Policy Replaced with LCD L34555
Effective February 26, 2018

BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

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

Policy #: 237
Category: Medical

Latest Review Date: November 2017
Policy Grade: **B**

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
    - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
    - *Furnished in a setting appropriate to the patient's medical needs and condition;*
    - *Ordered and furnished by qualified personnel;*
    - *One that meets, but does not exceed, the patient's medical need; and*
    - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

Noninvasive techniques to monitor liver fibrosis are being investigated as alternatives to liver biopsy in patients with chronic liver disease. There are two 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).

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 Key Points.

Hepatitis C Virus

Infection with the 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.

Non-alcoholic Fatty Liver Disease (NAFLD)
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 spectrum of the disease, there is usually no appreciable inflammation, hepatocyte death, or fibrosis. In contrast, non-alcoholic 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 histological scoring systems have been used to evaluate NAFLD. The NAFLD Activity Score 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 non-invasive laboratory tests are being evaluated as an alternative 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 ALT (alanine aminotransferase), AST (aspartate aminotransferase), 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, the 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 U.S.

FibroSURE™ (Also Known as FibroTest™)

HCV FibroSURE

The HCV FibroSURE uses a combination of six 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 apolipoprotein A1. 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.

ASH FibroSURE

ASH FibroSURE™ (ASH Test) uses a combination of ten 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 alcoholic steatohepatitis (ASH). The biochemical markers include alpha-2 macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, GGT, ALT, AST, total cholesterol, triglycerides, and fasting glucose. The test has been available in Europe under the name ASH Test ™ (BioPredictive); however, and the test is exclusively offered by LabCorp in the U.S. as ASH FibroSURE.

NASH FibroSURE

NASH FibroSURE (NASH Test) uses a proprietary algorithm of the same ten biochemical markers of liver function in combination with age, gender, height, and weight and is proposed to provide surrogate markers for liver fibrosis, hepatic steatosis, and NASH. The biochemical markers include alpha-2 macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, GGT, ALT, AST, total cholesterol, triglycerides, and fasting glucose. The test has been available in Europe under the name NASH Test™ (BioPredictive); however, the test is exclusively offered by LabCorp in the United States as NASH FibroSURE.

FIBROSpect II

FIBROSpect II uses a combination of three markers that directly measure fibrogenesis of the liver, analyzed with a patented algorithm. The markers include hyaluronic acid, TIMP-1, and alpha-2 macroglobulin. FIBROSpect II is offered exclusively by Prometheus Laboratories. The measures are combined using a logistic regression algorithm to generate a FIBROSpect II index score, ranging from 1 to 100 (or sometimes reported between 0 and 1), with higher scores indicating more severe disease.

Noninvasive Imaging Technologies

Noninvasive imaging technologies to detect liver fibrosis or cirrhosis among patients with chronic liver disease are also being evaluated as an alternative 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 (e.g., HI VISION Preirus). Noninvasive imaging tests have

been used in combination with multianalyte serum tests such as FibroTest or FibroSURE with FibroScan.

Transient Elastography

Transient elastography (FibroScan®) uses a mechanical vibrator to produce mild amplitude and low-frequency (50 Hz) waves, inducing an elastic shear wave that propagates throughout the liver. Ultrasound tracks the wave, measuring its speed in kilopascals (kPa), 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 ultrasound probe to produce an acoustic "push" pulse, which generates shear waves that propagate in tissue to assess liver stiffness. ARFI elastography evaluates the wave propagation speed (measured in meters per second) to assess liver stiffness. The faster the shearwave 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 well. The magnetic resonance imaging (MRI) equipment creates elastograms by processing the acquired images of propagating shear waves in the liver using an inversion algorithm. These elastograms represent the shear stiffness as a pixel value in kilopascals. MRE has several advantages over ultrasound elastography, including: (1) the ability to analyze larger liver volumes; (2) the ability to analyze liver volumes of obese patients or patients with ascites; and (3) the ability to precisely analysis of viscoelasticity using a 3-dimensional displacement vector.

Real-Time Tissue Elastography

RTE is a type of strain elastography which uses a combined autocorrelation method to measure tissue strain caused by manual compression or a person's heartbeat. The relative tissue strain is displayed on conventional color B mode ultrasound images in real time. Hitachi 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.

Policy:

Effective for dates of service on or after February 26, 2018 refer to LCD L34555

Effective for dates of service on or after March 8, 2017 and prior to February 26, 2018:
Blue Advantage will treat **a single transient elastography (FibroScan) imaging** for the **evaluation** of patients with chronic liver disease as a **covered benefit**.

Blue Advantage will treat **transient elastography (FibroScan) imaging** for the **monitoring** of patients with chronic liver disease as a **non-covered benefit** and as **investigational**.

Blue Advantage will treat the **use of other noninvasive imaging, including but not limited to magnetic resonance elastography, acoustic radiation force impulse imaging or real-time tissue elastrography** for the evaluation or monitoring of patients with chronic liver disease as a **non-covered benefit** and as **investigational.**

For Multianalyte assays for evaluation or monitoring of patients with chronic liver disease see MolDX

Effective for dates of service prior to March 8, 2017:
Blue Advantage will treat **combined serum markers of hepatic fibrosis, evaluated with algorithms to produce a predictive score** in the diagnosis and monitoring of patients with chronic liver disease, as a **non-covered** benefit and as **investigational**.

Blue Advantage will treat **noninvasive imaging, including but not limited to transient elastography, magnetic resonance elastography, acoustic radiation force impulse imaging or real-time tissue elastrography** for the evaluation and monitoring of chronic liver disease as a **non-covered benefit** and as **investigational.**

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent literature update was through September 11, 2017.

Multiple Noninvasive Tests

As mentioned in the Description, 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. These errors will bias estimates of performance characteristics of the noninvasive tests to which it is compared, and therefore such errors must be considered in apprising the body of evidence. Mehta et al (2009) estimated that even under the best scenario where sensitivity and specificity of liver biopsy are 90%, and the prevalence of significant disease (increased liver fibrosis, scored as Metavir ≥ F2) is 40%, a perfect alternative marker would have calculated area under the receiver operating characteristic (AUROC) curve of 0.90. 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.

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

The systematic review by Crossan et al (2015) was performed for the National Institute for Health Research. The first objective of the review was to determine the diagnostic accuracy of different noninvasive liver tests compared with liver biopsy in the diagnosis and monitoring of liver fibrosis and cirrhosis in patients with hepatitis C virus (HCV), hepatitis B virus (HBV), nonalcoholic fatty liver disease (NAFLD), and alcoholic liver disease (ALD). Also included in the Crossan et al systematic review were 302 publications and presentations from 1998 to April 2012. Patients with HCV were the most common population included in the studies while patients with ALD were the least common. FibroScan and FibroTest were the most commonly assessed tests across liver diseases. Aminotransferase to platelet ratio index (APRI) was also widely assessed in HBV and HCV but not in NAFLD or ALD. The estimates of diagnostic accuracy for each test by disease (as determined by Crossan et al) are discussed in further detail in the following sections. Briefly, for diagnosing significant fibrosis (stage ≥ F2) in HCV, the summary sensitivities and specificities were: FibroScan, 79% and 83%; FibroTest, 68% and 72%; APRI (low cutoff), 82% and 57%; acoustic radiation force impulse imaging (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. Test failures or reference standard(s) were frequently not captured in analyses. Most populations included in the studies were 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.

