

(20441)

Medical Benefit		Effective Date: 04/01/18	Next Review Date: 01/21
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Preauthorization is not required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

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

DESCRIPTION

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

SUMMARY OF EVIDENCE

MULTIANALYTE SERUM ASSAYS

For individuals who have chronic liver disease who receive FibroSURE serum panels, the evidence includes sys-

tematic reviews of more than 30 observational studies (more than 5,000 patients). Relevant outcomes are test validity, morbid events, and treatment-related morbidity. FibroSURE has been studied in populations with viral hepatitis, nonalcoholic fatty liver disease, and alcoholic liver disease. There are established cutoffs, although they were not consistently used in validation studies. Given these limitations and the imperfect reference standard, it is difficult to interpret performance characteristics. However, for the purposes of deciding whether a patient has severe fibrosis or cirrhosis, FibroSURE results provide data sufficiently useful to determine therapy. Specifically, FibroSURE has been used as an alternative to biopsy to establish eligibility regarding the presence of fibrosis or cirrhosis in several randomized controlled trials that showed the efficacy of hepatitis C virus treatments, which in turn demonstrated the test can identify patients who would benefit from therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

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

POLICY

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

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

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

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

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

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

POLICY GUIDELINES

Multianalyte assays with algorithmic analyses use the results from multiple assays of various types in an algorithmic analysis to determine and report a numeric score(s) or probability. The results of individual component assays are not reported separately.

This protocol does not address standard imaging with ultrasound (US) or magnetic resonance imaging.

BACKGROUND

BIOPSY FOR CHRONIC LIVER DISEASE

The diagnosis of non-neoplastic liver disease is often made from needle biopsy samples. In addition to establishing a disease etiology, liver biopsy can determine the degree of inflammation present and can stage the degree of fibrosis. The degree of inflammation and fibrosis may be assessed by different scoring schemes. Most of these scoring schemes grade inflammation from 0 (no or minimal inflammation) to 4 (severe) and fibrosis from 0 (no fibrosis) to 4 (cirrhosis). There are several limitations to liver biopsy, including its invasive nature, small tissue sample size, and subjective grading system. Regarding small tissue sample size, liver fibrosis can be patchy and thus missed on a biopsy sample, which includes only 0.002% of the liver tissue. A noninvasive alternative to liver biopsy would be particularly helpful, both to initially assess patients and then to monitoring response to therapy.

HEPATITIS C VIRUS

Infection with hepatitis C virus (HCV) can lead to permanent liver damage. Prior to noninvasive testing, liver biopsy was typically recommended before the initiation of antiviral therapy. Repeat biopsies may be performed to monitor fibrosis progression. Liver biopsies are analyzed according to a histologic scoring system; the most commonly used 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 the 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 recover fully, but a small portion develop chronic hepatitis B virus, 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 hepatitis B virus also uses the Metavir system.

ALCOHOLIC LIVER DISEASE

Alcoholic liver disease (ALD) is the leading cause of liver disease in most Western countries. Histologic features of ALD usually include steatosis, alcoholic steatohepatitis, hepatocyte necrosis, Mallory bodies (tangled proteins seen in degenerating hepatocytes), a large polymorphonuclear inflammatory infiltrate, and, with continued alcohol abuse, fibrosis, and possibly cirrhosis. The grading of fibrosis is similar to the scoring system used in hepatitis C. The commonly used Laënnec scoring system uses grades 0 to 4, with 4 being cirrhosis.

NONALCOHOLIC FATTY LIVER DISEASE

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

NONINVASIVE ALTERNATIVES TO LIVER BIOPSY

Multianalyte Assays

A variety of noninvasive laboratory tests are being evaluated as alternatives to liver biopsy. Biochemical tests can be broadly categorized into indirect and direct markers of liver fibrosis. Indirect markers include liver function tests such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), the ALT/AST ratio (also referred to as the AAR), platelet count, and prothrombin index. There has been a growing understanding of the underlying pathophysiology of fibrosis, leading to a direct measurement of the factors involved. For example, the central event in the pathophysiology of fibrosis is the activation of the hepatic stellate cell. Normally, stellate cells are quiescent but are activated in the setting of liver injury, producing a variety of extracellular matrix (ECM) proteins. In normal livers, the rate of ECM production equals its degradation, but, with fibrosis, production exceeds degradation. Metalloproteinases are involved in intracellular degradation of ECM, and a pro fibrogenic state exists when there is either a down-regulation of metalloproteinases or an increase in tissue inhibitors of metalloproteinases. Both metalloproteinases and tissue inhibitors of metalloproteinases can be measured in the serum, which directly reflects fibrotic activity. Other direct measures of ECM deposition include hyaluronic acid or α 2-macroglobulin.

