2.04.41	Multianalyte Assays with Algorithmic Analysis for the Evaluation and Monitoring of Patients with Chronic Liver Disease	
Section 2.0 Medicine	**Effective Date** September 30, 2014	
Subsection 2.04 Pathology/Laboratory	**Original Policy Date** June 28, 2013	**Next Review Date** September 2015

Description

Multianalyte serum assays with algorithmic analysis are being evaluated as a substitute for biopsy in the screening, evaluation, and monitoring of patients with chronic liver disease. Several commercially available tests are proposed to detect fibrosis, steatosis (fatty liver), or steatohepatitis (fatty liver with inflammation) in patients with hepatitis C, alcoholic liver disease, and nonalcoholic fatty liver disease.

Related Policies

- N/A

Policy

Multianalyte assays with algorithmic analyses are considered **investigational** for the diagnosis or monitoring of patients with chronic liver disease.

Policy Guidelines

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

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

* Note: Assessment of lipids as cardiac risk factors is addressed separately in Blue Shield of California Medical Policy: Coronary Heart Disease (CHD) - Assessment of Emerging Risk Factors.

Algorithm-based Tests	Laboratory	Proposed Indication for Use	CPT Codes
HCV FibroSure™ (FibroTest™) (uses combination of 6 markers)*	LabCorp Burlington, NC	Fibrosis and necroinflammatory activity	0001M**

ASH FibroSURE™ (ASH Test) (uses combination of 10 markers)*	LabCorp Burlington, NC	Liver fibrosis, hepatic steatosis, alcoholic steatohepatitis (ASH)	0002M**
NASH FibroSURE™ (NASH Test) (uses combination of 10 markers in combination with age, gender, height, weight)*	LabCorp Burlington, NC	Liver fibrosis, hepatic steatosis, non-alcoholic steatohepatitis (NASH)	0003M**
FibroSpect II (uses combination of 3 markers)*	Prometheus Labs San Diego, CA	Fibrogenesis of liver	Codes suggested by Prometheus lab and Mayo clinic: • 83883 (nephelometry) • 83520 x 2 ***

* See Rationale for biomarker list

** See Appendix for coding section

***There are no specific CPT codes that represent FibroSpect as a whole. At this time, it may be reported using the unlisted chemistry procedure code **84999** or with the codes for each component test. There is no specific CPT code for the use of the associated proprietary algorithm for FibroSpect.

FibroSpect

- Hyaluronic acid [CPT **83520** – Immunoassay, analyte, quantitative; not otherwise specified]
- Tissue inhibitor of metalloproteinase (TIMP-1) [CPT **83520** – Immunoassay, analyte, quantitative; not otherwise specified]
- Alpha-2 macroglobulin [CPT **83883** – Nephelometry, each analyte not elsewhere specified]

Both FibroSURE and FibroSpect are offered exclusively by reference laboratories, where the global charge will reflect the cost of the underlying laboratory analysis, and then, in addition, the charge associated with the use of the proprietary algorithm to analyze the data.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Rationale

Background

Biopsy for Chronic Liver Disease

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

Hepatitis C

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

Alcoholic Liver Disease

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

Non-alcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) is defined as a condition that pathologically resembles ALD but occurs in patients who are not heavy users of alcohol. It may be associated with a variety of conditions, including obesity, diabetes, and dyslipidemia. The characteristic feature of NAFLD is steatosis. At the benign end of the spectrum of the disease, there is usually no appreciable inflammation, hepatocyte death, or fibrosis. In contrast, nonalcoholic steatohepatitis (NASH), which shows overlapping histologic features with ALD, is an intermediate form of liver damage, and liver biopsy may show

steatosis, Mallory bodies, focal inflammation, and degenerating hepatocytes. NASH can progress to fibrosis and cirrhosis. A variety of histologic scoring systems have been used to evaluate NAFLD. The NAFLD activity score (NAS) system for NASH includes scores for steatosis (0-3), lobular inflammation (0-3), and ballooning (0-2). Cases with scores of 5 or greater are considered NASH, while cases with scores of 3 and 4 are considered borderline (probable or possible) NASH. The grading of fibrosis is similar to the scoring system used in hepatitis C. The commonly used Laënnec scoring system uses grades 0 to 4, with 4 being cirrhosis.

