoffs range, 9.2-26.5 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 (Year)</th>
<th>Dates</th>
<th>Studies</th>
<th>N</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bota et al (2013)50</td>
<td>Up to May 2012</td>
<td>13</td>
<td>1163</td>
<td>Chronic hepatitis</td>
</tr>
<tr>
<td>Friedrick-Rust et al (2008)52</td>
<td>2002 to Apr 2007</td>
<td>50</td>
<td>11275</td>
<td>All causes of liver disease</td>
</tr>
<tr>
<td>Friedrick-Rust et al (2012)52</td>
<td>Up to Oct 2010</td>
<td>8</td>
<td>518</td>
<td>All causes of liver disease</td>
</tr>
</tbody>
</table>
Noninvasive Techniques for the Evaluation and Monitoring of Patients With Chronic Liver Disease

### Study (Year) | Dates | Studies | N | Population
--- | --- | --- | --- | ---
Geng et al (2016) | Up to Jan 2015 | 57 | 10569 | Multiple causes of liver disease
Shi et al (2014) | Up to May 2013 | 9 | 1771 | All causes of steatosis
Steadman et al (2013) | 2001 to Jun 2011 | 64 | 6028 | HCV, HBV, NAFLD, chronic liver disease, liver transplant
Stebbing et al (2010) | NR, prior to Feb 2009 | 22 | 4625 | All causes of liver disease
Talwalkar et al (2007) | Up to Jun 2007 | 9 | 2083 | All causes of liver disease
Tsochatzis et al (2011) | Up to May 2009 | 40 | 7661 | All causes of liver disease
Xu et al (2015) | Up to Dec 2013 | 19 | 3113 | HBV

ALD: alcoholic 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>Significant Fibrosis (i.e., Metavir Stage F2-F4) AUROC (95% CI)</th>
<th>Sensitivity (95% CI) Specificity (95% CI)</th>
<th>Cirrhosis (i.e., Metavir Stage F4) AUROC (95% CI)</th>
<th>Sensitivity (95% CI) Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bota et al (2013)</td>
<td>Multiple diseases</td>
<td>10/1016</td>
<td>0.87 (0.83 to 0.89) 78% (72% to 83%) 84% (75% to 90%)</td>
<td>13/1163</td>
<td>0.93 (0.91 to 0.95) 89% (80% to 94%) 87% (82% to 91%)</td>
</tr>
<tr>
<td>Chon et al (2012)</td>
<td>Chronic HBV</td>
<td>12/2000</td>
<td>0.86 (0.86 to 0.86) 74.3% (NR) 78.3% (NR)</td>
<td>16/2614</td>
<td>0.93 (0.93 to 0.93) 84.6% (NR) 81.5% (NR)</td>
</tr>
<tr>
<td>Crossan et al (2015)</td>
<td>HCV</td>
<td>37/NR</td>
<td>79% (74% to 84%) 83% (77% to 88%)</td>
<td>36/NR</td>
<td>89% (84% to 92%) 91% (89% to 93%)</td>
</tr>
<tr>
<td>Crossan et al (2015)</td>
<td>HBV</td>
<td>13/NR</td>
<td>71% (62% to 78%) 84% (74% to 91%)</td>
<td>19/NR</td>
<td>86% (79% to 91%) 85% (78% to 89%)</td>
</tr>
<tr>
<td>Crossan et al (2015)</td>
<td>ALD</td>
<td>1/NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Friedrick-Rust (2008)</td>
<td>Multiple diseases</td>
<td>25/3685</td>
<td>0.84 (0.82 to 0.86) NR NR</td>
<td>25/4557</td>
<td>0.94 (0.93 to 0.95) NR NR</td>
</tr>
<tr>
<td>Friedrick-Rust et al (2012)</td>
<td>Multiple diseases</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Geng et al (2016)</td>
<td>Multiple diseases</td>
<td>57/10,569</td>
<td>0.93 (NR) 81% (79% to 83%) 88% (87% to 89%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kwok et al (2014)</td>
<td>NAFLD</td>
<td>7/800</td>
<td>0.83 (0.79 to 0.87) 0.79 (0.72 to 0.84) 0.75 (0.71 to 0.79)</td>
<td>6/639</td>
<td>0.96 (0.94 to 0.99) 92% (82% to 97%) 92% (86% to 98%)</td>
</tr>
<tr>
<td>Li et al (2016)</td>
<td>HBV</td>
<td>19/NR</td>
<td>0.88 (0.85 to 0.91)</td>
<td>24/NR</td>
<td>0.93 (0.91 to 0.95)</td>
</tr>
</tbody>
</table>
## Noninvasive Techniques for the Evaluation and Monitoring of Patients With Chronic Liver Disease

