BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

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

Policy #: 237
Latest Review Date: November 2023
Category: Medical

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).*

POLICY:

For magnetic resonance elastography (CPT code 76391), refer to PET, MRI, MRA, CT, CTA/CCTA (Advanced Imaging Guidelines)

For multianalyte assays for evaluation or monitoring of individuals with chronic liver disease, refer to MolDx.

Blue Advantage will treat **a single transient elastography (FibroScan®) imaging** for the evaluation of individuals with chronic liver disease as a **covered benefit**.

Blue Advantage will treat **transient elastography (FibroScan®) imaging** for the monitoring of individuals 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 acoustic radiation force impulse imaging or real-time tissue elastrography** for the evaluation or monitoring of individuals with 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.

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 2 options for noninvasive monitoring: (1) multianalyte serum assays with algorithmic analysis of either direct or indirect biomarkers; and (2) specialized radiologic methods, including magnetic resonance elastography, multiparametric magnetic resonance imaging (MRI), transient elastography, acoustic radiation force impulse imaging, and real-time transient elastography.

Biopsy for Chronic Liver Disease

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

patients and then to monitor response to therapy. The implications of using liver biopsy as a reference standard are discussed in the Rationale.

Hepatitis C Virus
Infection with hepatitis C virus (HCV) can lead to permanent liver damage. Prior to noninvasive testing, liver biopsy was typically recommended before the initiation of antiviral therapy. Repeat biopsies may be performed to monitor fibrosis progression. Liver biopsies are analyzed according to a histologic scoring system; the most commonly used one for HCV is the Metavir system, which scores the presence and degree of inflammatory activity and fibrosis. The fibrosis is graded from F0 to F4, with a Metavir score of F0 signifying no fibrosis and F4 signifying cirrhosis (which is defined as the presence throughout the liver of fibrous septa that subdivide the liver parenchyma into nodules, representing the final and irreversible form of the disease). The stage of fibrosis is the most important single predictor of morbidity and mortality in patients with hepatitis C. Biopsies for HCV are also evaluated according to the degree of inflammation present, referred to as the grade or activity level. For example, the Metavir system includes scores for necroinflammatory activity ranging from A0 to A3 (A0 = no activity, A1 = minimal activity, A2 = moderate activity, A3 = severe activity).

Hepatitis B Virus
Most people who become infected with hepatitis B virus (HBV) recover fully, but a small portion develops chronic HBV, which can lead to permanent liver damage. As with HCV, identification of liver fibrosis is needed to determine timing and management of treatment, and liver biopsy is the criterion standard for staging fibrosis. The grading of fibrosis in HBV also uses the Metavir system.

Alcoholic Liver Disease (ALD)
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 HCV. 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. Moreover, NAFLD may be associated with a variety of conditions, including obesity, diabetes, and dyslipidemia. The characteristic feature of NAFLD is steatosis. At the benign end of the disease spectrum, there is usually no appreciable inflammation, hepatocyte death, or fibrosis. In contrast, nonalcoholic steatohepatitis (NASH), which shows overlapping histologic features with ALD, is an intermediate form of liver damage, and liver biopsy may show steatosis, Mallory bodies, focal inflammation, and degenerating hepatocytes. NASH can progress to fibrosis and cirrhosis. A variety of histologic scoring systems have been used to evaluate NAFLD. The NAFLD Activity Score system for NASH includes scores for steatosis (0 to 3), lobular inflammation (0 to 3), and ballooning (0 to 2). Cases with scores of 5 or greater are considered NASH, while cases with scores of 3 and 4 are considered borderline (probable or possible) NASH. The grading of fibrosis

is similar to the scoring system used in hepatitis C. The commonly used Laënnec scoring system uses grades 0 to 4, with 4 being cirrhosis.

Noninvasive Alternatives to Liver Biopsy
Multianalyte Assays
A variety of noninvasive laboratory tests are being evaluated as alternatives to liver biopsy. Biochemical tests can be broadly categorized into indirect and direct markers of liver fibrosis. Indirect markers include liver function tests such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), the ALT/AST ratio (also referred to as the AAR), platelet count, and prothrombin index. There has been a growing understanding of the underlying pathophysiology of fibrosis, leading to a direct measurement of the factors involved. For example, the central event in the pathophysiology of fibrosis is the activation of the hepatic stellate cell. Normally, stellate cells are quiescent, but are activated in the setting of liver injury, producing a variety of extracellular matrix (ECM) proteins. In normal livers, the rate of ECM production equals its degradation, but with fibrosis, production exceeds degradation. Metalloproteinases are involved in intracellular degradation of ECM, and a profibrogenic state exists when there is either a down-regulation of metalloproteinases or an increase in tissue inhibitors of metalloproteinases. Both metalloproteinases and tissue inhibitors of metalloproteinases can be measured in the serum, which directly reflects the fibrotic activity. Other direct measures of ECM deposition include hyaluronic acid or α2-macroglobulin.

