Name of Policy:
Combination of Serum Markers for Liver Fibrosis in the Evaluation and Monitoring of Patients with Chronic Liver Disease

Policy #: 237
Category: Laboratory

Latest Review Date: August 2011
Policy Grade: Effective August 16, 2011: Active Policy but no longer scheduled for regular literature reviews and updates.

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
Description of Procedure or Service:
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 non-alcoholic fatty liver disease.

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 0-4 (with 0 being no or minimal inflammation and 4 being severe) and fibrosis from 0-4 (with 0 being no fibrosis and 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 prior to 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-F4, with a Metavir score of F0 signifying no fibrosis and F4 signifying cirrhosis (which is defined as the presence throughout the liver of fibrous septa that subdivide the liver parenchyma into nodules and represents the final and irreversible form of disease). The stage of fibrosis is the most important single predictor of morbidity and mortality in patients with hepatitis C. Biopsies for hepatitis C are also evaluated according to the degree of inflammation present, referred to as the grade or activity level. For example, the Metavir system includes scores for necroinflammatory activity ranging from A0 to A3 (A0=no activity, A1= minimal activity, A2=moderate activity, A3=severe activity.)

Alcoholic Liver Disease (ALD): 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 0-4, with 4 being cirrhosis.

Non-alcoholic Fatty Liver Disease (NAFLD): NAFLD is defined as a condition that pathologically resembles ALD but occurs in patients who are not heavy users of alcohol. It may be associated with a variety of conditions, including obesity, diabetes, and dyslipidemia. The characteristic feature of NAFLD is steatosis. At the benign end of the spectrum of the disease, there is usually no appreciable inflammation, hepatocyte death, or fibrosis. In contrast, non-alcoholic steatohepatitis (NASH), which shows overlapping histologic features with ALD, is an
intermediate form of liver damage, and liver biopsy may show steatosis, Mallory bodies, focal inflammation, and degenerating hepatocytes. NASH can progress to fibrosis and cirrhosis. A variety of histological scoring systems have been used to evaluate NAFLD. The 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 0-4, with 4 being cirrhosis.

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

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

HCV FibroSure™ (FibroTest™) uses a combination of 6 serum biochemical indirect markers of liver function plus age and gender 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, gamma glutamyl transeptidase (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, gender, 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™ 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, 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™ and is exclusively offered by LabCorp in this country as NASH FibroSure™.

**Policy:**
Combined serum markers of hepatic fibrosis, evaluated with algorithms to produce a predictive score in the diagnosis and monitoring of patients with chronic liver disease, do not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and are considered investigational.

*Blue Cross and Blue Shield of Alabama 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 Cross and Blue Shield of Alabama administer benefits based on the members’ contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*

**Key Points:**
Validation of the clinical use of any diagnostic test focuses on three main principles:

1. The technical feasibility of the test;
2. The diagnostic performance of the test, such as sensitivity, specificity and positive and negative predictive value in different populations of patients and compared to the gold standard; and
3. The clinical utility of the test, i.e. how the results of the diagnostic test will be used to improve the management of the patient.

**HCV FibroSure (FibroTest™)**

**Technical Feasibility**
Measurement of the serum levels of liver function tests (i.e., Alpha-2 macroglobulin, haptoglobin, gamma glutamyl transpeptidase [GGT], total bilirubin, and apolipoprotein A1) are...
readily available biochemical tests. However, measurement of serum factors that directly measure fibrogenesis are relatively novel, and not readily available.

**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, five were selected as the most informative, based on logistic regression, neural connection, and receiver operating characteristic (ROC) curves. Markers included Alpha-2 macroglobulin, haptoglobin, gamma globulin, apolipoprotein A1, gamma glutamyl transpeptidase, and total bilirubin. Using an algorithm-derived scoring system ranging from 0–1.0, the authors reported that a score of less than 0.10 was associated with a negative predictive value 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 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 hepatitis C who were participating in a randomized study of peginterferon and ribavirin. From the 1,530 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 to the METAVIR liver biopsy score. At a cutoff point of 0.30, the HCV FibroSure score had 90% sensitivity and 88% positive predictive value for the diagnosis of METAVIR F2-F4. The specificity was 36%, and the negative predictive value 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 virological 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 intra-laboratory and intra-patient variability were reported. Poynard and colleagues 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. 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 two 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 non-alcoholic fatty liver disease (NAFLD). As noted in two reviews, the bulk of the research regarding HCV FibroSure was conducted by researchers with an interest in the commercialization of the algorithm.