Multianalyte Serum Assays: FibroSURE (Fibrotest)

Assessment of a diagnostic technology typically focuses on three categories of evidence: (1) analytic validity (including test-retest reliability or interrater reliability); (2) clinical validity (sensitivity, specificity, positive [PPV] and negative predictive [NPV] values) in relevant populations of patients; and (3) clinical utility (i.e., demonstration that the diagnostic information can be used to improve patient outcomes).

Clinical Context and Test Purpose

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

The question addressed in this portion of the evidence review is: Does use of the FibroSURE multianalyte serum assay for detecting liver fibrosis lead to an improvement in health outcomes in patients with chronic liver disease?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is patients with chronic liver disease.

Interventions

The intervention of interest is the FibroSURE multianalyte serum assay.

Comparators

The comparator of interest is liver biopsy, noninvasive radiologic tests, or other multianalyte serum assays.

Outcomes
The outcomes of interest are test accuracy, test validity, morbid events, and treatment-related morbidity.

Timing
The timing of testing is when patients have been diagnosed with chronic liver disease and there is a need to know the degree of liver fibrosis.

Setting
The testing would be performed in the specialty setting.

Analytic Validity
Measurement of the serum levels of liver function tests (i.e., Alpha-2 macroglobulin, haptoglobin, gamma glutamyl transpeptidase [GGT], total bilirubin, and apolipoprotein A1) 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 intra-patient variability.

Hepatitis C Virus
Clinical Validity
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, five were selected as the most informative, based on logistic regression, neural connection, and receiver operating characteristic (ROC) curves. Markers included Alpha-2 macroglobulin, haptoglobin, γ-globulin, apolipoprotein A1, gamma glutamyl transpeptidase, and total bilirubin. Using an algorithm-derived scoring system ranging from 0 to 1.0, the 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% PPV of fibrosis (i.e., Metavir F2 - F4). The 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 2003 study focused on patients with HCV who were participating in a randomized study of pegylated interferon and ribavirin. 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 (2004) also evaluated discordant results in 537 patients who underwent liver biopsy and the HCV FibroSure and ActiTest on the same day; discordance was attributed to either the limitations in the biopsy or serum markers. In this study, cutoff values were used for the 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 two stages or grades in the Metavir system. Discordance was observed in 29% of patients. Risk factors for failure of HCV FibroSure scoring system were as follows: 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 non-attributed in 8.2% of patients. As noted in two reviews, the bulk of the research on HCV FibroSure was conducted by researchers with an interest in the commercialization of the algorithm.

One (2003) Australian study attempted to independently replicate the results of FibroSure in 125 patients with hepatitis C. Using the cutoff point 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 negative predictive value for a score <0.1 was 89%, and the positive predictive value 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. The study included 1893 subjects retrospectively extracted from four prospective cohorts: three cohorts with HCV (n=1289) and one 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 with 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%, respectively, for FibroScan.

In the Crossan (2015) systematic review, FibroTest was the most widely validated commercial serum test. 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.

Clinical Utility

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 in Europe) 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 for the purpose of establishing trial eligibility in terms of fibrosis or cirrhosis; however, several trials (ION-1,-3; VALENCE; ASTRAL-2, -3, -4) have already

established efficacy of HCV treatments. 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 non-invasive tests of fibrosis to determine their comparative efficacy. In particular, the proprietary, algorithmic tests should demonstrate superiority to other readily available, non-proprietary scoring systems to demonstrate that the tests improve health outcomes.

The FibroSURE 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
Clinical Validity
The diagnostic value of FibroSURE (FibroTest in Europe) has also been evaluated for the prediction of liver fibrosis in patients with ALD and NAFLD. 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 alcoholic liver disease (ALD). Biomarkers were initially assessed with a training group consisting of 70 patients, and a panel was constructed using a combination of the six biochemical components of the FibroTest-ActiTest plus aspartate aminotransferase (AST). The algorithm was subsequently studied in two validation groups (one prospective study for severe ALD and one retrospective study for non-severe ALD) that included 155 patients and 299 controls. The severity of ASH (none, mild, moderate, and severe) was blindly assessed from biopsy samples. In the validation groups there were 28 cases (18%) of discordance between the diagnosis of ASH predicted by the ASH-Test and biopsy; ten (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 area under the ROC curves was 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 cut-off value of 0.50, the ASH-Test had sensitivity of 80% and specificity of 84%, with positive and negative predictive values 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 in the currently commercially available test that includes ten biochemicals.

FibroTest has been studied in patients with ALD. In the Crossan (2015) systematic review, one 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%), respectively. The sensitivity and specificity for cirrhosis were 100% (95% CI, 95% to 100%) and 50% (95% CI, 42% to 58%), respectively.

Clinical Utility

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

Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

Clinical Validity

In 2006, Poynard et al reported the development of a panel of biomarkers (NASH FibroSure-NASH Test) for the prediction of non-alcoholic 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 three classes for NASH (NASH, borderline NASH, or no NASH). The main endpoint was steatohepatitis, defined as a histological NASH score (NAS) of 5 or greater. The area under the ROC 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 positive and negative predictive values of 66% and 81%, respectively. For borderline NASH or NASH there was sensitivity of 88%, specificity of 50% and positive and negative predictive values of 74% and 72%. Clinically significant discordance (two class difference) was observed in eight patients (8%). None of the 383 controls were considered to have NASH by NASH FibroSure-NASH Test. Authors proposed that this test would be suitable for mass screening for NAFLD in patients with obesity and diabetes.

A 2011 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/m^2), at least one comorbidity for at least five 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 three-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 histological NAS and the NASH Test was 43.1% with a weak kappa-reliability test (0.14). In 183 patients who were 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, seven (47%) were no NASH and four (27%) were possible NASH by biopsy. The negative predictive value 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

show poor concordance between the NASH Test and biopsy, particularly for intermediate values.

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

Clinical Utility

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

Hepatitis B Virus

Clinical Validity

While most multianalyte assay studies that have identified fibrosis have been in patients with HCV, studies are also being conducted in patients with chronic hepatitis B (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 patients (9.1%) for whom the FibroTest underestimated fibrosis in 25 patients and overestimated fibrosis in five patients. Those with Metavir liver fibrosis stages F3-F4 had a significantly higher discordance rate than F1-F2 (15.4% vs 3.0%, $p<0.001$). The only independent factor for discordance on multivariate analysis was a Metavir stages F3-F4 on liver biopsy ($p<0.001$).

In 2014 Salkic et al conducted a meta-analysis of studies on the diagnostic performance 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% confidence interval [CI], 0.78 to 0.88). At the recommended FibroTest threshold of 0.48 for a significant liver fibrosis diagnosis, the sensitivity was 60.9%, specificity was 79.9%, and the diagnostic odds ratio (OR) was 6.2. For liver cirrhosis (Metavir F4) diagnosis using all of the cirrhosis studies, the AUROC curve was 0.87 (95% CI, 0.85 to 0.9). At the recommended FibroTest threshold of 0.74 for cirrhosis diagnosis, the sensitivity was 61.5%, specificity was 90.8%, and the diagnostic OR was 15.7. While the results demonstrated FibroTest may be useful in excluding a diagnosis of cirrhosis in patients with chronic HBV, the ability to detect significant fibrosis and cirrhosis and exclude significant fibrosis is suboptimal. 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, the AUROC curve ranged from 0.69 to 0.90. Heterogeneity in the studies was statistically significant.