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

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

HCV FibroSure®
The HCV FibroSURE uses a combination of 6 serum biochemical indirect markers of liver function plus age and sex in a patented algorithm to generate a measure of fibrosis and necroinflammatory activity in the liver that corresponds to the Metavir scoring system for stage (ie, fibrosis) and grade (ie, necroinflammatory activity). The measures are combined using a linear regression equation to produce a score between 0 and 1, with higher values corresponding to more severe disease. The biochemical markers include the readily available measurements of α2-macroglobulin, haptoglobin, bilirubin, γ-glutamyl transpeptidase, ALT, and apolipoprotein AI. Developed in France, the test has been clinically available in Europe under the name FibroTest since 2003; it is exclusively offered by LabCorp in the U.S. as HCV FibroSURE.

ASH FibroSure®
ASH FibroSure™ (ASH Test) uses a combination of 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, 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 3 markers that directly measure fibrogenesis of the liver, analyzed with a patented algorithm. The markers include hyaluronic acid, tissue inhibitor of metalloproteinase 1, and α2-macroglobulin. FIBROSpect II is offered exclusively by Prometheus Laboratories. The measures are combined using a logistic regression algorithm to generate a FIBROSpect II index score, ranging from 1 to 100 (or sometimes reported between 0 and 1), with higher scores indicating more severe disease.

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

Noninvasive Imaging Technologies
Noninvasive imaging technologies to detect liver fibrosis or cirrhosis among patients with chronic liver disease are 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)
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 shear wave speed, the harder the object. ARFI technologies include Virtual Touch™ Quantification and Siemens Acuson S2000™ system. ARFI elastography can be performed at the same time as a liver sonographic evaluation, even in patients with a significant amount of ascites.

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

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

Multiparametric Magnetic Resonance Imaging
Multiparametric MRI combines proton density fat-fraction, T2*, and T1 mapping. Proton density fat-fraction provides an assessment of hepatic fat content and can be used to determine the grade of liver steatosis. T1 relaxation times are used to assess increases in extracellular fluid, which correlates with the extent of fibrosis and inflammation of the liver. Hepatic iron quantification is measured through T2* relaxation times as T1 relaxation times are decreased by excess iron in the liver tissue. LiverMultiScan® uses a clinical algorithm that accounts for an iron-corrected T1 value, based on the T2* relaxation time, and proton density fat-fraction to assess the presence of fat, inflammation, and fibrosis.

KEY POINTS:
The most recent literature update was through September 25, 2023.

Summary of Evidence

Multianalyte Serum Assays

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

For individuals who have chronic liver disease who receive multianalyte serum assays for liver function assessment other than FibroSure®, the evidence includes a number of observational studies. Relevant outcomes are test validity, morbid events, and treatment-related morbidity. Studies have frequently included varying cutoffs, some of which were standardized and others not validated. Cutoff thresholds have often been modified over time, may be specific to certain patient populations, and in some cases, guideline recommendations differ from cutoffs designated by manufacturers and those utilized in studies. A comparison of transient elastography to various serum-based tests found that the former was superior in detecting fibrosis, and a meta-analysis of 4 studies found higher multianalyte scores associated with an increased risk of mortality relative to lower scores, but the evidence is limited by the small number of included studies and high heterogeneity and imprecision for some estimates. Given these limitations and the imperfect reference standard, it is difficult to interpret performance characteristics. There is no direct evidence that other multianalyte serum assays improve health outcomes; further, it is not possible to construct a chain of evidence for clinical utility due to the lack of sufficient evidence on clinical validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Noninvasive Imaging

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

These trials showed the efficacy of HCV treatments, which in turn demonstrated that the test can identify patients who would benefit from therapy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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

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

Practice Guidelines and Position Statements

Nonalcoholic Fatty Liver Disease

American Gastroenterological Association et al

In 2018, the practice guidelines on the diagnosis and management of nonalcoholic fatty liver disease (NAFLD), developed by the American Gastroenterological Association (AGA), the American Association for the Study of Liver Diseases (AASLD), and the American College of Gastroenterology, stated that "NFS [NAFLD fibrosis score] or FIB-4 [Fibrosis-4] index are clinically useful tools for identifying NAFLD patients with a higher likelihood of having bridging fibrosis (stage 3) or cirrhosis (stage 4)." This guideline also cited vibration-controlled transient elastography (VCTE) and magnetic resonance elastography (MRE) as "clinically useful tools for identifying advanced fibrosis in patients with NAFLD."