Noninvasive Alternatives to Liver Biopsy

A variety of noninvasive laboratory tests are being evaluated as an alternative to liver biopsy. Biochemical tests can be broadly categorized into indirect and direct markers of liver fibrosis. Indirect markers include liver function tests such as ALT (alanine aminotransferase), AST (aspartate aminotransferase), the ALT/AST ratio (also referred to as the AAR), platelet count, and prothrombin index. In recent years, there has been growing understanding of the underlying pathophysiology of fibrosis, leading to direct measurement of the factors involved. For example, the central event in the pathophysiology of fibrosis is activation of the hepatic stellate cell. Normally, stellate cells are quiescent but are activated in the setting of liver injury, producing a variety of extracellular matrix (ECM) proteins. In normal livers, the rate of ECM production equals its degradation, but in the setting of fibrosis, production exceeds degradation. Metalloproteinases are involved in intracellular degradation of ECM, and a profibrogenic state exists when there is either a down regulation of metalloproteinases or an increase in tissue inhibitors of metalloproteinases (TIMP). Both metalloproteinases and TIMP can be measured in the serum, which directly reflects fibrotic activity. Other direct measures of ECM deposition include hyaluronic acid or alpha$_2$-macroglobulin.

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

- HCV FibroSURE™ (FibroTest™) uses a combination of 6 serum biochemical indirect markers of liver function plus age and sex in a patented algorithm to generate a measure of fibrosis and necroinflammatory activity in the liver that correspond to the Metavir scoring system for stage (i.e., fibrosis) and grade (i.e., necroinflammatory activity). The biochemical markers include the readily available measurements of alpha$_2$-macroglobulin, haptoglobin, bilirubin, γ-glutamyl transpeptidase (GGT), ALT, and apolipoprotein A1. Developed in France, the test has been clinically available in Europe under the name FibroTest™ since 2003 and is exclusively offered by LabCorp in the U.S. as HCV FibroSURE™.
- FibroSpect II uses a combination of 3 markers that directly measure fibrogenesis of the liver, analyzed with a patented algorithm. The markers include hyaluronic acid, TIMP-1, and alpha$_2$-macroglobulin. FibroSpect II is offered exclusively by Prometheus Laboratories.
- ASH FibroSURE™ (ASH Test) uses a combination of 10 serum biochemical markers of liver function together with age, sex, height, and weight in a proprietary algorithm and is proposed to provide surrogate markers for liver fibrosis, hepatic steatosis, and ASH. The biochemical markers include 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™ and is exclusively offered by LabCorp in the U.S. as ASH FibroSURE™.

- NASH FibroSURE™ (NASH Test) uses a proprietary algorithm of the same 10 biochemical markers of liver function in combination with age, sex, height, and weight and is proposed to provide surrogate markers for liver fibrosis, hepatic steatosis, and NASH. The biochemical markers include 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™ and is exclusively offered by LabCorp in the U.S. as NASH FibroSURE™.

Literature Review

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

Systematic Reviews: In a 2013 systematic review, Chou and Wasson evaluated the accuracy of a wide variety of blood tests in determining fibrosis and/or cirrhosis.(1) Both "simple" tests such as platelet count, and more complex scoring systems such as the FibroTest and FibroIndex were included. A total of 172 studies were identified that compared the diagnostic accuracy of blood tests with liver biopsy. Blood tests associated with areas under the receiver-operating characteristic (AUROC) curves of 0.70 or greater (range, 0.70-0.86) were considered fair to good for identifying fibrosis and AUROC curves of 0.80 or greater (range, 0.80-0.91) were considered good to excellent for identifying cirrhosis. Tests for identifying clinically significant fibrosis with AUROC curves of 0.70 to 0.86 included platelet count, age-platelet index, aspartate aminotransferase-platelet ratio index (APRI), FibroIndex, FibroTest, and Forns index with median positive likelihood ratios of 5 to 10 at commonly used cutoffs. Tests for identifying cirrhosis with AUROC curves of 0.80 to 0.91 included platelet count, age-platelet index, APRI, and Hepascore also with median positive likelihood ratios of 5 to 10. Most tests did not have high negative predictive values (NPV) for fibrosis, and negative likelihood ratios were found in the moderately useful range (0.10-0.20) at commonly used cutoffs, only with FibroIndex and FibroTest. This suboptimal NPV suggests that these tests perform better in identifying fibrosis than in ruling it out. Additionally, differences were small between the FibroTest or APRI and other blood tests, suggesting routinely available blood tests and simple calculations are not outperformed by additional blood tests and more complex algorithms in identifying fibrosis.