In the Crossan (2015) systematic review, six studies were included in the pooled estimate of the diagnostic accuracy of FibroTest for significant fibrosis (stage ≥ F2) in HBV. The cutoffs for positivity ranged from 0.40 to 0.48, and the summary sensitivities and specificities were 66% (95% CI, 57% to 75%) and 80% (95% CI, 72% to 86%), respectively. The accuracy for 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%).

Clinical Utility
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.

Section Summary: FibroSURE (FibroTest)
FibroSURE 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.

Multianalyte Serum Assays: Other than FibroSURE
Clinical Context and Test Purpose
The question addressed in portion of the evidence review is: Does use of multianalyte serum assays other than FibroSURE for detecting liver fibrosis lead to an improvement in health outcomes in patients with chronic liver disease?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is patients with chronic liver disease

Interventions
The intervention of interest is multianalyte serum assays for liver function assessment other than FibroSURE.

Comparators
The comparator of interest is liver biopsy, noninvasive radiologic tests or other multianalyte serum assays.

Outcomes
The outcomes of interest are test accuracy, test validity, morbid events and treatment-related morbidity.

Timing
The timing of testing is when patients have been diagnosed with chronic liver disease and there is a need to know the degree of liver fibrosis.

Setting
The testing would be performed in the specialty setting.

FibroSpect II

Analytic Validity

The FIBROSpect test consists of measurements of hyaluronic acid, tissue inhibitors of metalloproteinase-1 (TIMP-1), and Alpha-2 macroglobulin. In a 2004 review, Lichtinghagen and Bahr noted that the lack of standardization of assays of matrix metalloproteinases and tissue inhibitors of metalloproteinase (TIMP) limited the interpretation of studies.

Clinical Validity

Patel et al (2004) 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. 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 positive and negative predictive values were 74.3% and 75.8%, respectively. Using a FibroSpect II cutoff score of 0.42, Christensen et al (2006) reported a sensitivity of 93%, specificity of 66%, overall accuracy of 76%, and a negative predictive value of 94% for advanced fibrosis in 136 patients with HCV.

The published studies for this combination of markers continue to focus on test characteristics such as sensitivity, specificity, and accuracy. In Crossan et al (2015), the summary diagnostic accuracy for detecting significant fibrosis (stage ≥ F2) in five 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%).

Clinical Utility

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

Subsection Summary: FIBROSpect II

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

Other Multianalyte Scoring Systems

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

Table 1. Diagnostic Accuracy for APRI

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

Adapted from Crossan et al (2015).
ALD: alcoholic liver disease; APRI: aspartate aminotransferase–platelet ratio index; CI: confidence interval; HBV: hepatitis B virus; HCV: hepatitis C virus; NA: not available; NAFLD: nonalcoholic fatty liver disease.

Rosenberg et al (2004) 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 (2006) 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 seven 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 one 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 non-invasive tests of fibrosis with biopsy using ROC analysis. For example, Bourliere et al (2006) reported validation of FibroSure-FibroTest and found that based on ROC analysis that FibroSure-FibroTest was superior to APRI for identifying significant fibrosis with areas under the ROC curve of 0.81 and 0.71, respectively. A 2012 prospective multicenter study from France compared nine of the best-evaluated blood tests in 436 patients with hepatitis C and found similar performance for HCV (hepatitis C virus) FibroSure-FibroTest, Fibrometer and Hepascore (ROC curve: 0.84, 0.86, 0.84, respectively). These three tests were significantly superior to the six other tests with 70-73% 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 performance, algorithms that combine HCV FibroSure-FibroTest with

other tests such as 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 four 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.

Section Summary: Multianalyte Serum Assays Other than FibroSURE
For multianalyte serum assays other than FibroSURE (e.g., FIBROSpect II), there are a number of studies; however, all of those studies have 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 and a chain of evidence cannot be constructed given the inadequate data on clinical validity.

Noninvasive Imaging
Validation of the clinical use of any diagnostic test focuses on three main principles: (1) technical reliability of the test; (2) clinical validity of the test (e.g., sensitivity, specificity, and PPV and NPV 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).

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)
Clinical Context and Test Purpose
The question addressed in this portion of the evidence review is: Does use of transient elastography for detecting liver fibrosis lead to an improvement in health outcomes in patients with chronic liver disease?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is patients with chronic liver disease.

Interventions
The intervention of interest is transient electrography.

Comparators
The comparator of interest is liver biopsy, other noninvasive radiologic tests, or multianalyte serum assays.

Outcomes
The outcomes of interest are test accuracy, test validity, morbid events, and treatment-related morbidity.

Timing
The timing of testing is when patients have been diagnosed with chronic liver disease and there is a need to know the degree of liver fibrosis.

Setting
The testing would be performed in the specialty setting.

Technical Reliability
Fraquelli et al (2007) cited high intra- and interobserver agreement for transient elastography results of 96% to 98% and 89% to 98%, respectively. 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. Trained operators performed ten transient elastography measurements per patient in the target area. "Unsuccessful" results were those that obtained no values after at least ten 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 five-year period. Success and reliability were associated with BMI, operator experience, age, female sex, hypertension, Type 2 diabetes, and waist circumference.

Clinical Validity
There is extensive literature on the use of transient elastography to gauge liver fibrosis and cirrhosis. 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. The assessment focused on reviews of the diagnostic accuracy and effect on patient outcomes of transient elastography for liver fibrosis in patients with HCV, HBV, NAFLD, ALD, or cholestatic diseases. Fourteen systematic reviews of transient elastography with biopsy reference standard shown below were included in the Brener HTA, summarizing more than 150 primary studies. There was variation in the underlying cause of liver disease and the cutoff values of transient elastography stiffness used to define Metavir stages in the systematic reviews. There did not appear to be a substantial difference in diagnostic accuracy for one 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). 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 eight studies for stages ≥

F3; ALD, 11.0 to 12.5 in four 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

Study (Year)	Dates	Studies	N	Population
Bota et al (2013)	Up to May 2012	13	1163	Chronic hepatitis
Chon et al (2012)	2002 to Mar 2011	18	2772	HBV
Crossan et al (2015)	1998 to April 2012	66	NR	HCV, HBV, NAFLD, ALD
Friedrich-Rust et al (2008)	2002 to Apr 2007	50	11275	All causes of liver disease
Friedrick-Rust et al (2012)	Up to Oct 2010	8	518	All causes of liver disease
Geng et al (2016)	Up to Jan 2015	57	10569	Multiple causes of liver disease
Kwok et al (2014)	Up to Jun 2013	22	1047	NAFLD
Li et al (2016)	Jan 2003 to Nov 2014	27	4386	HBV
Njei et al (2016)	Up to Jan 2016	3	756	HCV/HIV coinfection
Pavlov et al (2015)	Up to Aug 2014	14	834	ALD
Poynard et al (2008)	1991 to 2008	66	NR	All causes of liver disease
Poynard et al (2011)	Feb 2001 to Dec 2010	18	2714	HBV
Shaheen et al (2007)	Jan 1997 to Oct 2006	12	1981	HCV
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)		9	2083	All causes of liver disease
Tsochatzis et al (2011)	Up to May 2009	40	7661	All causes of liver disease
Tsochatzis et al (2014)	1998 to Apr 2012	302	NR	HCV, HBV, ALD, NAFLD
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