A 2022 consensus-based clinical care pathway was published by the AGA on risk stratification and management of NAFLD, including some recommendations regarding the use of non-invasive testing for individuals with chronic liver disease. Among individuals with increased risk of NAFLD or nonalcoholic steatohepatitis (NASH)-related fibrosis (i.e., individuals with type-2 diabetes, ≥2 metabolic risk factors, or an incidental finding of hepatic steatosis or elevated aminotransferases), assessment with a nonproprietary fibrosis scoring system such as FIB-4 is recommended, although aspartate transaminase to platelet ratio index can be used in lieu of FIB-4 scoring. Depending on the fibrosis score, imaging-based testing for liver stiffness may be warranted with transient elastography (FibroScan), although bidimensional shear wave elastography or point shear wave elastography are also imaging options included in the clinical care pathway.

American Association for the Study of Liver Diseases
A 2023 updated practice guidance issued by the AASLD included the following guidance statements on the use of noninvasive techniques for diagnosis and management of NAFLD and hepatic steatosis.

- All patients with hepatic steatosis or clinically suspected NAFLD based on the presence of obesity and metabolic risk factors should undergo primary risk assessment with FIB-4
- In patients with pre-DM [diabetes mellitus], T2DM, or 2 or more metabolic risk factors (or imaging evidence of hepatic steatosis), primary risk assessment with FIB-4 should be repeated every 1–2 years
- Although standard ultrasound can detect hepatic steatosis, it is not recommended as a tool to identify hepatic steatosis due to low sensitivity across the NAFLD spectrum
- CAP [controlled attenuation parameter] as a point-of-care technique may be used to identify steatosis. MRI-PDFF [proton density fat fraction] can additionally quantify steatosis
- If FIB-4 is ≥ 1.3, VCTE, MRE, or ELF [Enhanced Liver Fibrosis] may be used to exclude advanced fibrosis
- Improvement in ALT or reduction in liver fat content by imaging in response to an intervention can be used as a surrogate for histological improvement in disease activity.

A 2022 joint clinical practice guideline issued by the American Association of Clinical Endocrinology and AASLD included the following recommendations on the use of noninvasive techniques for diagnosis of NAFLD with clinically significant fibrosis (stage F2 to F4):

- Clinicians should use liver fibrosis prediction calculations to assess the risk of NAFLD with liver fibrosis. The preferred noninvasive initial test is the FIB-4 (Grade B, Level 2 evidence)
- High-risk individuals with indeterminate or high FIB-4 score for further workup with an transient elastography or enhanced liver fibrosis test, as available (Grade B, Level 2 evidence)
- Clinicians should prefer the use of transient elastography as best validated to identify advanced disease and predict liver-related outcomes. Alternative imaging approaches may be considered, including shear wave elastography (less well validated) and/or magnetic resonance elastography (most accurate but with a high cost and limited

availability; best if ordered by liver specialist for selected cases) (Grade B, Level 2 evidence).

National Institute for Health and Care Excellence
In 2016, the NICE published guidance on the assessment and management of NAFLD. The guidance did not reference elastography. The guidance recommended the enhanced liver fibrosis test to test for advanced liver fibrosis, utilizing a cutoff enhanced liver fibrosis score of 10.51.

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

Hepatitis B and C Viruses
National Institute for Health and Care Excellence
In 2017, the NICE published updated guidance on the management and treatment of patients with hepatitis B virus. The guidance recommends offering transient elastography as the initial test in adults diagnosed with chronic hepatitis B, to inform the antiviral treatment decision (Table 1).

Table 1. Antiviral Treatment Recommendations by Transient Elasticity Score

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

ALT: alanine aminotransferase; kPa: kilopascal.