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

FibroSURE

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 corresponds to the Metavir scoring system for stage (i.e., fibrosis) and grade (i.e., necroinflammatory activity). The measures are combined using a linear regression equation to produce a score between 0 and 1, with higher values corresponding to more severe disease. The biochemical markers include the readily available measurements of α 2-macroglobulin, haptoglobin, bilirubin, γ -glutamyl transpeptidase, ALT, and apolipoprotein AI. Developed in France, the test has been clinically available in Europe under the name FibroTest since 2003; it is exclusively offered by LabCorp in the United States as HCV FibroSURE.

ASH FibroSURE

ASH FibroSURE (ASH Test) uses a combination of 10 serum biochemical markers of liver function together with age, sex, height, and weight in a proprietary algorithm; the test is proposed to provide surrogate markers for liver fibrosis, hepatic steatosis, and ASH. The biochemical markers include α 2-macroglobulin, haptoglobin, apolipoprotein AI, bilirubin, γ -glutamyl transpeptidase, ALT, AST, total cholesterol, triglycerides, and fasting glucose. The test has been available in Europe under the name AshTest™ (BioPredictive); the test is exclusively offered by LabCorp in the United States as ASH FibroSURE.

NASH FibroSURE

NASH FibroSURE (NASH Test) uses a proprietary algorithm of the same 10 biochemical markers of liver function in combination with age, sex, height, and weight and is proposed to provide surrogate markers for liver fibrosis, hepatic steatosis, and NASH. The biochemical markers include α 2-macroglobulin, haptoglobin, apolipoprotein AI, bilirubin, γ -glutamyl transpeptidase, ALT, AST, total cholesterol, triglycerides, and fasting glucose. The test has been available in Europe under the name NashTest™ (BioPredictive); the test is exclusively offered by LabCorp in the 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, tissue inhibitor of metalloproteinase 1, and α 2-macroglobulin. FIBROSpect II is offered exclusively by Prometheus Laboratories. The measures are combined using a logistic regression algorithm to generate a FIBROSpect II index score, ranging from 1 to 100 (or sometimes reported between 0 and 1), with higher scores indicating more severe disease.

NONINVASIVE IMAGING TECHNOLOGIES

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

Transient Elastography

Transient elastography (FibroScan) uses a mechanical vibrator to produce mild amplitude and low-frequency (50 Hz) waves, inducing an elastic shear wave that propagates throughout the liver. Ultrasound tracks the wave, measuring its speed in kilopascals, which correlates with liver stiffness. Increases in liver fibrosis also increase liver stiffness and resistance of liver blood flow. Transient elastography does not perform as well in patients with ascites, higher body mass index, or narrow intercostal margins. Although FibroScan may be used to measure fibrosis (unlike liver biopsy), it does not provide information on necroinflammatory activity and steatosis, nor is it accurate during acute hepatitis or hepatitis exacerbations.

ARFI Imaging

ARFI imaging uses an ultrasound probe to produce an acoustic “push” pulse, which generates shear waves that propagate in tissue to assess liver stiffness. ARFI elastography evaluates the wave propagation speed (measured in meters per second) to assess liver stiffness. The faster the shear wave speed, the harder the object. ARFI technologies include Virtual Touch Quantification and Siemens Acuson S2000 system. ARFI elastography can be performed at the same time as a liver sonographic evaluation, even in patients with a significant amount of ascites.

Magnetic Resonance Elastography

Magnetic resonance elastography uses a driver to generate 60-Hz mechanical waves on the patient’s chest wall. The magnetic resonance equipment creates elastograms by processing the acquired images of propagating shear waves in the liver using an inversion algorithm. These elastograms represent the shear stiffness as a pixel value in kilopascals. Magnetic resonance elastography has several advantages over ultrasound elastography, including: (1) the ability to analyze larger liver volumes; (2) the ability to analyze liver volumes of obese patients or patients with ascites; and (3) the ability to precisely analyze viscoelasticity using a three-dimensional displacement vector.

Real-Time Tissue Elastography

Real-time tissue elastography is a type of strain elastography that uses a combined autocorrelation method to measure tissue strain caused by manual compression or a person’s heartbeat. The relative tissue strain is displayed on conventional color B mode ultrasound images in real time. Hitachi manufactures real-time tissue elastography devices, including the HI VISION Preirus. The challenge is to identify a region of interest while avoiding areas likely to introduce artifacts, such as large blood vessels, the area near the ribs, and the surface of the liver. Areas of low strain increase as fibrosis progresses and strain distribution becomes more complex. Various subjective and quantitative methods have been developed to evaluate the results. Real-time tissue elastography can be performed in patients with ascites or inflammation. This technology does not perform as well in severely obese individuals.

REGULATORY STATUS

In 2008 Acuson S2000™ Virtual Touch (Siemens AG), which provides ARFI imaging, was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process (K072786)(K123622).

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

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

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

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

FDA product code: IYO.

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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