Study		**Significant Fibrosis (ie, Metavir Stage F2-F4)**		**Cirrhosis (ie, Metavir Stage F4)**	
	Population	**Studies/ Sample Size**	**AUROC (95% CI) Sensitivity (95% CI) Specificity (95% CI)**	**Studies/s Sample Size**	**AUROC (95% CI) Sensitivity (95% CI) Specificity (95% CI)**
Bota et al (2013)	Multiple diseases	10/1016	0.87 (0.83 to 0.89) 78% (72% to 83%) 84% (75% to 90%)	13/1163	0.93 (0.91 to 0.95) 89% (80% to 94%) 87% (82% to 91%)
	HCV			4/NR	NR 92% (78% to 97%) 86% (82% to 90%)
Chon et al (2012)	Chronic HBV	12/2000	0.86 (0.86 to 0.86) 74.3% (NR) 78.3% (NR)	16/2614	0.93 (0.93 to 0.93) 84.6% (NR) 81.5% (NR)
Crossan et al (2015)	HCV	37/NR	NR 79% (74% to 84%) 83% (77% to 88%)	36/NR	NR 89% (84% to 92%) 91% (89% to 93%)

Study		Significant Fibrosis (ie, Metavir Stage F2-F4)		Cirrhosis (ie, Metavir Stage F4)	
	HBV	13/NR	NR 71% (62% to 78%) 84% (74% to 91%)	19/NR	NR 86% (79% to 91%) 85% (78% to 89%)
	NAFLD			4/NR	NR 96% (83% to 99%) 89% (85% to 92%)
	ALD	1/NR	NR 81% (70% to 88%) 92% (76% to 98%)	4/NR	NR 87% (64% to 96%) 82% (67% to 91%)
Friedrich-Rust (2008)	Multiple diseases	25/3685	0.84 (0.82 to 0.86) NR NR	25/4557	0.94 (0.93 to 0.95) NR NR
	HCV	NR	0.84 (0.80 to 0.86) NR NR		
Friedrick-Rust et al (2012)	No summary statistics reported for transient elastography				
Geng et al (2016)	Multiple diseases			57/10,569	0.93 (NR) 81% (79% to 83%) 88% (87% to 89%)
Kwok et al (2014)	NAFLD	7/800	0.83 (0.79 to 0.87) 0.79 (0.72 to 0.84) 0.75 (0.71 to 0.79)	6/639	0.96 (0.94 to 0.99) 92% (82% to 97%) 92% (86% to 98%)
Li et al (2016)	HBV	19/NR	0.88 (0.85 to 0.91) 81% (76% to 85%) 82% (71% to 87%)	24/NR	0.93 (0.91 to 0.95) 86% (82% to 90%) 88% (84% to 90%)
Njei et al (2016)	HCV/HIV	6/756	NR 97% (82% to 91%) 64% (45% to 79%)	6/756	NR 90% (74% to 91%) 87% (80% to 92%
Pavlov et al (2015)	ALD	7/338	NR 94% (86% to 97%) 89% (76% to 95%)	7/330	NR 95% (87% to 98%) 71% (56% to 82%)
Poynard et al (2008)	No summary statistics reported for transient elastography				
Poynard et al (2011)	HBV	4/NR	0.84 (0.78 to 0.89) NR NR	NR	0.93 (0.87 to 0.99) NR NR
Shaheen et al (2007)	HCV	4/NR	0.84 (0.78 to 0.89) NR NR	NR	0.93 (0.87 to 0.99) NR NR
Shi et al (2014)	No summary statistics reported. Concluded that transient elastography controlled attenuation parameter has good sensitivity and specificity for diagnosing steatosis, but it has limited utility				
Steadman et al (2013)	Multiple diseases	45/NR	0.88 (0.84 to 0.90) 80% (76% to 83%) 81% (77% to 85%)	49/NR	0.94 (0.91 to 0.96) 86% (82% to 89%) 89% (87% to 91%)
	HBV	5/710	0.81 (0.78 to 0.84) 77% (68% to 84%) 72% (55% to 85%)	8/1092	0.86 (0.82 to 0.89) 67% (57% to 75%) 87% (83% to 91%)
	HCV	13/2732	0.89 (0.86 to 0.91) 76% (61% to 86%) 86% (77% to 92%)	12/2887	0.94 (0.92 to 0.96) 85% (77% to 91%) 91% (87% to 93%)
	NAFLD	5/630	0.78 (0.74 to 0.82)	4/469	0.96 (0.94 to 0.97)

Study		Significant Fibrosis (ie, Metavir Stage F2-F4)		Cirrhosis (ie, Metavir Stage F4)	
			77% (70% to 83%) 75% (70% to 79%)		92% (77% to 98%) 95% (88% to 98%)
Stebbing et al (2010)	Multiple diseases	17/3066	NR 72% (71% to 72%) 82% (82% to 83%)	17/4052	NR 84% (84% to 85%) 95% (94% to 95%)
Talwalkar et al (2007)	Multiple diseases	7/>1100	0.87 (0.83 to 0.91) 70% (67% to 73%) 84% (80% to 88%)	9/2083	0.96 (0.94 to 0.98) 87% (84% to 90%) 91% (89% to 92%)
Tsochatzis et al (2011)	Multiple diseases	31/5919	NR 79% (74% to 82%) 78% (72% to 83%)	30/6530	NR 83% (79% to 86%) 89% (87% to 91%)
	HCV	14/NR	NR 78% (71% to 84%) 80% (71% to 86%)	11/NR	NR 83% (77% to 88%) 90% (87% to 93%)
	HBV	4/NR	NR 84% (67% to 93%) 78% (68% to 85%)	6/NR	NR 80% (61% to 91%) 86% (82% to 94%)
Tsochatzis et al (2014)	HCV	37/NR	0.87 (0.83 to 0.90) 79% (74% to 84%) 83% (77% to 88%)	36/NR	0.96 (0.94 to 0.97) 89% (84% to 92%) 91% (89% to 93%)
	HBV	13/NR	0.83 (0.76 to 0.90) 71% (62% to 78%) 84% (74% to 91%)	13/NR	0.92 (0.89 to 0.96) 86% (79% to 91%) 85% (78% to 89%)
	NAFLD			4/NR	0.96 (0.94 to 0.99) 96% (83% to 99%) 89% (85% to 92%)
	ALD			6/NR	0.90 (0.87 to 0.94) 86% (76% to 92%) 83% (74% to 89%)
Xu et al (2015)	HBV	14/2318	0.82 (0.78 to 0.86) NR NR	18/2996	0.91 (0.89 to 0.93) NR NR

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

Clinical Utility

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; however, failures were frequently missed 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.

Other Noninvasive Imaging

Clinical Context and Test Purpose

The question addressed in this portion of the evidence review is: Does use of noninvasive imaging other than transient elastography for detecting liver fibrosis lead to an improvement in health outcomes in patients with chronic liver disease?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is patients with chronic liver disease.

Interventions

The intervention of interest is noninvasive imaging other than transient elastography.

Comparators

The comparator of interest is liver biopsy, other noninvasive radiologic tests, or multianalyte serum assays.

Outcomes

The outcomes of interest are test accuracy, test validity, morbid events, and treatment-related morbidity.