American Association for the Study of Liver Diseases and Infectious Diseases Society of America
In 2020, AASLD and Infectious Diseases Society of America (IDSA) guidelines for testing, managing, and treating hepatitis C virus (HCV) recommended that for counseling and pretreatment assessment purposes, the following should be completed:

"Evaluation for advanced fibrosis using noninvasive markers and/or elastography, and rarely liver biopsy, is recommended for all persons with HCV infection to facilitate decision making regarding HCV treatment strategy and determine the need for initiating additional measures for the management of cirrhosis (eg, hepatocellular carcinoma screening) Rating: Class I, Level A [evidence and/or general agreement; data derived from multiple randomized trials, or meta-analyses]"

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

Chronic Liver Disease
American College of Radiology
In 2020, the American College of Radiology appropriateness criteria rated ultrasound shear wave elastography as a 8 (usually appropriate) for the diagnosis of liver fibrosis in patients with chronic liver disease. The criteria noted, that high-quality data can be difficult to obtain in obese patients, and assessments of liver stiffness can be confounded by parenchyma, edema, inflammation, and cholestasis.

U.S. Preventive Services Task Force Recommendations
A 2020 U.S. Preventive Services Task Force Recommendation Statement for HCV screening notes that a diagnostic evaluation for fibrosis stage or cirrhosis with a noninvasive test reduces the risk for harm compared to a liver biopsy. This statement does not give preference to a specific noninvasive test.

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, ActiTest™, SteatoTest™, Hepatitis B, HBV, Hepatitis C, HCV, nonalcoholic fatty liver disease, NAFLD, acoustic radiation force impulse imaging, ARFI, nonalcoholic steatohepatitis, NASH, ASH FibroSure®, NASH FibroSure®, and NASH Test™, transient elastography, ElastQ®, Centaur ELF™ Test, Multiparametric Magnetic Resonance Imaging

APPROVED BY GOVERNING BODIES:

In November 2008, Acuson S2000™ Virtual Touch (Siemens AG), 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 June 2015, LiverMultiScan (Perspectum), which is a magnetic resonance diagnostic device software application, was cleared formarketing by the FDA through the 510(k) process (K143020).

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

In August 2021, ADVIA Centaur ELFTM test (Siemens Healthcare) was cleared for marketing by the FDA through the 513(f)(2) DeNovo review pathway (DEN190056). In 2018, the device had been granted a Breakthrough Device designation.

BENEFIT APPLICATION:

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

CURRENT CODING:

CPT code:

76391	Magnetic resonance (e.g., vibration) elastography
76981	Ultrasound elastography, parenchyma (e.g., organ)
76982	Ultrasound elastography; first target lesion
76983	Ultrasound, elastography; each additional target lesion (List separately in addition to code for primary procedure)
81517	Liver disease, analysis of 3 biomarkers (hyaluronic acid [HA], procollagen III amino terminal peptide [PIIINP], tissue inhibitor of metalloproteinase 1 [TIMP-1]), using immunoassays, utilizing serum, prognostic algorithm reported as a risk score and risk of liver fibrosis and liver related clinical events within 5 years (Effective 01/01/2024)
81596	Infectious disease, chronic hepatitis C virus (HCV) infection, six biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, and haptoglobin) utilizing serum, prognostic algorithm reported as scores for fibrosis and necroinflammatory activity in liver
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
91200	Liver elastography, mechanically induced shear wave (e.g., vibration), without imaging, with interpretation and report
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)
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)
0689T	Quantitative ultrasound tissue characterization (non-elastographic), including

	interpretation and report, obtained without diagnostic ultrasound examination for the same anatomy (e.g. organ, gland, tissue, target structure). (Effective 01/01/22)
0690T	Quantitative ultrasound tissue characterization (non-elastographic), including interpretation and report, obtained with diagnostic ultrasound examination for the same anatomy (e.g. organ, gland, tissue, target structure). (Effective 01/01/22)
0166U	Liver disease, 10 biochemical assays (?2-macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, GGT, ALT, AST, triglycerides, cholesterol, fasting glucose) and biometric and demographic data, utilizing serum, algorithm reported as scores for fibrosis, necroinflammatory activity, and steatosis with a summary interpretation

PREVIOUS CODING:

CPT Codes:

0014M	Liver disease, analysis of 3 biomarkers (hyaluronic acid [HA], procollagen III amino terminal peptide [PIIINP], tissue inhibitor of metalloproteinase 1 (Deleted 12/31/2023)