### Study Significance Fibrosis (i.e., Metavir Stage F2-F4) Cirrhosis (i.e., Metavir Stage F4)

<table>
<thead>
<tr>
<th>Study</th>
<th>Significant Fibrosis (i.e., Metavir Stage F2-F4)</th>
<th>Cirrhosis (i.e., Metavir Stage F4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pavlov et al (2015)</strong></td>
<td>81% (76% to 85%) 82% (71% to 87%)</td>
<td>86% (82% to 90%) 88% (84% to 90%)</td>
</tr>
<tr>
<td><strong>Poynard et al (2008)</strong></td>
<td>94% (86% to 97%) 89% (76% to 95%)</td>
<td>95% (87% to 98%) 71% (56% to 82%)</td>
</tr>
<tr>
<td><strong>Poynard et al (2011)</strong></td>
<td>81% (76% to 85%) 82% (71% to 87%)</td>
<td>86% (82% to 90%) 88% (84% to 90%)</td>
</tr>
<tr>
<td><strong>Shaheen et al (2007)</strong></td>
<td>86% (82% to 90%) 88% (84% to 90%)</td>
<td>95% (87% to 98%) 71% (56% to 82%)</td>
</tr>
<tr>
<td><strong>Steadman et al (2013)</strong></td>
<td>45/NR 0.88 (0.84 to 0.90) 80% (76% to 83%) 81% (77% to 85%)</td>
<td>49/NR 0.94 (0.91 to 0.96) 86% (82% to 89%) 89% (87% to 91%)</td>
</tr>
<tr>
<td><strong>Stebbing et al (2010)</strong></td>
<td>5/710 0.81 (0.78 to 0.84) 77% (68% to 84%) 72% (55% to 85%)</td>
<td>8/1092 0.86 (0.82 to 0.89) 67% (57% to 75%) 87% (83% to 91%)</td>
</tr>
<tr>
<td><strong>Talwalkar et al (2007)</strong></td>
<td>13/2732 0.89 (0.86 to 0.91) 76% (61% to 86%) 86% (77% to 92%)</td>
<td>12/2887 0.94 (0.92 to 0.96) 85% (77% to 91%) 91% (87% to 93%)</td>
</tr>
<tr>
<td><strong>Tsochatzis et al (2011)</strong></td>
<td>31/5919 0.78 (0.74 to 0.82) 77% (70% to 83%) 75% (70% to 79%)</td>
<td>4/469 0.96 (0.94 to 0.97) 92% (77% to 98%) 95% (88% to 99%)</td>
</tr>
<tr>
<td><strong>Tsochatzis et al (2014)</strong></td>
<td>37/NR 0.87 (0.83 to 0.90) 79% (74% to 84%) 83% (77% to 88%)</td>
<td>36/NR 0.96 (0.94 to 0.97) 89% (84% to 92%) 91% (89% to 93%)</td>
</tr>
<tr>
<td><strong>Xu et al (2015)</strong></td>
<td>14/2318 0.82 (0.78 to 0.86) 84% (74% to 91%)</td>
<td>18/2996 0.91 (0.89 to 0.93) NR NR</td>
</tr>
</tbody>
</table>

**Note:**
- ALD: Alcoholic Liver Disease
- HBV: Hepatitis B Virus
- HCV: Hepatitis C Virus
- NAFLD: Nonalcoholic Fatty Liver Disease
- NR: Not reported.

**Comments:**
- Poynard et al (2011): Transient elastography controlled attenuation parameter has good sensitivity and specificity for diagnosing steatosis, but it has limited utility.
- Shi et al (2014): Transient elastography controlled attenuation parameter has good sensitivity and specificity for diagnosing steatosis, but it has limited utility.
- Steadman et al (2013): Transient elastography controlled attenuation parameter has good sensitivity and specificity for diagnosing steatosis, but it has limited utility.
- Talwalkar et al (2007): Transient elastography controlled attenuation parameter has good sensitivity and specificity for diagnosing steatosis, but it has limited utility.
- Tsochatzis et al (2011): Transient elastography controlled attenuation parameter has good sensitivity and specificity for diagnosing steatosis, but it has limited utility.
- Tsochatzis et al (2014): Transient elastography controlled attenuation parameter has good sensitivity and specificity for diagnosing steatosis, but it has limited utility.
- Xu et al (2015): Transient elastography controlled attenuation parameter has good sensitivity and specificity for diagnosing steatosis, but it has limited utility.
Effect on Patient Outcomes