HCV FibroSURE (FibroTest™)

Technical Feasibility

Measurement of the serum levels of liver function tests (i.e., alpha-2 macroglobulin, haptoglobin, GGT, total bilirubin, apolipoprotein A1) are readily available biochemical tests. However, measurement of serum factors that directly measure fibrogenesis are relatively novel, and not readily available.

Diagnostic Performance

Initial research into the HCV FibroSURE algorithm involved testing an initial panel of 11 serum markers in 339 patients with liver fibrosis who had undergone liver biopsy. From the original group of 11 markers, 5 were selected as the most informative, based on logistic

regression, neural connection, and receiver operating characteristic (ROC) curves. Markers included alpha$_2$-macroglobulin, haptoglobin, γ-globulin, apolipoprotein A1, γ-glutamyl transpeptidase, and total bilirubin.(2) Using an algorithm-derived scoring system ranging from 0 to 1.0, the authors reported that a score of less than 0.10 was associated with a NPV of 100% (i.e., absence of fibrosis, as judged by liver biopsy scores of Metavir F2-F4). A score greater than 0.60 was associated with a 90% positive predictive value (PPV) of fibrosis (i.e., Metavir F2-F4). The authors concluded that liver biopsy might be deferred in patients with a score less than 0.10.

The next step in the development of this test was the further evaluation of the algorithm in a cross section of patients, including patients with hepatitis C virus (HCV) participating in large clinical trials before and after the initiation of antiviral therapy. One study focused on patients with HCV who were participating in a randomized study of pegylated interferon and ribavirin.(3) From the 1530 participants, 352 patients with stored serum samples and liver biopsies at study entry and at 24-week follow-up were selected. The HCV FibroSURE score was calculated and then compared with the Metavir liver biopsy score. At a cutoff point of 0.30, the HCV FibroSURE score had 90% sensitivity and 88% PPV for the diagnosis of Metavir F2-F4. The specificity was 36%, and the NPV was 40%. There was a large overlap in scores for patients in the Metavir F2-F4 categories, and thus the scoring system has been primarily used to subdivide patients with and without fibrosis (i.e., Metavir F0-F1 vs F2-F4). When used as a monitoring test, patients can serve as their own baseline. Patients with a sustained virologic response to interferon also experienced reductions in the FibroTest and ActiTest scores.

Further studies were done to formally validate the parameters used to calculate the HCV FibroSURE scores. Acceptable levels of intralaboratory and intrapatient variability were reported.(4,5) Poynard et al. also evaluated discordant results in 537 patients who underwent liver biopsy and the HCV FibroSURE and Actitest on the same day; with the discordance attributed to either the limitations in the biopsy or serum markers.(6) In this study, cutoff values were used for the individual Metavir scores (i.e., F0-F4) and also for combinations of Metavir scores (i.e., F0-F1, F1-F2, etc.) The definition of a significant discordance between FibroTest and ActiTest and biopsy scores was a discordance of at least 2 stages or grades in the Metavir system. Discordance was observed in 29% of patients. Risk factors for biopsy failure included the biopsy size, number of fragments, and the number of portal tracts represented in the biopsy sample. Risk factors for failure of HCV FibroSURE scoring system were presence of hemolysis, inflammation, possible Gilbert syndrome, acute hepatitis, drugs inducing cholestasis, or an increase in transaminases. Discordance was attributable to markers in 2.4% of patients and to the biopsy in 18% and nonattributed in 8.2% of patients. The authors suggest that biopsy failure, frequently to the small size of the biopsy sample, is a common problem. The diagnostic value of FibroSURE-FibroTest has also been evaluated for the prediction of liver fibrosis in patients with alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD).(7,8) As noted in 2 reviews, the bulk of the research regarding HCV FibroSURE was conducted by researchers with an interest in the commercialization of the algorithm.(9,10)

