Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual

Topic: Multianalyte Assays with Algorithmic Analysis for the Evaluation and Monitoring of Patients with Chronic Liver Disease

Date of Origin: June 2013

Section: Laboratory

Last Reviewed Date: May 2014

Policy No: 47

Effective Date: August 1, 2014

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

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 non-alcoholic fatty liver disease.

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 0-4 (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 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 0-4, 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 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™. This test is not recommended for patients during combined interferon/ribavirin therapy and not for use in patients with the following: Gilbert's disease, acute hepatitis, extrahepatic cholestasis, acute sepsis, or transplant patients. Recently the Elasto-FibroTest ® was developed and combines the FibroTest and liver stiffness measurement (LSM).

- 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™.

MEDICAL POLICY CRITERIA

Multianalyte assays with algorithmic analyses, including but not limited to the following tests, are considered **investigational** for the diagnosis or monitoring of patients with chronic liver disease:

1. HCV FibroSure™ (FibroTest™)
2. Elasto-FibroTest ®
3. FibroSpect II
4. ASH FibroSURE™ (ASH Test)
5. NASH FibroSURE™ (NASH Test)

SCIENTIFIC EVIDENCE

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 to the gold standard; and
3. 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™)

Diagnostic Performance

Systematic Review/Meta-analysis

- 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 to liver biopsy. Blood tests associated with areas under the receiver-operating characteristic curve (AUROCs) of 0.70 or greater (range, 0.70 to 0.86) were considered fair to good for identifying fibrosis and AUROCs of 0.80 or greater (range, 0.80 to 0.91) were considered good to excellent for identifying cirrhosis. Tests for identifying clinically significant fibrosis with AUROCs of 0.70 – 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 AUROCs 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 for fibrosis, and negative likelihood ratios were found in the moderately useful range (0.10 to 0.20) at commonly used cutoffs, only with FibroIndex and FibroTest. This

suboptimal negative predictive value 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.

- In a meta-analysis by Salkic and others, the authors systematically reviewed studies describing the diagnostic accuracy of the FibroTest (FT) for predicting chronic hepatitis B (CHB) -related fibrosis.[2] The authors included 16 studies (N=2494) and 13 studies (N=1754) in the heterogenous meta-analysis for liver fibrosis and cirrhosis, respectively. The area under the hierarchical summary receiver operating curve for significant liver fibrosis and for all included studies was 0.84 (95% confidence interval (CI): 0.78-0.88). At the FT threshold of 0.48, the sensitivity, specificity, and diagnostic odds ratio (DOR) of FT for significant fibrosis were 61 (48-72%), 80 (72-86%), and 6.2% (3.3-11.9), respectively. The area under the hierarchical summary receiver operating curve for liver cirrhosis and for all included studies was 0.87 (95% CI: 0.85-0.90). At the FT threshold of 0.74, the sensitivity, specificity, and DOR of FT for cirrhosis were 62 (47-75%), 91 (88-93%), and 15.7% (8.6-28.8), respectively. The authors concluded the FibroTest has suboptimal accuracy in the detection of significant fibrosis and cirrhosis.

Nonrandomized Studies

- 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 logisitic regression, neural connection, and receiver operating characteristic (ROC) curves. Markers included alpha-2 macroglobulin, haptoglobin, gamma globulin, apolipoprotein A1, gamma glutamyl transpepetidase, and total bilirubin.[3] 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.[4] 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.[5,6]

- 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.[7] 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 non-alcoholic fatty liver disease (NAFLD).[8,9] 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.[10,11]

- One Australian study attempted to independently replicate the results of FibroSure in 125 patients with hepatitis C.[12] 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.

- Poynard et al assessed the performance of a new test the Elasto-FibroTest(®) (EFT) combining FibroTest(®) and liver stiffness measurement (LSM). Authors used a data base of 1289 patients with biopsy and 604 healthy volunteers to analyze the Elasto-FiberTest (EFT).[13] Authors concluded for the diagnosis of cirrhosis the Elasto-FibroTest(®) had higher performances compared to FibroTest(®) or FibroScan(®) alone. No improvement in performance has been observed for the diagnosis of advanced fibrosis vs. FibroTest(®) alone.