There are currently no published studies that directly demonstrate the effect on patient outcomes of FibroScan. FibroScan is used extensively in practice to make management decisions. In addition, FibroScan was allowed as an alternative to biopsy for to diagnose fibrosis or cirrhosis to establish trial eligibility in several trials (ION-1,-3; VALENCE; ASTRAL-2, -3, -4) that confirmed efficacy of HCV treatments. For example, in the VALENCE trial, cirrhosis could be defined by liver biopsy, FibroTest, or “Fibroscan (in countries where locally approved) showing cirrhosis or results ≥ 12.5 kPa.” In VALENCE, FibroScan was used to determine cirrhosis in 74% of the participants.

Section Summary: Transient Elastography (FibroScan)

Transient elastography (FibroScan) is the most widely validated of the noninvasive methods. FibroScan has been studied in populations with viral hepatitis, NAFLD, and ALD. FibroScan validation studies have suggested that it can provide good detection of significant fibrosis and good-to-excellent detection of cirrhosis compared to liver biopsy for HCV and HBV. There are limited data on NAFLD and ALD. There are no established or validated cutoffs, and the quality of the validation studies was generally not high. Failures of the test are not uncommon, particularly for those with high BMI, but were frequently not captured in analyses of the validation studies. Newer more sensitive probes may lessen this limitation. There is no direct evidence that FibroScan improves health outcomes. However, FibroScan has been allowed as an alternative to biopsy to diagnose fibrosis or cirrhosis to establish trial eligibility in several RCTs that established efficacy of HCV treatments.

Acoustic Radiation Force Impulse Imaging

Technical Performance

Piscaglia et al (2011) demonstrated that the interoperator reproducibility of ARFI was high ($r=0.874$) in a study of 133 patients with chronic liver disease, and the method was feasible for all patients enrolled. Piscaglia et al (2011) demonstrated that the interoperator reproducibility of ARFI was high ($r=0.874$) in a study of 133 patients with chronic liver disease, and the method was feasible for all patients enrolled.68 Other measures of technical performance were not found.

Diagnostic Accuracy

The systematic reviews in Tables 4 and 5 have reported on diagnostic accuracy of ARFI.

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Dates</th>
<th>Studies</th>
<th>N</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al (2015)</td>
<td>Up to Jul 2014</td>
<td>7</td>
<td>723</td>
<td>Nonalcoholic fatty liver disease</td>
</tr>
</tbody>
</table>

<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>
<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>Nierhoff et al (2013)</td>
<td>Multiple diseases</td>
<td>26/NR</td>
<td>0.83 (0.80 to 0.86)</td>
<td>NR</td>
<td>NR</td>
<td>27/NR</td>
<td>0.91 (0.89 to 0.93)</td>
<td>NR</td>
<td>NR</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>
<td>NR</td>
<td>NR</td>
<td>92 (0.87 to 0.98)</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Crossan et al</td>
<td>HCV</td>
<td>4/NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
Noninvasive Techniques for the Evaluation and Monitoring of Patients With Chronic Liver Disease

2.04.41

### Effect on Patient Outcomes

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

### Section Summary: Acoustic Radiation Force Impulse Imaging

ARFI has been evaluated in viral hepatitis and NAFLD. ARFI has potential advantages over FibroScan; it 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 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

#### Technical Performance

A phase 1 study examined the interobserver agreement between 2 pathologists who assessed with MRE using biopsy results from 103 patients with chronic hepatitis B and C. The intraclass correlation coefficient (ICC) was very high at 0.99 (95% CI, 0.98 to 1.00). For the same patients, the ICC for these 2 pathologists using Metavir was 0.91 (95% CI, 0.86 to 0.94; difference with 23 MRE, p < 0.001). In a second phase 1 study of 110 patients and 10 normative volunteers, the ICC for 2 raters was 0.993 for MRE. The absolute differences in elasticity assigned by the 2 raters were less than 0.8 kPa for more than 95% of the subjects. Twenty-one patients had also undergone liver biopsy. Shi et al (2014) demonstrated that, in 22 healthy volunteers liver, MRE had good short and mid-term (within 6 mo) repeatability. Venkatesh et al (2014) showed that liver stiffness measurements on MRE performed 4 to 6 weeks apart in a study of 41 healthy Asian volunteers had an ICC of 0.9 (95% CI, 0.78 to 0.96) and a within-subject coefficient of variation of 2.2% to 11.4%. Yin et al (2016) retrospectively analyzed 1377 consecutive MRE examinations performed between 2007 and 2010 for patients with various chronic liver diseases. MRE had a success rate of 94% and highly reproducible measurements (r = 0.972, p < 0.001). BMI was not associated with success.

