Name of Blue Advantage Policy:

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

Policy #: 237
Latest Review Date: December 2024
Category: Medicine

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 (i.e. once per lifetime) 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.

Of note, in 2023, NAFLD was renamed to metabolic dysfunction-associated steatotic liver disease (MASLD) due to concerns over exclusionary and stigmatizing language. A consensus-driven process found that the new term better reflects the metabolic nature of the disease. Similarly, NASH was renamed to metabolic-dysfunction associated steatohepatitis (MASH). Additionally, a new term, metabolic and alcohol-related/associated liver disease (MetALD) was introduced to characterize disease with both metabolic dysfunction and significant alcohol intake. Due to this recent change, unless a publication specifically refers to MASLD or MASH, the abbreviations NAFLD and NASH, respectively, will continue to be used throughout this policy.

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 (i.e., necroinflammatory activity). The measures are combined using a linear regression equation to produce a score between 0 and 1, with higher values corresponding to more severe disease. The biochemical markers include the readily available measurements of α2-macroglobulin, haptoglobin, bilirubin, γ-glutamyl transpeptidase, ALT, and apolipoprotein AI. Developed in France, the test has been clinically available in Europe under the name FibroTest since 2003; it is exclusively offered by LabCorp in the U.S. as HCV FibroSURE.

ASH FibroSure®
ASH FibroSure™ (ASH Test) uses a combination of 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 27, 2024.

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)/metabolic dysfunction-associated steatotic liver disease (MASLD), 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. Authors of one meta-analysis concluded that when compared to biopsy, the following noninvasive scoring systems demonstrated better diagnostic accuracy for predicting liver fibrosis severity in individuals with MASLD: fibrosis-4 index (FIB-4) for any fibrosis, FibroMeter for significant fibrosis, Enhanced Liver Fibrosis (ELF) for advanced fibrosis, and FIB-4 for cirrhosis. 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 two 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 and a comparative study with 5-year follow up. Relevant outcomes are test validity, morbid events, and treatment-related morbidity. Other radiologic methods (e.g., 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. In the comparative study, ARFI elastography was found to be at least as effective as liver histology in predicting liver-related survival, and was superior to both histology and the FIB-4 score in predicting certain liver-related complications.

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.

In 2023, the AGA published an expert review on the role of noninvasive tests [NITs] in the evaluation and management of NAFLD. The following practice advice statements were made.

- "A Fibrosis 4 Index score [FIB-4] <1.3 is associated with strong negative predictive value for advanced hepatic fibrosis and may be useful for exclusion of advanced hepatic fibrosis in patients with NAFLD
- A combination of 2 or more NITs combining serum biomarkers and/or imaging-based biomarkers is preferred for staging and risk stratification of patients with NAFLD whose Fibrosis 4 Index score [FIB-4] is >1.3
- Use of NITs in accordance with manufacturer's specifications can minimize risk of discordant results and adverse events
- NITs should be interpreted with context and consideration of pertinent clinical data...to optimize positive predictive value in the identification of patients with advanced fibrosis
- Liver biopsy should be considered for patients with NIT results that are indeterminate or discordant; conflict with other clinical, laboratory, or radiologic findings; or when alternative etiologies for liver disease are suspected

- Serial longitudinal monitoring using NITs for assessment of disease progression or regression may inform clinical management
- Patients with NAFLD and NITs results suggestive of advanced fibrosis or cirrhosis should be considered for surveillance of liver complications...Patients with NAFLD and NITs suggestive of advanced hepatic fibrosis should be monitored with serial liver stiffness measurement; vibration controlled transient elastography; or magnetic resonance elastography, given its correlation with clinically significant portal hypertension and clinical decompensation."