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)

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).[14] 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 (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)

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.[15] 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 3 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 (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.[16] Included were patients with severe or morbid obesity (body mass index [BMI] >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 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 4 (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

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.[17] 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.[18]

The published studies for this combination of markers continue to focus on test characteristics such as sensitivity, specificity, and accuracy.[19-21]

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

Diagnostic Performance

Nonrandomized Studies

- 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.[22] 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.[23] 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.[24]

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).[25-27]

- In a 2013 study, Park and colleagues compared liver biopsy and the FibroTest results obtained on the same day from 330 patients with chronic HBV.[28] 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 ($p<0.001$).

- A number of studies have compared HCV FibroSure-FibroTest and other non-invasive tests of fibrosis with biopsy using ROC analysis. 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.[29]

- 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 (hepatitis C virus) FibroSure-

FibroTest, Fibrometer and Hepascore (ROC curve: 0.84, 0.86, 0.84, respectively).[30] These 3 tests were significantly superior to the 6 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.[30-32]

- In a recent study by Zarski and others, authors studied 507 patients with histologically proven chronic hepatitis C (CHC) in which fibrosis was evaluated by liver biopsy (METAVIR) and tests: Fibrometer, Fibrotest, Hepascore®, Apri, ELFG, MP3, Forn's, hyaluronic acid, tissue inhibitor of metalloproteinase-1 (TIMP1), MMP1, collagen IV and when possible Fibroscan.[30] Authors concluded that performance of Fibroscan™ was reduced due to uninterpretable results. Fibrotest®, interpretable Fibroscan™, Fibrometer®, and Hepascore® performed best and similarly for diagnosis of significant fibrosis and cirrhosis.

- 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.[29]

- Michalak and others compared eight diagnostic algorithms for liver fibrosis, including the sequential algorithm for fibrosis evaluation (SAFE) and the Bordeaux algorithm (BA), which cross-check FibroTest with the aspartate aminotransferase-to-platelet ratio index (APRI) or FibroScan.[32] The study included 1785 patients with chronic hepatitis C, liver biopsy, blood fibrosis tests, and FibroScan (the latter in 729 patients). The most accurate synchronous combination of FibroScan with a blood test (FibroMeter) provided a new detailed (six classes) classification (FM+FS). Authors concluded SAFE and BA for significant fibrosis or cirrhosis are very accurate. However, their successive use induces a significant decrease in diagnostic accuracy and a significant increase in required liver biopsy.

Guidelines

American Association for the Study of Liver Diseases (AASLD) and the American College of Gastroenterology (ACG)

- In the 2012 AASLD and ACG guidelines on the Diagnosis and Management of Non-Alcoholic Fatty Liver Disease (NAFLD the FibroTest or other available analyses are not addressed.[33] There is strong evidence outlined in the guidelines that include imaging and liver biochemistries for the detection of NAFLD.

- The 2009 AASLD 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]

- In the 2007 guidelines (reviewed in 2009) for the Prevention and Management of Gastroesophageal Varices and Variceal Hemorrhage in Cirrhosis approved by AASLD and the ACG, the FibroTest is described as having limited predictive accuracy.[35] Guidelines recommend that large prospective

studies of noninvasive markers need to be performed, and until the data is available, endoscopic screening is still the main means of assessing for the presence of esophageal varices.

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. There are less published data regarding the ASH FibroSure and NASH FibroSure tests and the FibroSpect test. There were no studies identified that used the results of any of the tests to either clinically manage patients or to reduce the number of biopsies performed. Further, clinical practice guidelines do not address these tests. The scientific data is insufficient to permit conclusions on whether multianalyte assays with algorithmic analyses can improve health outcomes; therefore, multianalyte assays are considered investigational.