Timing

The timing of testing is when patients have been diagnosed with chronic liver disease and there is a need to know the degree of liver fibrosis.

Setting

The testing would be performed in the specialty setting.

Acoustic Radiation Force Impulse Imaging

Technical Reliability

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. Other measures of technical performance were not found.

Clinical Validity

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

Table 4. Acoustic Radiation Force Impulse Imaging Systematic Review Characteristics

Study (Year)	Dates	Studies	N	Population
Nierhoff et al (2013)	2007 to Feb 2012	36	3951	Multiple diseases
Bota et al (2013)	Up to May 2012	6	518	Chronic hepatitis
Crossan et al (2015)	1998 to Apr 2012	4	Not reported	Hepatitis C virus
Guo et al (2015)	Up to Jun 2013	15	2128	Multiple diseases
Liu et al (2015)	Up to Jul 2014	7	723	Nonalcoholic fatty liver disease
Hu et al (2017)	Up to Apr 2016	23	2691	Chronic Hepatitis B or C

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

Study		**Significant Fibrosis (i.e., Metavir Stages F2-F4)**		**Cirrhosis (i.e., Metavir Stage F4)**	
	Population	**Studies/ Sample Size**	**AUROC (95% CI) Sensitivity (95% CI) Specificity (95% CI)**	**Studies/ Sample Size**	**AUROC (95% CI) Sensitivity (95% CI) Specificity (95% CI)**
Nierhoff et al (2013)	Multiple diseases	26/NR	0.83 (0.80 to 0.86) NR NR	27/NR	0.91 (0.89 to 0.93) NR NR
Bota et al (2013)	Chronic hepatitis	6/518	0.88 (0.83 to 0.93) NR NR		0.92 (0.87 to 0.98) NR NR
Crossan et al (2015)	HCV	4/NR	NR 85% (69% to 94%) 89% (72% to 97%)		
Guo et al (2015)	Multiple diseases	13/NR	NR 76% (73% to 78%) 80% (77% to 83%)	14/NR	NR 88% (84% to 91%) 80% (81% to 84%)
Liu et al (2016)	NAFLD	7/723	NR 80% (76% to 84%) 85% (81% to 89%)		
Hu et al (2017)	HBV/HCV	15/NR	88% (85% to 91%) 75% (69% to 78%) 85% (81% to 89%)		

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

Clinical Utility

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

Subsection Summary: Acoustic Radiation Force Impulse Imaging

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

A 2014 Phase 1 study examined the interobserver agreement between two pathologists who assessed with MRE using biopsy results from103 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 two 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 ten normative volunteers, the ICC for two raters was 0.993 for MRE. The absolute differences in elasticity assigned by the two 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 four to six 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.

Clinical Validity

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

Study (Year)	Dates	Studies	N	Population
Crossan et al (2015)	1998 to Apr 2012	3	Not reported	Chronic liver disease
Guo et al (2015)	Up to Jun 2013	11	982	Multiple diseases
Singh et al (2015)	2003 to Sep 2013	12	697	Chronic liver disease
Singh et al (2016)	Up to Oct 2014	9	232	Nonalcoholic fatty liver disease

Table 7. Magnetic Resonance Elastography Systematic Reviews of Diagnostic Accuracy

Study		**Significant Fibrosis (i.e., Stage F2-F4)**		**Cirrhosis (i.e., Stage F4)**	
	Population	**Studies/ Sample Size**	**AUROC (95% CI) Sensitivity (95% CI) Specificity (95% CI)**	**Studies/ Sample Size**	**AUROC (95% CI) Sensitivity (95% CI) Specificity (95% CI)**
Crossan et al (2015)	Chronic liver disease	3/NR	NR 94% (13% to 100%) 92% (72% to 98%)		
Guo et al (2015)	Multiple diseases	9/NR	NR 87% (84% to 90%) 94% (91% to 97%)		NR 93% (88% to 96%) 91% (88% to 93%)
Singh et al (2015)	Chronic hepatitis	12/697	0.84 (0.76 to 0.92) 73% (NR) 79% (NR)	12/697	0.92 (0.90 to 0.94) 91% (NR) 81% (NR)
Singh et al (2016)	NAFLD	9/232	0.87 (0.82 to 0.93) 79% (76% to 90%) 81% (72% to 91%)	9/232	0.91 (0.76 to 0.95) 88% (82% to 100%) 87% (77% to 97%)

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

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

Subsection 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 Reliability
In a study of 70 hospitalized patients with HCV, RTE using the HI VISION 15 Preirus was performed at four liver locations by two 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 two examiners ($R2=0.869$, $p<.001$) and consistent across liver locations ($\kappa=0.835$, ICC=0.966). Other measures of technical performance were not found.

Clinical Validity
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.

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

Subsection Summary: Real-Time Tissue Elastography
RTE has been evaluated in multiple diseases with varying scoring methods and cutoffs. Although data are limited, the accuracy of RTE appears to be similar to FibroScan for the evaluation of significant liver fibrosis, but less accurate for the evaluation of cirrhosis. However, there was evidence of publication bias in the systematic review and the diagnostic accuracy may be overestimated.

Section Summary: Noninvasive Radiological Methods Other Than Transient Elastography
The available studies suggest that other radiologic methods (AFRI, MRE, RTE) may have similar performance for detection of significant fibrosis or cirrhosis. However, the 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 and an indirect chain cannot be constructed due to the lack of sufficient evidence on clinical validity.

Summary of Evidence
Multianalyte Serum Assays
For individuals who have chronic liver disease who receive FibroSURE serum panels, the evidence includes systematic reviews of more than 30 observational studies (>5000 patients). Relevant outcomes are test accuracy and validity, morbid events, and treatment-related morbidity. FibroSURE has been studied in populations with viral hepatitis, nonalcoholic fatty liver disease, and alcoholic liver disease. There are established cutoffs, although they were not consistently used in validation studies. Given these limitations and the imperfect reference standard, it is difficult to interpret performance characteristics. However, for the purposes of deciding whether a patient has severe fibrosis or cirrhosis, FibroSURE results provide data sufficiently useful to determine therapy. Specifically, FibroSURE 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 hepatitis C virus treatments, which in turn demonstrated that the test can identify patients who would benefit from therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have chronic liver disease who receive multianalyte serum assays for liver function assessment other than FibroSURE, 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; further, it is not possible to construct a chain of evidence for clinical utility due to the lack of sufficient evidence on clinical validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

Noninvasive Imaging

For individuals who have chronic liver disease who receive transient elastography, the evidence includes many systematic reviews of more than 50 observational studies (>10,000 patients). Relevant outcomes are test accuracy and validity, morbid events, and treatment-related morbidity. Transient elastography (FibroScan) has been studied in populations with viral hepatitis, nonalcoholic fatty liver disease, and alcoholic liver disease. There are varying cutoffs for positivity. Failures of the test are not uncommon, particularly for those with high body mass index, but these failures often went undetected in analyses of the validation studies. Given these limitations and the imperfect reference standard, it can be difficult to interpret performance characteristics. However, for the purposes of deciding whether a patient has severe fibrosis or cirrhosis, the FibroScan results provide data sufficiently useful to determine therapy. In fact, FibroScan has been used as an alternative to biopsy to establish eligibility regarding the presence of fibrosis or cirrhosis in the participants of several RCTs. These RCTs showed the efficacy of hepatitis C virus treatments, which in turn demonstrated that the test can identify patients who would benefit from therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have chronic liver disease who receive noninvasive radiologic methods other than transient elastography for liver fibrosis measurement, the evidence includes systematic reviews of observational studies. Relevant outcomes are test accuracy and validity, morbid events, and treatment-related morbidity. Other radiologic methods (e.g., magnetic resonance elastography, real-time transient elastography, acoustic radiation force impulse imaging) may have similar performance for detecting significant fibrosis or cirrhosis. Studies have frequently included varying cutoffs not prespecified or validated. Given these limitations and the imperfect reference standard, it is difficult to interpret performance characteristics. There is no direct evidence that other noninvasive radiologic methods improve health outcomes; further, it is not possible to construct a chain of evidence for clinical utility due to the lack of sufficient evidence on clinical validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

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. 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 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

multianalyte assays with algorithmic analyses. The guidance recommended the enhanced liver fibrosis test to test for advanced liver fibrosis.