One Australian study attempted to independently replicate the results of FibroSURE in 125 patients with hepatitis C. (11) Using the cutoff point of less than 0.1 to identify lack of bridging fibrosis (i.e., Metavir stages F0-F1) and greater than 0.6 to identify fibrosis (i.e., Metavir stages F2-F4). The NPV for a score of less than 0.1 was 89%, compared with the 100% originally reported by Imbert-Bismut, and the PPV of a score greater than 0.6 was 78% compared with 90%. The reasons for the inferior results in this study are unclear, but the authors concluded that the FibroSURE score did not accurately predict the presence or absence of fibrosis and could not reliably be used to reduce the need for liver biopsy.

Clinical Utility

The clinical utility of a test depends on the demonstration that the test can be used to improve patient management. The primary benefit of the HCV FibroSURE-FibroTest is its ability to avoid liver biopsy in patients without significant fibrosis. Thus, empiric data are needed that demonstrate that the FibroSURE test impacts clinician decision making on whether a biopsy should be performed and that the net effect is to reduce the overall number of biopsies while achieving similar clinical outcomes. There are currently no such published studies to demonstrate clinical utility.

These tests also need to be adequately compared with other noninvasive tests of fibrosis to determine their comparative efficacy. In particular, the proprietary, algorithmic tests should demonstrate superiority to other readily available, nonproprietary scoring systems to demonstrate that the tests improve health outcomes.

The test also has potential clinical utility as a means to follow response to therapy. In this case, evidence needs to demonstrate that the use of the test for response to therapy impacts decision making and that these changes in management decisions lead to improved outcomes. Although the FibroSURE-FibroTest is reported to be widely disseminated and accepted in France, literature searches of English language publications have not identified any clinical articles in which the HCV FibroSURE was actively used in the management of the patient. It is not clear whether the HCV FibroSURE could be used in lieu of an initial liver biopsy, or whether it could be used as an interval test in patients receiving therapy to determine whether an additional liver biopsy was necessary.

ASH FibroSURE (ASH Test)

Technical Feasibility

As above.

Diagnostic Performance

In 2006, Thabut et al. reported the development of a panel of biomarkers (ASH FibroSURE-ASH Test) for the diagnosis of alcoholic steatohepatitis (ASH) in patients with chronic ALD. (12) Biomarkers were initially assessed with a training group consisting of 70 patients, and a panel was constructed using a combination of the 6 biochemical components of the FibroTest-ActiTest plus aspartate aminotransferase (AST). The algorithm was subsequently studied in 2 validation groups (1 prospective study for severe ALD, 1 retrospective study for nonsevere ALD) that included 155 patients and 299 controls. The severity of ASH (none, mild, moderate, severe) was blindly assessed from biopsy samples. In the validation groups there were 28 cases (18%) of discordance between the diagnosis of ASH predicted by the ASH Test and biopsy; 10 (36%) were considered to be false negatives of the ASH Test, and 11 were suspected to be failures of biopsy. Seven cases were indeterminate by biopsy. The AUROC curves were 0.88 and 0.89 in the validation groups. The median ASH Test value was 0.005 in controls, 0.05 in patients without or with mild ASH, 0.64 in the moderate ASH grade, and 0.84 in severe ASH grade 3. Using a cutoff value of 0.50, the ASH Test had sensitivity of 80% and specificity of 84%, with PPVs and NPVs of 72% and 89%, respectively.

Several of the authors have an interest in the commercialization of this test, and no independent studies on the diagnostic performance of ASH FibroSURE-ASH Test were identified. In addition, it is not clear if the algorithm used in this study is the same as in the currently commercially available test that includes 10 biochemicals.

Clinical Utility

The issues of clinical utility are similar to those discussed for the FibroSURE-FibroTest. No studies were identified that assessed clinical outcomes following use of ASH FibroSURE-ASH Test.

NASH FibroSURE (NASH Test)

Technical Feasibility

As above.