### Diagnostic Accuracy

The systematic reviews in Tables 6 and 7 summarize the diagnostic accuracy of MRE. MRE has been studied primarily in hepatitis and NAFLD.

#### Table 6. Magnetic Resonance Elastography Systematic Review Characteristics

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Dates</th>
<th>Studies</th>
<th>N</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crossan et al (2015)</td>
<td>1998 to Apr 2012</td>
<td>3</td>
<td>Not reported</td>
<td>Chronic liver disease</td>
</tr>
<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>Singh et al (2016)</td>
<td>Up to Oct 2014</td>
<td>9</td>
<td>232</td>
<td>Nonalcoholic fatty liver disease</td>
</tr>
</tbody>
</table>
Table 7. Magnetic Resonance Elastography Systematic Reviews of Diagnostic Accuracy

<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>
<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>
<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></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<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>79% (NR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| AUROC: area under the receiver operating characteristic curve; CI: confidence interval; NAFLD: nonalcoholic fatty liver disease; NR: not reported.

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

Section Summary: Magnetic Resonance Elastography
MRE has a high success rate and is highly reproducible across operators and time. The diagnostic accuracy also appears to be high. In particular, MRE has high diagnostic accuracy for detection of fibrosis in NAFLD, independent of BMI and degree of inflammation. However, further validation is needed to determine standard cutoffs and confirm performance characteristics because confidence intervals for estimates are wide. MRE is not widely available.

Real-Time Tissue Elastography (HI VISION 15 Preirus)

Technical Performance
In a study of 70 hospitalized patients with HCV, RTE was performed at 4 liver locations by 2 independent observers. The elastic ratio (ratio of the value in the intrahepatic venous small vessels divided by the value in the hepatic parenchyma) was highly correlated between the 2 examiners ($R^2=0.869, p<.001$) and consistent across liver locations ($k=0.835, ICC=0.966$). Other measures of technical performance were not found.

Diagnostic Accuracy
In 2014, Hong et al reported results of a meta-analysis RTE for staging fibrosis in multiple diseases. Thirteen studies (total N=1347 patients) published between April 2000 and April 2014 that used liver biopsy or transient elastography as the reference standard were included. Different quantitative methods were used to measure liver stiffness: Liver Fibrosis Index (LFI), Elasticity Index (EI), elastic ratio 1 (ER1), and elastic ratio 2 (ER2) in the included studies. 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 ER2 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 ER2, 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 EI were not performed due to insufficient data.

Kobayashi et al published results of a meta-analysis of RTE for staging liver fibrosis in 2015. They included 15 studies (total N=1626 patients) 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%), respectively, 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. 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.

**Effect on Patient Outcomes**

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

**Section 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.

**Combined Use of Multianalyte Assays and Noninvasive Imaging**

The combined use of multianalyte assays with algorithmic analyses and noninvasive imaging has been considered for evaluating fibrosis in patients with chronic liver disease. Few studies have evaluated the incremental accuracy of the combined use of tests.

One such algorithm was described by Castera et al (2010) and is called the Bordeaux algorithm.81 It is a synchronous test of FibroTest and FibroScan that was developed in patients with HCV. The algorithm states that if FibroScan <7.1 kPa and FibroTest ≤0.48 then fibrosis stage is F0 or F1. If FibroScan ≥7.1 and FibroTest >0.48, then fibrosis stage is ≥F2. If there is disagreement between the 2 tests then a biopsy is performed. Crossan et al (2015) found 1 study describing the performance characteristics of the Bordeaux algorithm in HCV for detecting significant (stage ≥F2) fibrosis.6 Summary sensitivity and specificity were 88% (95% CI, 85% to 91%) and 89% (95% CI, 85% to 92%), respectively. For detecting cirrhosis, summary sensitivity and specificity from 1 study were 87% (95% CI, 80% to 92%) and 95% (95% CI, 93% to 96%), respectively.