American College of Gastroenterology
In 2017, the American College of Gastroenterology published guidelines on the role of elastography in chronic liver disease. The guidelines indicated that, in adults with NAFLD, vibration-controlled transient elastography (VCTE) has better diagnostic performance for diagnosing cirrhosis than the aspartate aminotransferase to platelet ratio index and Fibrosis-4 Index (FIB-4) (very low quality of evidence). Moreover, the guidelines stated that, in adults with NAFLD, magnetic resonance-guided elastography has little or no increased diagnostic accuracy for identifying cirrhosis compared with VCTE in patients who have cirrhosis, and has higher diagnostic accuracy than VCTE in patients who do not have cirrhosis (very low quality of evidence).

Hepatitis B and C Viruses
National Institute for Health and Care Excellence
In 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 8. Antiviral Treatment Recommendations by Transient Elasticity Score

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

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.

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

Chronic Liver Disease
American College of Radiology
The 2017 American College of Radiology appropriateness criteria rated 1-dimensional transient elastography as a 7 (usually appropriate) for the diagnosis of liver fibrosis in patients with chronic liver disease. The criteria noted, "This procedure is less reliable in diagnosing liver fibrosis and cirrhosis in patients with obesity or ascites."

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 joint recommendations for serum biomarkers and transient elastography is provided in Table 9.

Table 9. Recommendations for Serum Biomarkers and Transient Elastography

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

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

U.S. Preventive Services Task Force Recommendations
Not applicable.

Key Words:

Serum markers, liver fibrosis, chronic liver disease, FibroSure™, FibroSpect, FibroTest™, biochemical markers, biochemical serum markers, Fibroscan®, Acuson S2000™, HI VISION™ Preirus™, AIXPLORER®, Virtual Touch

Approved by Governing Bodies:

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 FDA through the 510(k) process (K091970).

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

In April 2013, FibroScan® (EchoSens, 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).

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

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:

CPT code:

83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
83883	Nephelometry, each analyte not elsewhere specified
84999	Unlisted chemistry procedure
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 **(Effective 09/15/2012)**
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) **(Effective 09/15/2012)**
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) **(Effective 09/15/2012)**
91200	Liver elastography, mechanically induced shear wave (e.g., vibration), without imaging, with interpretation and report

If liver elastography is performed with ultrasound imaging, the following CPT category III code would be reported for the elastography in addition to the code for the ultrasound:

0346T	Ultrasound, elastography (**Effective 01/01/2014**)

References:

1. Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. Apr 17 2014; 370(16):1483-1493.
2. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. May 15 2014; 370(20):1889-1898.
3. Afdhal NH, Nunes D. Evaluation of liver fibrosis: A concise review. Am J Gastroenterol 2004; 99:1160-74.
4. American Association for the Study of Liver Diseases and Infectious Diseases Society of America. Recommendations for Testing, Managing, and Treating Hepatitis C. 2016; hcvguidelines.org/sites/default/files/HCV-Guidance_October_2016_a.pdf. Accessed September 28, 2017.
5. American Medical Association (AMA). Multianalyte Assays with Algorithmic Analyses (MAAA) for 2013. MAAA v2 Mar 16, 2012.
6. Blue Cross Blue Shield Association Technology Evaluation Center (TEC). Use of noninvasive imaging to detect liver fibrosis and cirrhosis among patients with chronic Hepatitis C. TEC Assessments 2014; June 2014. [in press]
7. Bota S, Herkner H, Sporea I, et al. Meta-analysis: ARFI elastography versus transient elastography for the evaluation of liver fibrosis. Liver Int. Sep 2013; 33(8):1138-1147.
8. Bourliere M, Penaranda G, et al. Validation and comparison of indexes for fibrosis and cirrhosis prediction in chronic hepatitis C patients: Proposal for a pragmatic approach classification without liver biopsies. J Viral Hepat 2006; 13(10): 659-670.
9. Boursier J, de Ledinghen V, Zarski JP et al. Comparison of eight diagnostic algorithms for liver fibrosis in hepatitis C: new algorithms are more precise and entirely noninvasive. Hepatology 2012; 55(1):58-67.
10. Brener S. Transient elastography for assessment of liver fibrosis and steatosis: an evidence-based analysis. Ont Health Technol Assess Ser. 2015; 15(18):1-45.
11. Castera L, Foucher J, Bernard PH, et al. Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. Hepatology. Mar 2010; 51(3):828-835.

12. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology. Jun 2012; 142(7):1592-1609.
13. Cho SW and Cheong JY. [Clinical application of non-invasive diagnosis for hepatic fibrosis]. Korean J Hepatol, June 2007; 13(2): 129-137. (Abstract)
14. Chou R, Wasson N. Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection: a systematic review. Ann Intern Med. Jun 4 2013; 158(11):807-820.
15. Christensen C, Bruden D, Livingston S, et al. Diagnostic accuracy of a fibrosis serum panel (FIBROSpectII) compared with Knodell and Ishak liver biopsy scores in chronic hepatitis C patients. J Viral Hepat 2006; 13(10): 652-658.
16. Crossan C, Tsochatzis EA, Longworth L, et al. Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: systematic review and economic evaluation. Health Technol Assess. Jan 2015; 19(9):1-409, v-vi.
17. Curry MP, O'Leary JG, Bzowej N, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med. Dec 31 2015; 373(27):2618-2628.
18. European Association for Study of Liver. Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol. Jul 2015; 63(1):237-264.
19. Ferraioli G, Tinelli C, Malfitano A, et al. Performance of real-time strain elastography, transient elastography, and aspartate-to-platelet ratio index in the assessment of fibrosis in chronic hepatitis C. AJR Am J Roentgenol. Jul 2012; 199(1):19-25.
20. Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. N Engl J Med. Dec 31 2015; 373(27):2608-2617.
21. Foucher J, Chanteloup E, Vergniol J, et al. Diagnosis of cirrhosis by transient elastography (FibroScan): A prospective study. Gut 2006; 55(3): 403-408.
22. Fraquelli M, Rigamonti C, Casazza G, et al. Reproducibility of transient elastography in the evaluation of liver fibrosis in patients with chronic liver disease. Gut. Jul 2007; 56(7):968-973.
23. Friedrich-Rust M, Nierhoff J, Lupsor M, et al. Performance of Acoustic Radiation Force Impulse imaging for the staging of liver fibrosis: a pooled meta-analysis. J Viral Hepat. Feb 2012; 19(2):e212-219.
24. Geng XX, Huang RG, Lin JM, et al. Transient elastography in clinical detection of liver cirrhosis: A systematic review and meta-analysis. Saudi J Gastroenterol. Jul-Aug 2016; 22(4):294-303.
25. Giannini EG, Zaman A, Ceppa P, et al. A simple approach to noninvasively identifying significant fibrosis in chronic hepatitis C patients in clinical practice. J Clin Gastroenterol 2006; 40(6): 521-527.
26. Guo Y, Parthasarathy S, Goyal P, et al. Magnetic resonance elastography and acoustic radiation force impulse for staging hepatic fibrosis: a meta-analysis. Abdom Imaging. Apr 2015; 40(4):818-834.
27. Halfon, P, Imbert-Bismut F, et al. A prospective assessment of the interlaboratory variability of biochemical markers of fibrosis (FibroTest) and activity test (ActiTest) in patients with chronic liver disease. Comp Hepatol 2002; 1:3.