REFERENCES:

1. Abdel Alem S, Elsharkawy A, El Akel W, et al. Liver stiffness measurements and FIB-4 are predictors of response to sofosbuvir-bases treatment regimens in 7256 chronic HCV patients. Expert Rev Gastroenterol. Oct 2019.; 13 (10): 1009-1016.
2. 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.
3. 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.
4. Afdhal NH, Nunes D. Evaluation of liver fibrosis: A concise review. Am J Gastroenterol 2004; 99:1160-74.
5. American Association for the Study of Liver Diseases, Infectious Diseases Society of America. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. Last updated September 29, 2021. https://www.hcvguidelines.org.
6. American Association for the Study of Liver Diseases, Infectious Diseases Society of America. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. Last updated October 24, 2022;www.hcvguidelines.org.
7. Arndtz K, Shumbayawonda E, Hodson J, et al. Multiparametric Magnetic Resonance Imaging, Autoimmune Hepatitis, andPrediction of Disease Activity. Hepatol Commun. Jun 2021; 5(6): 1009-1020.
8. Bashir MR, Horowitz JM, Kamel IR, et al. ACR Appropriateness Criteria(R) Chronic Liver Disease. J Am Coll Radiol. May 2020;17(5S): S70-S80.

9. Beyer C, Hutton C, Andersson A, et al. Comparison between magnetic resonance and ultrasound-derived indicators of hepatic steatosis in a pooled NAFLD cohort. PLoS One. 2021; 16(4): e0249491.
10. 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.
11. 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.
12. 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.
13. Bradley C, Scott RA, Cox E, et al. Short-term changes observed in multiparametric liver MRI following therapy with direct-actingantivirals in chronic hepatitis C virus patients. Eur Radiol. Jun 2019; 29(6): 3100-3107.
14. 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.
15. Cai, C, Song X, Chen X, et al. Transient Elastography in Alcoholic Liver Disease and Nonalcoholic Fatty Liver Disease: A Systemic Revie and Meta-Analysis. Can J Gastroenterol Hepatol. 2021; 2021: 8859338.
16. Castellana M, Donghia R, Guerra V, et al. Fibrosis-4 Index vs Nonalcoholic Fatty Liver Disease Fibrosis Score in Identifying Advanced Fibrosis in Subjects with Nonalcoholic Fatty Liver disease: A mEta-Analysis. Am J Gastroenterol. Sep 01 2021; 116(9): 1833-1841.
17. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: Practice guideline from the American Association for the Study of Liver Diseases. Hepatology. Jan 2018; 67(1):328-357.
18. Chon YE, Choi EH, Song KJ, et al. Performance of transient elastography for the staging of liver fibrosis in patients with chronic hepatitis B: a meta-analysis. PLoS One. Oct 2012;7(9):e44930.
19. Cianci N, Subhani M, Hill T, et al. Prognostic non-invasive biomarkers for all-cause mortality in non-alcoholic fatty liver disease: A systematic review and meta-analysis. World J Hepatol. May 27 2022; 14(5): 1025-1037.
20. 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.
21. 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.
22. Cusi K, Isaacs S, Barb D, et al. American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings: Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD). Endocr Pract. May 2022; 28(5): 528-562.

23. 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.
24. 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.
25. Friedrich-Rust M, Ong MF, Martens S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology. Apr 2008;134(4):960-974.
26. 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.
27. 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.
28. 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.
29. Harrison SA, Dennis A, Fiore MM, et al. Utility and variability of three non-invasive liver fibrosis imaging modalities to evaluate efficacy of GR-MD-02 in subjects with NASH and bridging fibrosis during a phase-2 randomized clinical trial. PLoS One. 2018; 13(9): e0203054.
30. Heneghan MA, Shumbayawonda E, Dennis A, et al. Quantitative magnetic resonance imaging to aid clinical decision making in autoimmune hepatitis. EClinicalMedicine. Apr 2022; 46: 101325.
31. 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.
32. Horowitz JM, Kamel IR, Arif-Tiwari H, et al. ACR Appropriateness Criteria(R) Chronic Liver Disease. J Am Coll Radiol. May 2017;14(5s):S103-s117.
33. 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.
34. Hu X, Qiu L, Liu D, et al. Acoustic Radiation Force Impulse (ARFI) Elastography for noninvasive evaluation of hepatic fibrosis in chronic hepatitis B and C patients: a systematic review and meta-analysis. Med Ultrason. Jan 31 2017;19(1):23-31.
35. Imajo K, Tetlow L, Dennis A, et al. Quantitative multiparametric magnetic resonance imaging can aid non-alcoholic steatohepatitis diagnosis in a Japanese cohort. World J Gastroenterol. Feb 21 2021; 27(7); 609-623.
36. 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.
37. Janowski K, Shumbayawonda E, Dennis A, et al. Multiparametric MRI as a Noninvasive Monitoring Tool for Children WithAutoimmune Hepatitis. J Pediatr Gastroenterol Nutr. Jan 01 2021; 72(1): 108-114.