Diagnostic Performance

In 2006, Poynard et al. reported the development of a panel of biomarkers (NASH FibroSURE-NASH Test) for the prediction of nonalcoholic steatohepatitis (NASH) in patients with NAFLD.(13) Biomarkers were initially assessed with a training group consisting of 160 patients, and a panel was constructed using a combination of 13 of 14 parameters of the currently available test (see description). The algorithm was subsequently studied in a validation group of 97 patients and 383 controls. Patients in the validation group were from a prospective multicenter study with hepatic steatosis at biopsy and suspicion of NAFLD. Histologic diagnoses used Kleiner et al.'s scoring system, with 3 classes for NASH (NASH, borderline NASH, no NASH). The main end point was steatohepatitis, defined as a histologic NASH score (NAS) of 5 or greater. The area under the ROC curve for the validation group was 0.79 for the diagnosis of NASH, 0.69 for the diagnosis of borderline NASH, and 0.83 for the diagnosis of no NASH. Results showed sensitivity of 33% and specificity of 94% for NASH with PPVs and NPVS of 66% and 81%, respectively. For borderline NASH or NASH, there was sensitivity of 88%, specificity of 50%, and PPVs and NPVs of 74% and 72%, respectively. Clinically significant discordance (2 class difference) was observed in 8 patients (8%). None of the 383 controls were considered to have NASH by NASH FibroSURE-NASH Test. The authors propose that this test would be suitable for mass screening for NAFLD in patients with obesity and diabetes.

An independent study from France was a prospective validation of the NASH Test (along with the FibroTest, Steatotest, and Actitest) in a cohort of 288 patients treated with bariatric surgery.(14) Included were patients with severe or morbid obesity (body mass index, >35 kg/m^2), at least 1 comorbidity for at least 5 years, and resistance to medical treatment. Excluded were patients with current excessive drinking, long-term consumption of hepatotoxic drugs, and positive screening for chronic liver diseases including hepatitis. Histology and biochemical measurements were centralized and blinded to other characteristics. The NASH test provided a 3-category score for no NASH (0.25), possible NASH (0.50), and NASH (0.75). The prevalence of NASH was 6.9%, while the prevalence of NASH or possible NASH was 27%. The concordance rate between histologic NASH and the NASH Test was 43.1% with a weak kappa reliability test (0.14). In 183 patients who were categorized as possible-NASH by the NASH Test, 124 (68%) were classified as no NASH by biopsy. In 15 patients categorized as NASH by the NASH Test, 7 (47%) were no NASH and 4 (27%) were possible NASH by biopsy. The NPV of the NASH Test for possible NASH or NASH was 47.5%. The authors suggest that the power of this study to validate agreement between the NASH Test and biopsy was low, due to the low prevalence of NASH. However, the results show poor concordance between the NASH Test and biopsy, particularly for intermediate values.

Clinical Utility

The issues of clinical utility are similar to those discussed for the FibroSURE-FibroTest. No studies were identified that assessed clinical outcomes following use of NASH FibroSURE-NASH Test.

FibroSpect II

Technical Feasibility

As previously noted, the FibroSpect test consists of measurements of hyaluronic acid, TIMP-1, and alpha$_2$-macroglobulin. In a 2004 review, Lichtinghagen and Bahr noted that the lack of standardization of assays of matrix metalloproteinases and tissue inhibitors of metalloproteinase (TIMP) limited the interpretation of studies.(10)

Diagnostic Performance

Patel et al. investigated the use of these serum markers in an initial training set of 294 patients with HCV and further validated the resulting algorithm in a validation set of 402 patients.(15) The algorithm was designed to distinguish between no/mild fibrosis (F0-F1) and moderate to severe fibrosis (F2-F4). With the prevalence of F2-F4 disease of 52% and a cutoff value of 0.36; the PPVs and NPVs were 74.3% and 75.8%, respectively. Using a FibroSpect II cutoff score of 0.42, Christensen et al. reported a sensitivity of 93%, specificity of 66%, overall accuracy of 76%, and a NPV of 94% for advanced fibrosis in 136 patients with HCV.(16)

The published studies for this combination of markers continue to focus on test characteristics such as sensitivity, specificity, and accuracy.(17-19)

Clinical Utility

The issues of clinical utility are similar to those discussed for the FibroSURE-FibroTest. No studies were identified in the published literature in which results of the FibroSpect test were actively used in the management of the patient.