28. Hong H, Li J, Jin Y, et al. Performance of real-time elastography for the staging of hepatic fibrosis: a meta-analysis. PLoS One. 2014; 9(12):e115702.
29. Houot M, Ngo Y, Munteanu M, et al. Systematic review with meta-analysis: direct comparisons of biomarkers for the diagnosis of fibrosis in chronic hepatitis C and B. Aliment Pharmacol Ther. Jan 2016; 43(1):16-29.
30. Ichikawa S, Motosugi U, Ichikawa T, et al. Magnetic resonance elastography for staging liver fibrosis in chronic hepatitis C. Magn Reson Med Sci. 2012;11(4):291-297.
31. Imbert-Bismut F, Messous D, et al. Intra-laboratory analytical variability of biochemical markers of fibrosis (FibroTest) and activity (ActiTest) and reference ranges in health blood donors. Clinic Chem Lab Med 2004; 42: 323-333.
32. Imbert-Bismut F, Ratio V, et al. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: A prospective study. Lancet 2001; 357: 1069-75.
33. Ji D, Shao Q, Han P, et al. The frequency and determinants of liver stiffness measurement failure: a retrospective study of "real-life" 38,464 examinations. PLoS One. 2014; 9(8):e105183.
34. Kobayashi K, Nakao H, Nishiyama T, et al. Diagnostic accuracy of real-time tissue elastography for the staging of liver fibrosis: a meta-analysis. Eur Radiol. Jan 2015; 25(1):230-238.
35. Koizumi Y, Hirooka M, Kisaka Y, et al. Liver fibrosis in patients with chronic hepatitis C: noninvasive diagnosis by means of real-time tissue elastography--establishment of the method for measurement. Radiology. Feb 2011; 258(2):610-617.
36. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. May 15 2014; 370(20):1879-1888.
37. Lassailly G, Caiazzo R, Hollebecque A et al. Validation of noninvasive biomarkers (FibroTest, SteatoTest, and Nash Test) for prediction of liver injury in patients with morbid obesity. Eur J Gastroenterol Hepatol 2011; 23(6):499-506.
38. Li Y, Huang YS, Wang ZZ, et al. Systematic review with meta-analysis: the diagnostic accuracy of transient elastography for the staging of liver fibrosis in patients with chronic hepatitis B. Aliment Pharmacol Ther. Feb 2016; 43(4):458-469.
39. Lichtinghagen R, Bahr MJ. Noninvasive diagnosis of fibrosis in chronic liver disease. Expert Rev Mol Diagn 2004; 4:715-26.
40. Liu H, Fu J, Hong R, et al. Acoustic radiation force impulse elastography for the non-invasive evaluation of hepatic fibrosis in non-alcoholic fatty liver disease patients: a systematic review & meta-analysis. PLoS One. 2015; 10(7):e0127782.
41. Liu H, Fu J, Hong R, et al. Acoustic radiation force impulse elastography for the non-invasive evaluation of hepatic fibrosis in non-alcoholic fatty liver disease patients: a systematic review & meta-analysis. PLoS One. Jul 2015; 10(7):e0127782.
42. Mehta P, Ploutz-Snyder R, Nandi J, et al. Diagnostic accuracy of serum hyaluronic acid, FIBROSpect II, and YKL-40 for discriminating fibrosis stages in chronic hepatitis C. Am J Gastroenterol, April 2008; 103(4): 928-936.
43. Mehta SH, Lau B, Afdhal NH, et al. Exceeding the limits of liver histology markers. J Hepatol. Jan 2009; 50(1):36-41.
44. Mohamadnejad M, Montazeri G, Fazlollahi A, et al. Noninvasive markers of liver fibrosis and inflammation in chronic hepatitis B-virus related liver disease. Am J Gastroenterol 2006; 101(11): 2537-2545.

45. National Institute for Health and Care Excellence (NICE). Hepatitis B (chronic): diagnosis and management [CG165]. 2013 June; www.nice.org.uk/guidance/CG165/chapter/1-Recommendations. Accessed September 28, 2017.
46. National Institute for Health and Care Excellence (NICE). Non-alcoholic fatty liver disease (NAFLD): assessment and management [NG49]. 2016; www.nice.org.uk/guidance/ng49. Accessed September 28, 2017.
47. Naveau S, Raynard B, Ratziu V et al. Biomarkers for the prediction of liver fibrosis in patients with chronic alcoholic liver disease. Clin Gastroenterol Hepatol 2005; 3(2):167-74.
48. Nierhoff J, Chavez Ortiz AA, Herrmann E, et al. The efficiency of acoustic radiation force impulse imaging for the staging of liver fibrosis: a meta-analysis. Eur Radiol. Nov 2013; 23(11):3040-3053.
49. Njei B, McCarty TR, Luk J, et al. Use of transient elastography in patients with HIV-HCV coinfection: A systematic review and meta-analysis. J Gastroenterol Hepatol. Oct 2016; 31(10):1684-1693.
50. O'Shea RS, Dasarathy S, McCullough AJ, et al. Alcoholic liver disease. Hepatology. Jan 2010; 51(1):307-328.
51. Park MS, Kim BK, Cheong JY, et al. Discordance between liver biopsy and FibroTest in assessing liver fibrosis in chronic hepatitis B. PLoS One. 2013; 8(2):e55759.
52. Patel K, Gordon SC, et al. Evaluation of a panel of non-invasive serum markers to differentiate mild from moderate-to-advanced liver fibrosis in chronic hepatitis C patients. J Hepatol 2004; 41:935-42.
53. Patel K, Nelson DR, Rockey DC, et al. Correlation of FIBROSpect II with histologic and morphometric evaluation of liver fibrosis in chronic hepatitis C. Clin Gastroenterol Hepatol, February 2008; 6(2): 242-247.
54. Pavlov CS, Casazza G, Nikolova D, et al. Transient elastography for diagnosis of stages of hepatic fibrosis and cirrhosis in people with alcoholic liver disease. Cochrane Database Syst Rev. 2015; 1:CD010542.
55. Piscaglia F, Salvatore V, Di Donato R, et al. Accuracy of VirtualTouch Acoustic Radiation Force Impulse (ARFI) imaging for the diagnosis of cirrhosis during liver ultrasonography. Ultraschall Med. Apr 2011; 32(2):167-175.
56. Poynard T, de Ledinghen V, Zarski JP, et al. Relative performances of FibroTest, Fibroscan, and biopsy for the assessment of the stage of liver fibrosis in patients with chronic hepatitis C: a step toward the truth in the absence of a gold standard. J Hepatol. Mar 2012; 56(3):541-548.
57. Poynard T, McHutchison J, et al. Biochemical surrogate markers of liver fibrosis and activity in a randomized trial of peginterferon alfa 2b and ribavirin. Hepatol 2003; 38:481-92.
58. Poynard T, Muntreanu M, et al. Prospective analysis of discordant results between biochemical markers and biopsy in patients with chronic hepatitis C. Clin Chemistry 2004; 50:1344-55.
59. Poynard T, Ratziu V, Charlotte F et al. Diagnostic value of biochemical markers (NashTest) for the prediction of nonalcoholic steatohepatitis in patients with non-alcoholic fatty liver disease. BMC Gastroenterol 2006; 6:34.
60. Ratziu V, Massard J, Charlotte F et al. Diagnostic value of biochemical markers (FibroTest-FibroSURE) for the prediction of liver fibrosis in patients with non-alcoholic fatty liver disease. BMC Gastroenterol 2006; 6:6.