38. Jayaswal ANA, Levick C, Collier J, et al. Liver cT 1 decreases following direct-acting antiviral therapy in patients with chronichepatitis C virus. Abdom Radiol (NY). May 2021; 46(5): 1947-1957.
39. Jayaswal ANA, Levick C, Selvaraj EA, et al. Prognostic value of multiparametric magnetic resonance imaging, transient elastrography and blood-based fibrosis markers in patients with chronic liver disease. Liver Int. Dec 2020; 40(12): 3071-3082.
40. Jiang W, Huang S, Teng H, et al. Diagnostic accuracy of point shear wave elastography and transient elastography for staging hepatic fibrosis in patients with non-alcoholic fatty liver disease: a meta-analysis. BMJ Open. Aug 23 2018;8(8):e021787.
41. 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.
42. 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.
43. Kwok R, Tse YK, Wong GL, et al. Systematic review with meta-analysis: non-invasive assessment of nonalcoholic fatty liver disease--the role of transient elastography and plasma cytokeratin-18 fragments. Aliment Pharmacol Ther. Feb 2014; 39 (3):254-269.
44. 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.
45. 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.
46. Lichtinghagen R, Bahr MJ. Noninvasive diagnosis of fibrosis in chronic liver disease. Expert Rev Mol Diagn 2004; 4:715-26.
47. Lin Y, Li H, Jin C, et al. The diagnostic accuracy of liver fibrosis in non-viral liver diseases using acoustic radiation force impulse elastography: A systematic review and meta-analysis. PLoS One. 2020; 15(1): e0227358.
48. 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.
49. McDonald N. Eddowes PJ, Hodson J, et al. Multiparametric magnetic resonance imaging for quantitation of liver disease: a two-centre cross-sectional observational study. Sci Rep. Jun 15 2018; 8(1): 9189.
50. 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.
51. Mehta SH, Lau B, Afdhal NH, et al. Exceeding the limits of liver histology markers. J Hepatol. Jan 2009; 50(1):36-41.
52. 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.

53. Mozes FE, Lee JA, Selvaraj EA, et all. Diagnostic accuracy of non-invasive tests for advanced fibrosis in patients with NAFLD: an individual patient dat mets-analysis. Gut. May 17 2021.
54. Mózes FE, Lee JA, Vali Y, et al. Performance of non-invasive tests and histology for the prediction of clinical outcomes in patients with non-alcoholic fatty liver disease: an individual participant data meta-analysis. Lancet Gastroenterol Hepatol. Aug 2023; 8(8): 704-713.
55. Nakajima A, Eguchi Y, Yoneda M, et al. Randomised clinical trial: Pemafibrate, a novel selective peroxisome proliferator-activated receptor modulator (SPPARM), versus placebo in patients with non-alcoholic fatty liver disease. Aliment PharmacolTher. Nov 2021; 54(10): 1263-1277.
56. 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.
57. 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.
58. 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.
59. 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.
60. 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.
61. Owens DK, Davidson KW, Kristi AH, et al. Screening for Hepatitis C Virus Infection in Adolescents and Adults: US Preventive Services Task Force Recommendation Statement. JAMA. Mar 02 2020.
62. 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.
63. 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.
64. 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.
65. Pavlides M, Banerjee R, Sellwood J, et al. Multiparametric magnetic resonance imaging predicts clinical outcomes in patients with chronic liver disease. J Hepatol. Feb 2016; 64(2); 308-315.
66. 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.