Hepatitis B

While most of the studies to identify fibrosis have been in patients with HCV, studies are also being conducted in patients with chronic hepatitis B (HBV).(20,21) In a 2013 study, Park et al. compared liver biopsy and the FibroTest results obtained on the same day from 330 patients with chronic HBV.(22) Discordance was found in 30 patients (9.1%) of which the FibroTest underestimated fibrosis in 25 patients and overestimated fibrosis in 5 patients. Those with liver fibrosis F3-F4 had a significantly higher discordance rate than F1-F2 (15.4% vs 3.0%, respectively, $p<0.001$). The only independent factor for discordance on multivariate analysis was F3-F4 on liver biopsy ($p<0.001$).

In 2014 Salkic et al. conducted a meta-analysis of studies on the diagnostic performance of FibroTest in chronic HBV.(23) Included in the meta-analysis were 16 studies (N=2494) on liver fibrosis diagnosis and 13 studies (N=1754) on cirrhosis diagnosis. There was strong evidence of heterogeneity in the 16 fibrosis studies and evidence of heterogeneity in the cirrhosis studies. For significant liver fibrosis (Metavir F2-F4) diagnosis using all of the fibrosis studies, the AUROC curve was 0.84 (95% confidence interval [CI], 0.78 to 0.88). At the recommended FibroTest threshold of 0.48 for a significant liver fibrosis diagnosis, the sensitivity was 60.9%, specificity was 79.9%, and the diagnostic odds ratio (OR) was 6.2. For liver cirrhosis (Metavir F4) diagnosis using all of the cirrhosis studies, the AUROC curve was 0.87 (95% CI, 0.85 to 0.9). At the recommended FibroTest threshold of 0.74 for cirrhosis diagnosis, the sensitivity was 61.5%, specificity was 90.8%, and the diagnostic OR was 15.7. While the results demonstrated FibroTest may be useful in excluding a diagnosis of cirrhosis in patients with chronic HBV, the ability to detect significant fibrosis and cirrhosis and exclude significant fibrosis is suboptimal.

There are no studies of the clinical utility for these patients. Of note, some researchers have noted that different markers (e.g., HBV FibroSURE) may be needed for this assessment in patients with hepatitis B.(24)

Other Scoring Systems

Other scoring systems have been developed. For example, the APRI scoring system requires only the serum level of AST and the number of platelets and uses a simple nonproprietary formula that can be calculated at the bedside to produce a score for the prediction of fibrosis.(25) Using an optimized cutoff value derived from a training set and validation set of patients with HCV, the authors reported that the NPV for fibrosis was 86% and that the PPV was 88%.

Rosenberg et al. developed a scoring system based on an algorithm combining hyaluronic acid, amino terminal propeptide of type III collagen, and TIMP-1.(26) The algorithm was developed in a test set of 400 patients with a wide variety of chronic liver diseases and then validated in another 521 patients. The algorithm was designed to discriminate between no or mild fibrosis and moderate to severe fibrosis. The NPV for fibrosis was 92%.

Giannini et al. reported that use of the AST to alanine aminotransferase (ALT) ratio (AST/ALT ratio) and platelet counts in a diagnostic algorithm would have avoided liver biopsy in 69% of their patients and would have correctly identified the absence/presence of significant fibrosis in 80.5% of these cases.(27)

A number of studies have compared HCV FibroSURE-FibroTest and other noninvasive tests of fibrosis with biopsy using ROC analysis. For example, Bourliere et al. reported validation of FibroSURE-FibroTest and reported that based on ROC analysis that FibroSURE-FibroTest was superior to APRI (AST to platelet ratio index) for identifying significant fibrosis with AUROC curves of 0.81 and 0.71, respectively. (28) A 2012 prospective multicenter study from France compared 9 of the best-evaluated blood tests in 436 patients with hepatitis C and found similar performance for HCV FibroSURE-FibroTest, Fibrometer, and Hepascore (ROC curve=0.84, 0.86, 0.84, respectively).(29) These 3 tests were significantly superior to the 6 other tests with 70% to 73% of patients considered well-classified according to a dichotomized score (F0/F1 vs ≥F2). The number of "theoretically avoided liver biopsies" for the diagnosis of significant fibrosis was calculated to be 35.6% for HCV FibroSURE-FibroTest. To improve diagnostic performance, algorithms that combine HCV FibroSURE-FibroTest with other tests such as APRI are also being evaluated.(29-31)

Ongoing and Unpublished Clinical Trials

A search of online database ClinicalTrials.gov on June 18, 2014 identified no active phase 3 or randomized studies. In the SHEARWAVE trial, shear wave elastography and FibroTest/Fibromax will be compared with liver biopsy fibrosis score in children (NCT02041780). This study will enroll 80 patients and is estimated for completion in December 2015.