61. Regev A, Berho M, Jeffers LJ, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol. Oct 2002; 97(10):2614-2618.
62. Rockey DC and Bissell DM. Noninvasive measures of liver fibrosis. Hepatology 2006; 43 (2 Suppl 1): S113-120.
63. Rockey DC, Caldwell SH, Goodman ZD, et al. Liver biopsy. Hepatology. Mar 2009; 49(3):1017-1044.
64. Rosenberg WMC, Voelker M, et al. Serum markers detect the presence of liver fibrosis: A cohort study. Gastroenterol 2004; 127:1704-13.
65. Rossi E, Adams L, et al. Validation of the FibroTest biochemical markers score in assessing liver fibrosis in hepatitis C patients. Clin Chem 2003; 49:450-54.
66. Runge JH, Bohte AE, Verheij J, et al. Comparison of interobserver agreement of magnetic resonance elastography with histopathological staging of liver fibrosis. Abdom Imaging. Apr 2014; 39(2):283-290.
67. Salkic NN, Jovanovic P, Hauser G, et al. FibroTest/Fibrosure for significant liver fibrosis and cirrhosis in chronic Hepatitis B: a meta-analysis. Am J Gastroenterol. Jun 2014; 109(6):796-809.
68. Sebastiani G, Halfon P, Castera L et al. SAFE biopsy: a validated method for large-scale staging of liver fibrosis in chronic hepatitis C. Hepatology 2009; 49(6):1821-7.
69. Sebastiani G, Vario A, Guido M and Alberti A. Performance of noninvasive markers for liver fibrosis is reduced in chronic hepatitis C with normal transaminases. J Viral Hepat, March 2008; 15(3): 212-218.
70. Shi Y, Guo Q, Xia F, et al. Short- and midterm repeatability of magnetic resonance elastography in healthy volunteers at 3.0 T. Magn Reson Imaging. Jul 2014; 32(6):665-670.
71. Singh S, Venkatesh SK, Loomba R, et al. Magnetic resonance elastography for staging liver fibrosis in non-alcoholic fatty liver disease: a diagnostic accuracy systematic review and individual participant data pooled analysis. Eur Radiol. May 2016; 26(5):1431-1440.
72. Singh S, Venkatesh SK, Wang Z, et al. Diagnostic performance of magnetic resonance elastography in staging liver fibrosis: a systematic review and meta-analysis of individual participant data. Clin Gastroenterol Hepatol. Mar 2015; 13(3):440-451 e446.
73. Snyder N, Nguyen A, Gajula L, et al. The APRI may be enhanced by the use of the FIBROSpect II in the estimation of fibrosis in chronic hepatitis C. Clin Chim Acta, June 2007; 381(2): 119-123.
74. Steadman R, Myers RP, Leggett L, et al. A health technology assessment of transient elastography in adult liver disease. Can J Gastroenterol. Mar 2013; 27(3):149-158.
75. Stebbing J, Farouk L, Panos G, et al. A meta-analysis of transient elastography for the detection of hepatic fibrosis. J Clin Gastroenterol. Mar 2010; 44(3):214-219.
76. Thabut D, Naveau S, Charlotte F et al. The diagnostic value of biomarkers (AshTest) for the prediction of alcoholic steato-hepatitis in patients with chronic alcoholic liver disease. J Hepatol 2006; 44(6):1175-85.
77. Thuluvath PJ and Krok KL. Noninvasive markers of fibrosis for longitudinal assessment of fibrosis in chronic liver disease: Are they ready for prime time? Am J Gastroenterol 2005; 100(9): 1981-1983.
78. Trikalinos TA, Balion CM. Chapter 9: options for summarizing medical test performance in the absence of a "gold standard". J Gen Intern Med. Jun 2012; 27 Suppl 1:S67-75.

79. Tsochatzis EA, Gurusamy KS, Ntaoula S, et al. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. J Hepatol. Apr 2011; 54(4):650-659.
80. Venkatesh SK, Wang G, Teo LL, et al. Magnetic resonance elastography of liver in healthy Asians: normal liver stiffness quantification and reproducibility assessment. J Magn Reson Imaging. Jan 2014; 39(1):1-8.
81. Wai CT, Cheng CL, Wee A, et al. Non-invasive models for predicting histology in patients with chronic hepatitis B. Liver Int 2006; 26(6): 666-672.
82. Wai CT, Greenson JK, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatol 2003; 38:518-26.
83. Xu X, Su Y, Song R, et al. Performance of transient elastography assessing fibrosis of single hepatitis B virus infection: a systematic review and meta-analysis of a diagnostic test. Hepatol Int. Oct 2015; 9(4):558-566.
84. Xu XY, Kong H, Song RX, et al. The effectiveness of noninvasive biomarkers to predict hepatitis B-related significant fibrosis and cirrhosis: a systematic review and meta-analysis of diagnostic test accuracy. PLoS One. 2014; 9(6):e100182.
85. Yin M, Glaser KJ, Talwalkar JA, et al. Hepatic MR Elastography: clinical performance in a series of 1377 consecutive examinations. Radiology. Jan 2016; 278(1):114-124.
86. Zarski JP, Sturm N, Guechot J et al. Comparison of nine blood tests and transient elastography for liver fibrosis in chronic hepatitis C: the ANRS HCEP-23 study. J Hepatol 2012; 56(1):55-62.
87. Zeng MD, Lu LG, Mao YM, et al. Prediction of significant fibrosis in HBeAG-positive patients with chronic hepatitis B by a noninvasive model. Hepatology 2005; 42(6): 1437-1445.
88. Zeuzem S, Dusheiko GM, Salupere R, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med. May 22 2014; 370(21):1993-2001.

Policy History:

Adopted for Blue Advantage, August 2005
Available for comment August 30-October 13, 2005
Medical Policy Group, July 2007
Medical Policy Group, July 2009
Medical Policy Group, August 16, 2011
Medical Policy Group, August 2012
Medical Policy Group, February 2015
Medical Policy Group, April 2016
Available for comment April 12 through May 27, 2016
Medical Policy Group, June 2016
Medical Policy Group, February 2017
Available for comment March 8 through April 21, 2017
Medical Policy Group, November 2017
Medical Policy Group, February 2018

hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.