There is insufficient evidence to determine the incremental benefit of combining multianalyte assays with noninvasive imaging and its effects on health outcomes cannot be determined.

**Summary of Evidence**

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 accuracy and validity, morbid events, and treatment-related morbidity. Transient elastography (FibroScan) has been studied in populations with viral hepatitis, nonalcoholic fatty liver disease (NAFLD), and alcoholic liver disease (ALD). There are varying cutoffs for positivity. Failures of the test are not uncommon, particularly for those with high body mass index, but were frequently not captured in analyses of the 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, the FibroScan results provide data sufficiently useful to determine therapy. Specifically, FibroScan has been used as an alternative to biopsy to establish eligibility regarding presence of fibrosis or cirrhosis in several randomized controlled trials (RCTs) that showed the efficacy of hepatitis C virus (HCV) treatments, which in turn demonstrated that the test can identify patients who would benefit from therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
For individuals who have chronic liver disease who noninvasive radiologic methods other than transient elastography for liver fibrosis measurement, the evidence includes systematic reviews of observational studies. Relevant outcomes are test accuracy and validity, morbid events, and treatment-related morbidity. Other radiologic methods (acoustic radiation force impulse imaging, magnetic resonance elastography, real-time transient elastography) may have similar performance for detection of 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have chronic liver disease who receive FibroSURE (FibroTest) serum panels, the evidence includes systematic reviews of more than 30 observational studies (>5000 patients). Relevant outcomes are test accuracy and validity, morbid events, and treatment-related morbidity. 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 result provide data sufficiently useful to determine therapy. Specifically, FibroSURE has been used as an alternative to biopsy to establish eligibility regarding the presence of fibrosis or cirrhosis in several RCTs that showed the efficacy of HCV treatments, which in turn demonstrated that the test can identify patients who would benefit from therapy. 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 other than FibroSURE (FibroTest), the evidence includes systematic reviews of observational studies. Relevant outcomes are test accuracy and validity, morbid events, and treatment-related morbidity. Studies have frequently included varying cutoffs, some of which were standardized and others not validated. 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. 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 during this process, through the provision of appropriate reviewers, 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 from Blue Cross Blue Shield Association, input was received from 3 physician specialty societies and 3 academic medical centers in 2014. 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**

The 2012 practice guidelines on the diagnosis and management of nonalcoholic fatty liver disease (NAFLD), developed by the American Gastroenterological Association, the American Association for the Study of Liver Diseases (AASLD), and the American College of Gastroenterology (ACG) do not reference multianalyte assays with algorithmic analyses (MAAAs) for liver fibrosis evaluation and management.\(^{92}\) The guidelines mentioned that while
transient elastography has shown high sensitivity and specificity in identifying advanced fibrosis in patients with NAFLD, the test is not as accurate when used in patients with high body mass index.

**National Institute for Health and Care Excellence**

In July 2016, the National Institute for Health and Care Excellence (NICE) published guidance on the assessment and management of NAFLD. The guidance did not reference elastography or MAAAs. The guidance recommended the enhanced liver fibrosis test to test for advanced liver fibrosis.

**Alcoholic Liver Disease**

**American College of Gastroenterology**

The 2010 ACG guidelines on alcoholic liver disease do not reference elastography or MAAAs.

**Hepatitis B and C Viruses**

**National Institute for Health and Care Excellence**

In June 2013, NICE published guidance on the management and treatment of patients with hepatitis B. The guidance recommended offering transient elastography as the initial test in adults diagnosed with chronic hepatitis B, to inform the antiviral treatment decision (see Table 8).

<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>6-10 kPa</td>
<td>Offer liver biopsy to confirm fibrosis level prior to offering antiviral treatment</td>
</tr>
<tr>
<td>&lt;6 kPa+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.

As of September 2016, NICE has placed a pause on the development of the guidance on hepatitis C, citing instability and costs in the availability of treatments for the condition.

**American Association for the Study of Liver Diseases and Infectious Diseases Society of America**

The 2016 AASLD and Infectious Diseases Society of America (IDSA) guidelines for testing, managing, and treating hepatitis C virus (HCV) recommend that for counseling and pretreatment assessment purposes, the following should be completed:

> “Evaluation for advanced fibrosis, using liver biopsy, imaging, or noninvasive markers, is recommended in all persons with HCV infection to facilitate an appropriate decision 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]”

The guidelines note that there are several noninvasive tests to stage the degree of fibrosis in patients with hepatitis C. Tests included indirect serum biomarkers, direct serum biomarkers, and vibration-controlled liver elastography. The guidelines assert that no single method is recognized to have high accuracy alone and careful interpretation of these tests is required.