Another study using the FibroTest and transient elastography for liver fibrosis screening in diabetic patients (NCT01306110). This study had an estimated enrollment of 500 and completion date of June 2012, however, the status of the study is unknown.

Another study compared FibroTest to transient elastography in alcoholic liver disease (NCT00708617). This study had an estimated enrollment of 227 and has been completed but results have not been published. No active phase 3 or randomized studies were identified.

Summary

The hepatitis C virus (HCV) FibroSURE test has been developed and extensively tested as a noninvasive measure of fibrosis, with the main body of literature published by the same group of investigators who developed the test. Data on the diagnostic accuracy and

predictive value are variable. Although the negative predictive value (NPV) for the FibroSURE was reported as 100% by the authors who developed the test, another group of investigators reported an 89% NPV, suggesting that 11% of patients would potentially forego initial antiviral therapy. A few studies have compared the diagnostic accuracy of FibroSURE with other noninvasive tests and report that the area under the curve on receiver operating characteristic analysis is higher than for nonproprietary tests.

There are less published data regarding the ASH FibroSURE and NASH FibroSURE tests and the FibroSpect test. In 1 study, the NPV of FibroSpect was 75.8%, which is substantially lower than that reported for FibroSURE. Because of the limited evidence on these other tests, the diagnostic accuracy and predictive ability is uncertain.

There were no studies identified that actually used the results of any of the tests to reduce the number of biopsies, or in the management of patients who are being treated. Therefore, there are inadequate scientific data to permit conclusions on whether HCV FibroSURE, ASH FibroSURE, NASH FibroSURE or FibroSpect improve health outcomes, and therefore these tests are considered investigational.

Practice Guidelines and Position Statements

The 2012 practice guidelines on the diagnosis and management of nonalcoholic fatty liver disease, developed by the American Gastroenterological Association, the American Association for the Study of Liver Diseases, and the American College of Gastroenterology do not reference multianalyte assays with algorithmic analyses (MAAAs) for liver fibrosis evaluation and management.(32) The 2010 American College of Gastroenterology guidelines on alcoholic liver disease also do not reference MAAAs.(33) The 2009 American Association for the Study of Liver Diseases guidelines on the diagnosis, management, and treatment of hepatitis C indicate: “noninvasive tests may be useful in defining the presence or absence of advanced fibrosis in persons with chronic hepatitis C infection, but should not replace the liver biopsy in routine clinical practice” (Class IIb, Level C- consensus opinion; efficacy less well established by evidence).(34)

U.S. Preventive Services Task Force Recommendations

The use of MAAAs with algorithmic analysis for chronic liver disease is not a preventive service.

Medicare National Coverage

No national coverage determination (NCD) was identified. In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

References

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Documentation Required for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

IE

The following services are considered investigational and therefore not covered for any indication.

Type	Code	Description
CPT®	0001M	Infectious disease, HCV, six biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, and haptoglobin) utilizing serum, prognostic algorithm reported as scores for fibrosis and necroinflammatory activity in liver
	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)
	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
HCPC	None	
ICD-9 Procedure	None	
ICD-10 Procedure	***For dates of service on or after 10/01/2015***	
	None	
ICD-9 Diagnosis	All Diagnoses	
ICD-10 Diagnosis	***For dates of service on or after 10/01/2015***	
	All Diagnoses	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
6/28/2013	BCBSA Medical Policy adoption	Medical Policy Committee
9/30/2014	Policy revision without position change	Medical Policy Committee

Definitions of Decision Determinations

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

Investigational/Experimental: A treatment, procedure or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a Split Evaluation, where a treatment, procedure or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).

For instances when the indication is **medically necessary**, clinical evidence is required to determine **medical necessity**.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.