American Association for the Study of Liver Diseases
A 2023 updated practice guidance focused on the clinical assessment and management NAFLD and hepatic steatosis 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 2024 publication from the AASLD describes the impact of new nomenclature on the AASLD practice guidance on NAFLD and hepatic steatosis described above. Briefly, available data suggest a near complete overlap (99%) between the metabolic dysfunction-associated steatotic liver disease (MASLD)-defined population and the historical NAFLD-defined population. Therefore, all recommendations on the clinical assessment and management of NAFLD AND NASH can be applied to patients with MASLD and metabolic-dysfunction associated steatohepatitis (MASH). Additionally, data from biomarker validation studies among patients with NAFLD and NASH are applicable to patients with MASLD and MASH, respectively, until further guidance.

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).

In 2024, the AASLD published 2 guidelines focused on blood-based and imaging-based noninvasive liver disease assessment (NILDA) of hepatic fibrosis and steatosis. Recommendations are provided in Table 1 and include guidance for individuals with various etiologies of chronic liver disease, including hepatocellular (hepatitis C virus [HCV], HCV/HIV, hepatitis B virus [HBV], HCV/HBV, HBV/HIV, NAFLD, alcohol-associated liver disease [ALD]) and cholestatic disorders (primary sclerosing cholangitis [PSC], primary biliary cholangitis [PBC]).

Table 1. AASLD Recommendations for Blood- and Imaging-based Noninvasive Liver Disease Assessment.

Blood-based
• In adult patients with chronic HBV and HCV undergoing fibrosis staging prior to antiviral therapy, AASLD recommends using simple blood-based NILDA such as APRI or FIB-4 as an initial test to detect significant (F2-4), advanced fibrosis (F3-4) or cirrhosis (F4) compared with no test (strong recommendation, moderate quality of evidence) • In adult patients with NAFLD undergoing fibrosis staging, AASLD recommends using simple blood-based NILDA tests such as FIB-4 to detect advanced fibrosis (F3-4) compared to no test (strong recommendation, moderate quality of evidence) • In adult patients with ALD or chronic cholestatic liver disease undergoing fibrosis staging, there is insufficient evidence to recommend using blood-based NILDA for staging • In patients with chronic HCV who require fibrosis staging, AASLD recommends using simple, less costly, and readily available blood-based NILDA such as FIB-4 over complex proprietary tests (strong recommendation, moderate quality of evidence) • In patients with NAFLD who require fibrosis staging, AASLD recommends the use of simple, less costly, and readily available blood-based NILDA tests such as FIB-4 or NAFLD fibrosis score over complex proprietary tests for the detection of advanced fibrosis (F3-4; strong recommendation, moderate quality of evidence) • In patients with chronic untreated HCV, AASLD suggests a sequential combination of blood-based markers may perform better than a single biomarker for F2-4 or F4 (ungraded statement) • In patients with NAFLD, AASLD suggests the sequential combination of blood-based NILDA may be considered for diagnosis of advanced fibrosis (F3-4) over using a single test alone (ungraded statement) • AASLD suggests against the use of blood-based NILDA tests to follow progression, stability,