**Chronic Liver Disease**

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

The European Association for the Study of Liver Disease and the Asociacion Latinoamericana para el Estudio del Higado (EASL-ALEH) convened a panel of experts to develop clinical practice guidelines on the use of noninvasive tests to evaluate liver disease severity and prognosis, with results published in 2015. The publication provided a summary of the advantages and disadvantages of noninvasive techniques (serum biomarkers, imaging techniques). A summary of the EASL-ALEH recommendations for serum biomarkers and transient elastography is provided in Table 9.
**Table 9. EASL-ALEH Recommendations for Serum Biomarkers and Transient Elastography**

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Evidence Quality</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Serum biomarkers can be used in clinical practice due to high applicability (&gt;95%) and good reproducibility.”</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>“TE can be considered the non-invasive standard for the measure of LS.”</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>“Serum biomarkers are well-validated for chronic viral hepatitis… They are less well-validated for NAFLD not validated in other chronic kidney diseases.”</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>“For the diagnosis of significant fibrosis a combination of tests with concordance may provide the highest diagnostic accuracy”</td>
<td>High</td>
<td>Weak</td>
</tr>
<tr>
<td>“All HCV patients should be screened to exclude cirrhosis by TE [or] serum biomarkers…”</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>“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”</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>“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”</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
</tbody>
</table>

ALEH: Asociacion Latinoamericana para el Estudio del Higado; EASL: European Association for the Study of Liver Disease; HCV: hepatitis C virus; LS: liver stiffness; NAFLD: nonalcoholic fatty liver disease; TE: transient elastography.

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

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

**Ongoing and Unpublished Clinical Trials**

Some currently 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>NCT02569567</td>
<td>Comparison of Smart-Shear Wave Elastography and Transient Elastography (SMART)</td>
<td>105</td>
<td>Jun 2016 (ongoing)</td>
</tr>
<tr>
<td>NCT01789008</td>
<td>Transient Elastography in the Determination of Advanced Fibrosis in Alcoholic Liver Disease (FIBRO-OH)</td>
<td>300</td>
<td>Aug 2017</td>
</tr>
<tr>
<td>Unpublished</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02041780</td>
<td>Non Invasive Assessment of Liver Fibrosis in Children: Evaluation of Diagnostic Performances of ShearWave Elastography (SWE) and Fibrotest®/Fibromax® by Comparison With Fibrosis Score on Liver Biopsy</td>
<td>220</td>
<td>May 2016 (completed)</td>
</tr>
<tr>
<td>NCT00708617a</td>
<td>Non Invasive Diagnostic Methods for Fibrosis in Alcoholic Liver Disease: FIBROSCAN Validation and Comparison of Fibrotest - FIBROSCAN Association With FIBROSCAN Alone</td>
<td>227</td>
<td>Jul 2013 (completed)</td>
</tr>
<tr>
<td>NCT01306110</td>
<td>Screening for Liver Fibrosis by Using Non-invasive Methods in Patients With Diabetes. A Prospective Study</td>
<td>277</td>
<td>Dec 2010 (completed)</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 (if/when requested):

- History and physical and/or consultation notes including:
  - Laboratory report including: specific name and test requested
  - Reason for testing

**Post Service:**

- Results/reports of tests performed

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms.
MN/IE
The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>0001M</td>
<td>Infectious disease, HCV, 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</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>83520</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified</td>
</tr>
<tr>
<td></td>
<td>83883</td>
<td>Nephelometry, each analyte not elsewhere specified</td>
</tr>
<tr>
<td></td>
<td>84999</td>
<td>Unlisted chemistry procedure</td>
</tr>
<tr>
<td></td>
<td>91200</td>
<td>Liver elastography, mechanically induced shear wave (e.g., vibration), without imaging, with interpretation and report</td>
</tr>
<tr>
<td>HCPCS</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>ICD-10 Procedure</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All Diagnoses</td>
<td></td>
</tr>
</tbody>
</table>

**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>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/28/2013</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>09/30/2014</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</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</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>02/01/2016</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>03/01/2017</td>
<td>Policy revision with position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>04/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>
Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**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. Please call (800) 541-6652 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.