One Australian study attempted to independently replicate the results of FibroSure in 125 patients with hepatitis C. Using the cutoff point of less than 0.1 to identify lack of bridging fibrosis (i.e., Metavir stages F0-F1) and greater than 0.6 to identify fibrosis (i.e., Metavir stages F2-F4). The negative predictive value for a score <0.1 was 89%, compared to the 100% originally reported by Imbert-Bismut, and the positive predictive value of a score greater than 0.6 was 78% compared to 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 to other non-invasive tests of fibrosis to determine their comparative efficacy. In particular, the proprietary, algorithmic tests should demonstrate superiority to other readily available, non-proprietary scoring systems in order 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 alcoholic
liver disease (ALD). Biomarkers were initially assessed with a training group consisting of 70 patients, and a panel was constructed using a combination of the 6 biochemical components of the FibroTest-ActiTest plus aspartate aminotransferase (AST). The algorithm was subsequently studied in two validation groups (one prospective study for severe ALD and one retrospective study for non-severe ALD) that included 155 patients and 299 controls. The severity of ASH (none, mild, moderate, and severe) was blindly assessed from biopsy samples. In the validation groups there were 28 cases (18%) of discordance between the diagnosis of ASH predicted by the ASH-Test and biopsy; 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 area under the ROC curves was 0.88 and 0.89 in the validation groups. The median ASH-Test value was 0.005 in controls, 0.05 in patients without or with mild ASH, 0.64 in the moderate ASH grade, and 0.84 in severe ASH grade 3. Using a cut-off value of 0.50, the ASH-Test had sensitivity of 80% and specificity of 84%, with positive and negative predictive values of 72% and 89%, respectively.

Several 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-Fibro test. 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 non-alcoholic steatohepatitis (NASH) in patients with NAFLD. Biomarkers were initially assessed with a training group consisting of 160 patients, and a panel was constructed using a combination of 13 of 14 parameters of the currently available test (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. Histological diagnoses used Kleiner et al’s scoring system, with three classes for NASH (NASH, borderline NASH, or no NASH). The main endpoint was steatohepatitis, defined as a histological NASH score (NAS) of 5 or greater. The area under the ROC curve for the validation group was 0.79 for the diagnosis of NASH, 0.69 for the diagnosis of borderline NASH, and 0.83 for the diagnosis of no NASH. Results showed sensitivity of 33% and specificity of 94% for NASH with positive and negative predictive values of 66% and 81%, respectively. For borderline NASH or NASH there was sensitivity of 88%, specificity of 50% and positive and negative predictive values of 74% and 72%, respectively. Clinically significant discordance (two 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. Included were patients with severe or morbid obesity (body mass index [BMI] >35 kg/m²), at least 1 comorbidity for at least five years, and resistance to medical treatment. Excluded were patients with current excessive drinking, long-term consumption of hepatotoxic drugs, and positive screening for chronic liver diseases including hepatitis. Histology and biochemical measurements were centralized and blinded to other characteristics. The NASH test provided a 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 histological NAS and the NASH Test was 43.1% with a weak kappa-reliability test (0.14). In 183 patients who were categorized as possible-NASH by the NASH Test, 124 (68%) were classified as no NASH by biopsy. In 15 patients categorized as NASH by the NASH Test, 7 (47%) were no NASH and four (27%) were possible NASH by biopsy. The negative predictive value of the NASH Test for possible NASH or NASH was 47.5%. 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-Fibro Test. No studies were identified that assessed clinical outcomes following use of NASH FibroSure-NASH Test.

FibroSpect II
Technical Feasibility
As noted above, 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.

Diagnostic Performance
Patel and colleagues investigated the use of these serum markers in an initial training set of 294 patients with hepatitis C and further validated the resulting algorithm in a validation set of 402 patients. 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 positive and negative predictive values were 74.3% and 75.8%, respectively. Using a FibroSpect II cutoff score of 0.42, Christensen and colleagues reported a sensitivity of 93%, specificity of 66%, overall accuracy of 76%, and a negative predictive value of 94% for advanced fibrosis in 136 patients with hepatitis C.