67. 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.
68. 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; 38:481-492.
69. Poynard T, Morra R, Ingiliz P, et al. Assesment of liver fibrosis: noninvasive means. Saudi J Gastroenterol. Oct 2008; 14(4): 163-73.
70. 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.
71. Poynard T, Ngo Y, Munteanu M, et al. Noninvasive markers of hepatic fibrosis in chronic hepatitis B. Curr Hepat Rep. Jun 2011;10(2):87-97.
72. 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.
73. 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.
74. 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.
75. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. May 01 2023; 77(5): 1797-1835.
76. Rockey DC, Caldwell SH, Goodman ZD, et al. Liver biopsy. Hepatology. Mar 2009; 49(3):1017-1044.
77. Rosenberg WMC, Voelker M, et al. Serum markers detect the presence of liver fibrosis: A cohort study. Gastroenterol 2004; 127:1704-13.
78. 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.
79. Sanyal AJ, Harrison SA, Ratziu V et al. The Natural History of Advanced Fibrosis Due to Nonalcoholic Steatohepatitis: Data From the Simtuzumab Trials. Hepatology, 2019 Apr 18.
80. 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):1821-1827.
81. 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.

82. Shaheen AA, Wan AF, Myers RP. FibroTest and FibroScan for the prediction of hepatitis C-related fibrosis: a systematic review of diagnostic test accuracy. Am J Gastroenterol. Nov 2007; 102(11):2589-2600.
83. Sharma C, Cococcia S, Ellis N, et al. Systematic review: Accuracy of the enhanced liver fibrosis test for diagnosing advanced liver fibrosis and cirrhosis. J Gastrenterol Hepatol. Jul 2021; 36(7): 1788-1802.
84. Shi KQ, Tang JZ, Zhu XL, et al. Controlled attenuation parameter for the detection of steatosis severity in chronic liver disease: a meta-analysis of diagnostic accuracy. J Gastroenterol Hepatol. Jun 2014; 29(6):1149-1158.
85. 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.
86. Siemens Healthineers. Liver Fibrosis Assays: Enhanced Liver Fibrosis (ELF) Test. 2019. https://www.siemens-healthineers.com/laboratory-diagnostics/assays-by-diseases-conditions/liver-disease/elf-test.
87. Singh S, Muir AJ, Dieterich DT, et al. American Gastroenterological Association Institute Technical Review on the role of elastography in chronic liver diseases. Gastroenterology. May 2017; 152(6):1544-1577.
88. 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.
89. 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.
90. 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.
91. 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.
92. 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.
93. Sterling RK, Lissen E, Clumeck N et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology, 2006 May 27; 43(6).
94. Talwalkar JA, Kurtz DM, Schoenleber SJ, et al. Ultrasound-based transient elastography for the detection of hepatic fibrosis: systematic review and meta-analysis. Clin Gastroenterol Hepatol. Oct 2007; 5(10):1214-1220.
95. 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.
96. Tsochatzis EA, Crossan C, Longworth L, et al. Cost-effectiveness of noninvasive liver fibrosis tests for treatment decisions in patients with chronic hepatitis C. Hepatology. Sep 2014; 60(3):832-843.

97. 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.
98. Vallet-Pichard A, Mallet V, Nalpas B et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. Hepatology, 2007 Jun 15; 46(1).
99. 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.
100. 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.
101. Xiao G, Zhu S, Xiao X et al. Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to detect fibrosis in patients with nonalcoholic fatty liver disease: A meta-analysis. Hepatology, 2017 Jun 7; 66(5).
102. 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.
103. 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.
104. Xu XY, Wang WS, Zhang QM, et al. Performance of common imaging techniques vs serum biomarkers in assessing fibrosis in patients with chronic hepatitis C. Hepatology. Sept 2014; 60(3): 832-43.
105. Yan LT, Wang LL, Yao J, et al. Total bile acid-to-cholesterol ratio as a novel noninvasive marker for significant liver fibrosis and cirrhosis in patients with non-cholestatic chronic hepatitis B virus infection. Medicine (Bltimore). Fen 2020; 99 (8): e19248.
106. Younossi ZM, Felix S, Jeffers T, et al. Performance of the Enhanced Liver Fibrosis Test to Estimate Advanced Fibrosis Among Patients with Nonalcoholic Fatty Liver disease. JAMA Netw Open. Sep 01 2021; 4(9); e2123923.
107. 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.
108. 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.
109. 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
Medical Policy Group, August 2020
Medical Policy Group, November 2021
Medical Policy Group, December 2022
Medical Policy Group, November 2023
Medical Policy Group, November 2023: 2024 Annual Coding Update. Added CPT code 81517 to Current Coding Section and created Previous Coding Section to include deleted code 0014M.