REFERENCES

1. Chou, R, Wasson, N. Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection: a systematic review. *Ann Intern Med*. 2013;158:807-20. PMID: 23732714
2. Salkic, NN, Jovanovic, P, Hauser, G, Brcic, M. FibroTest/Fibrosure for Significant Liver Fibrosis and Cirrhosis in Chronic Hepatitis B: A Meta-Analysis. *Am J Gastroenterol*. 2014. PMID: 24535095
3. Imbert-Bismut, F, Ratziu, V, Pieroni, L, Charlotte, F, Benhamou, Y, Poynard, T. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. *Lancet*. 2001 Apr 7;357(9262):1069-75. PMID: 11297957
4. Poynard, T, McHutchison, J, Manns, M, Myers, RP, Albrecht, J. Biochemical surrogate markers of liver fibrosis and activity in a randomized trial of peginterferon alfa-2b and ribavirin. *Hepatology*. 2003 Aug;38(2):481-92. PMID: 12883493
5. Halfon, P, Imbert-Bismut, F, Messous, D, et al. A prospective assessment of the inter-laboratory variability of biochemical markers of fibrosis (FibroTest) and activity (ActiTest) in patients with chronic liver disease. *Comparative hepatology*. 2002 Dec 30;1(1):3. PMID: 12537583
6. Imbert-Bismut, F, Messous, D, Thibault, V, et al. Intra-laboratory analytical variability of biochemical markers of fibrosis (Fibrotest) and activity (Actitest) and reference ranges in healthy blood donors. *Clin Chem Lab Med*. 2004 Mar;42(3):323-33. PMID: 15080567
7. Poynard, T, Munteanu, M, Imbert-Bismut, F, et al. Prospective analysis of discordant results between biochemical markers and biopsy in patients with chronic hepatitis C. *Clin Chem*. 2004 Aug;50(8):1344-55. PMID: 15192028
8. Naveau, S, Raynard, B, Ratziu, V, et al. Biomarkers for the prediction of liver fibrosis in patients with chronic alcoholic liver disease. *Clin Gastroenterol Hepatol*. 2005 Feb;3(2):167-74. PMID: 15704051
9. Ratziu, V, Massard, J, Charlotte, F, et al. Diagnostic value of biochemical markers (FibroTest-FibroSURE) for the prediction of liver fibrosis in patients with non-alcoholic fatty liver disease. *BMC Gastroenterol*. 2006;6:6. PMID: 16503961
10. Afdhal, NH, Nunes, D. Evaluation of liver fibrosis: a concise review. *Am J Gastroenterol*. 2004 Jun;99(6):1160-74. PMID: 15180741
11. Lichtinghagen, R, Bahr, MJ. Noninvasive diagnosis of fibrosis in chronic liver disease. *Expert review of molecular diagnostics*. 2004 Sep;4(5):715-26. PMID: 15347264