The published studies for this combination of markers continue to focus on test characteristics such as sensitivity, specificity, and accuracy.
Clinical Utility
The issues of clinical utility are similar to those discussed for the FibroSure-Fibro Test. No studies were identified in the published literature in which results of the FibroSpect test were actively used in the management of the patient.

Other Scoring Systems
Other scoring systems have been developed. For example the APRI scoring system (aspartate aminotransferase [AST] to platelet ratio) requires only the serum level of AST and the number of platelets, and uses a simple non-proprietary formula that can be calculated at the bedside to produce a score for the prediction of fibrosis. Using an optimized cutoff value derived from a training set and validation set of patients with hepatitis C, the authors reported that the negative predictive value for fibrosis was 86% and that the positive predictive value was 88%.

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

Giannini et al reported that use of the AST to alanine aminotransferase ratio (AST/ALT ratio) 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.

While most of the studies to identify fibrosis have been in patients with hepatitis C, studies are also being conducted in patients with chronic hepatitis B (HBV). 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.

A number of studies have compared HCV FibroSure-FibroTest and other non-invasive tests of fibrosis with biopsy using ROC analysis. For example, Bourliere and colleagues 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 areas under the ROC curve of 0.81 and 0.71, respectively. A 2012 prospective multicenter study from France compared nine of the best-evaluated blood tests in 436 patients with hepatitis C and found similar performance for HCV (hepatitis C virus) FibroSure-FibroTest, Fibrometer and Hepascore (ROC curve: 0.84, 0.86, 0.84, respectively). These three tests were significantly superior to the six other tests with 70-73% of patients considered well-classified according to a dichotomized score (F0/F1 vs. ≥ F2). The number of “theoretically avoided liver biopsies” for the diagnosis of significant fibrosis was calculated to be 35.6% for HCV FibroSure-FibroTest. In order to improve diagnostic performance, algorithms that combine HCV FibroSure-FibroTest with other tests such as APRI are also being evaluated.
Summary
The HCV FibroSure test has been developed and extensively tested as a non-invasive 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 is variable. Although the negative predictive value for the FibroSure was reported as 100% by the authors who developed the test, another group of investigators reported a 89% negative predictive value, suggesting that 11% of patients would potentially forego initial antiviral therapy. A few studies have compared the diagnostic accuracy of FibroSure with other non-invasive tests and report that the area under the curve on ROC analysis is higher than for non-proprietary tests.

There are less published data regarding the ASH FibroSure and NASH FibroSure tests and the FibroSpect test. In one study, the negative predictive value (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.

Key Words:
Serum markers, liver fibrosis, chronic liver disease, FibroSure, FibroSpect, biochemical markers, biochemical serum markers, Fibroscan

Approved by Governing Bodies:
FDA approved

Benefit Application:
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP contracts: FDA approved services are not considered investigational by FEB. Will be reviewed for medical necessity.
Current Coding:

CPT code:

83520  Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified

83883  Nephelometry, each analyte not elsewhere specified

84999  Unlisted chemistry procedure

0001M  Infectious disease, HCV, six biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, and haptoglobin) utilizing serum, prognostic algorithm reported as a scores for fibrosis and necroinflammatory activity in liver (Effective 09/15/2012)

0002M  Liver disease, ten biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, haptoglobin, AST, glucose, total cholesterol and triglycerides) utilizing serum, prognostic algorithm reported as quantitative scores for fibrosis, steatosis and alcoholic steatohepatitis (ASH) (Effective 09/15/2012)

0003M  Liver disease, ten biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, haptoglobin, AST, glucose, total cholesterol and triglycerides) utilizing serum, prognostic algorithm reported as quantitative scores for fibrosis, steatosis and nonalcoholic steatohepatitis (NASH) (Effective 09/15/2012)

References:


Policy History:
Medical Policy Group, July 2005 (2)
Medical Policy Administration Committee, July 2005
Available for comment July 28-September 10, 2005
Medical Policy Group, July 2007 (1)
Medical Policy Group, July 2009 (1)
Medical Policy Group, August 16, 2011; Active Policy but no longer scheduled for regular literature reviews and updates.
Medical Policy Group, August 2012 (3): Added Administrative Codes for Multianalyte Assays with algorithmic analyses (0001M, 0002M, & 0003M)

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

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