or regression in histologic stage (as determined by biopsy) in chronic liver disease (ungraded statement).
Imaging-based
• In adults with chronic HCV, chronic HBV, and NAFLD, AASLD recommends using imaging-based NILDA tests to detect significant fibrosis (F2-4), advanced fibrosis (F3-4), and cirrhosis (F4) (strong recommendation, moderate quality of evidence) • In adults with ALD or chronic cholestatic liver disease, AASLD suggests using imaging-based NILDA tests to detect advanced fibrosis (F3-4) and cirrhosis (F4) (conditional recommendation, low quality of evidence) • In adults with CLD, AASLD recommends utilizing either US-based elastography methods or MRE to stage fibrosis. Depending on local availability and expertise, it is reasonable to perform MRE as an investigation when concomitant cross-sectional imaging is needed or for patients in whom the accuracy of US-based elastography might be compromised (ungraded statement) • In adults with CLD, AASLD suggests imaging-based NILDA be incorporated into the initial fibrosis staging process because it is more accurate than blood-based NILDA (conditional recommendation, low quality of evidence) • In adults with CLD undergoing initial fibrosis staging, AASLD suggests combining blood-based and imaging-based NILDA, particularly for the detection of significant fibrosis (F2-4) and advanced fibrosis (F3-4 (conditional recommendation, low quality of evidence) • AASLD suggests against the use of imaging-based NILDA as a standalone test to assess regression or progression of liver fibrosis (ungraded statement) • AASLD suggests interpreting a longitudinal decrease or increase in liver stiffness within an individualized clinical context that considers the effect of NILDA modifiers and other supportive evidence of improving or worsening clinical course (ungraded statement) • In patients with treated HBV and HCV, AASLD suggests using the LSM obtained prior to the start of antiviral therapy as the most accurate longitudinal NILDA parameter for the effect of prognostication, given the limited amount of evidence associating LSM with clinical outcomes once viral suppression or eradication is achieved (ungraded statement) • In adults, TE-CAP has good diagnostic accuracy to grade steatosis and can be used in clinical practice (ungraded statement) • In adults, imaging-based NILDA, specifically TE-CAP and MRI-PDFF or MRS, are superior to blood-based NILDA tests and should be used in the assessment of hepatic steatosis where available (ungraded statement) • In the pediatric population, there is insufficient evidence to recommend a single imaging-based NILDA over another to assess liver fibrosis or steatosis (ungraded statement) • Recognizing that liver histology is an imperfect reference standard, prior to considering a liver biopsy to assess fibrosis staging in patients with CLD, AASLD recommends using blood and imaging-based NILDA as the initial tests to detect significant (F2-4) to advanced fibrosis (F3-4) and cirrhosis (F4) (ungraded statement)

Abbreviations: AASLD: American Association for the Study of Liver Diseases; ALD: alcohol-associated liver disease; APRI: acoustic radiation force impulse; CLD: chronic liver disease;

FIB-4: Fibrosis-4 Index; HBV: hepatitis C virus; HCV: hepatitis C virus; LSM: liver stiffness measurement; MRE: magnetic resonance elastography; MRI-PDFF: magnetic resonance imagine proton density fat fraction; MRS: magnetic resonance spectroscopy; NILDA: noninvasive liver disease assessment; TE-CAP: US: ultrasound

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
American Association for the Study of Liver Diseases
In 2024, the AASLD published 2 guidelines focused on blood-based and imaging-based NILDA of hepatic fibrosis and steatosis.107,108, Recommendations regarding the use of these noninvasive assessments for patients with HBV and HCV are found in Table 1.

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 NTIs 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.

A 2023 update of this guideline includes noninvasive liver markers such as HCV FibroSure, FIB-4, and FibroScan in their simplified treatment algorithm for HCV. Specific recommendations for a preferred noninvasive testing strategy are not provided.

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).

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 2).

Table 2. 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 a
<6 kPa plus abnormal ALT	Offer liver biopsy to confirm fibrosis level prior to offering a
<6 kPa plus normal ALT	Do not offer antiviral treatment

ALT: alanine aminotransferase; kPa: kilopascal.

Chronic Liver Disease
In 2024, the AASLD published 2 guidelines focused on blood-based and imaging-based NILDA of hepatic fibrosis and steatosis.107,108, Recommendations regarding the use of these noninvasive assessments for patients with chronic liver disease, including hepatocellular (HCV, HCV/HIV, HBV, HCV/HBV, HBV/HIV, NAFLD, ALD) and cholestatic disorders (PSC, PBC) are found in Table 1.

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 Enhanced Liver Fibrosis (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 for predicting disease progression in patients with advanced fibrosis due to NAFLD.

In July 2023, the Enhanced Liver Fibrosis (ELF™) Test was granted a Breakthrough Device Designation to aid in the identification of advanced fibrosis (≥F3) and cirrhosis (F4) in patients with NAFLD.

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)

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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.
UM Committee, December 2023: Policy approved by UM Committee for use for Blue Advantage business.
Medical Policy Group, June 2024: Clarification to Policy Statement to include "i.e. once per lifetime" to criteria for FibroScan®. No change to policy intent.
Medical Policy Group, December 2024
UM Committee, December 2024: Annual review of policy approved by UM Committee for use for Blue Advantage business.

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.