12. Rossi, E, Adams, L, Prins, A, et al. Validation of the FibroTest biochemical markers score in assessing liver fibrosis in hepatitis C patients. *Clin Chem*. 2003 Mar;49(3):450-4. PMID: 12600957
13. Poynard, T, de Ledinghen, V, Zarski, JP, et al. Performances of Elasto-FibroTest((R)), a combination between FibroTest((R)) and liver stiffness measurements for assessing the stage of liver fibrosis in patients with chronic hepatitis C. *Clinics and research in hepatology and gastroenterology*. 2012 Oct;36(5):455-63. PMID: 22959098
14. Thabut, D, Naveau, S, Charlotte, F, et al. The diagnostic value of biomarkers (AshTest) for the prediction of alcoholic steato-hepatitis in patients with chronic alcoholic liver disease. *J Hepatol*. 2006 Jun;44(6):1175-85. PMID: 16580087
15. Poynard, T, Ratziu, V, Charlotte, F, et al. Diagnostic value of biochemical markers (NashTest) for the prediction of non alcoholo steato hepatitis in patients with non-alcoholic fatty liver disease. *BMC Gastroenterol*. 2006;6:34. PMID: 17096854
16. Lassailly, G, Caiazzo, R, Hollebecque, A, et al. Validation of noninvasive biomarkers (FibroTest, SteatoTest, and NashTest) for prediction of liver injury in patients with morbid obesity. *Eur J Gastroenterol Hepatol*. 2011 Jun;23(6):499-506. PMID: 21499110
17. Patel, K, Gordon, SC, Jacobson, I, et al. Evaluation of a panel of non-invasive serum markers to differentiate mild from moderate-to-advanced liver fibrosis in chronic hepatitis C patients. *J Hepatol*. 2004 Dec;41(6):935-42. PMID: 15582126
18. Christensen, C, Bruden, D, Livingston, S, et al. Diagnostic accuracy of a fibrosis serum panel (FIBROSpect II) compared with Knodell and Ishak liver biopsy scores in chronic hepatitis C patients. *J Viral Hepat*. 2006 Oct;13(10):652-8. PMID: 16970596
19. Mehta, P, Ploutz-Snyder, R, Nandi, J, Rawlins, SR, Sanderson, SO, Levine, RA. Diagnostic accuracy of serum hyaluronic acid, FIBROSpect II, and YKL-40 for discriminating fibrosis stages in chronic hepatitis C. *Am J Gastroenterol*. 2008 Apr;103(4):928-36. PMID: 18371145
20. Patel, K, Nelson, DR, Rockey, DC, et al. Correlation of FIBROSpect II with histologic and morphometric evaluation of liver fibrosis in chronic hepatitis C. *Clin Gastroenterol Hepatol*. 2008 Feb;6(2):242-7. PMID: 18187364
21. Snyder, N, Nguyen, A, Gajula, L, et al. The APRI may be enhanced by the use of the FIBROSpect II in the estimation of fibrosis in chronic hepatitis C. *Clin Chim Acta*. 2007 Jun;381(2):119-23. PMID: 17442291
22. Wai, CT, Greenson, JK, Fontana, RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology*. 2003 Aug;38(2):518-26. PMID: 12883497
23. Rosenberg, WM, Voelker, M, Thiel, R, et al. Serum markers detect the presence of liver fibrosis: a cohort study. *Gastroenterology*. 2004 Dec;127(6):1704-13. PMID: 15578508
24. Giannini, EG, Zaman, A, Ceppa, P, Mastracci, L, Risso, D, Testa, R. A simple approach to noninvasively identifying significant fibrosis in chronic hepatitis C patients in clinical practice. *J Clin Gastroenterol*. 2006 Jul;40(6):521-7. PMID: 16825935
25. Mohamadnejad, M, Montazeri, G, Fazlollahi, A, et al. Noninvasive markers of liver fibrosis and inflammation in chronic hepatitis B-virus related liver disease. *Am J Gastroenterol*. 2006 Nov;101(11):2537-45. PMID: 17029616
26. Zeng, MD, Lu, LG, Mao, YM, et al. Prediction of significant fibrosis in HBeAg-positive patients with chronic hepatitis B by a noninvasive model. *Hepatology*. 2005 Dec;42(6):1437-45. PMID: 16317674
27. Nguyen, NH, Nguyen, V, Trinh, HN, Lin, B, Nguyen, MH. Treatment eligibility of patients with chronic hepatitis B initially ineligible for therapy. *Clin Gastroenterol Hepatol*. 2013 May;11(5):565-71. PMID: 23333662

28. Park, MS, Kim, BK, Cheong, JY, et al. Discordance between liver biopsy and FibroTest in assessing liver fibrosis in chronic hepatitis B. *PLoS One*. 2013;8:e55759. PMID: 23405210
29. Bourliere, M, Penaranda, G, Renou, C, et al. Validation and comparison of indexes for fibrosis and cirrhosis prediction in chronic hepatitis C patients: proposal for a pragmatic approach classification without liver biopsies. *J Viral Hepat*. 2006 Oct;13(10):659-70. PMID: 16970597
30. Zarski, JP, Sturm, N, Guechot, J, et al. Comparison of nine blood tests and transient elastography for liver fibrosis in chronic hepatitis C: the ANRS HCEP-23 study. *J Hepatol*. 2012 Jan;56(1):55-62. PMID: 21781944
31. Sebastiani, G, Halfon, P, Castera, L, et al. SAFE biopsy: a validated method for large-scale staging of liver fibrosis in chronic hepatitis C. *Hepatology*. 2009 Jun;49(6):1821-7. PMID: 19291784
32. Boursier, J, de Ledinghen, V, Zarski, JP, et al. Comparison of eight diagnostic algorithms for liver fibrosis in hepatitis C: new algorithms are more precise and entirely noninvasive. *Hepatology*. 2012 Jan;55(1):58-67. PMID: 21898504
33. Chalasani, N, Younossi, Z, Lavine, JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. *Gastroenterology*. 2012 Jun;142(7):1592-609. PMID: 22656328. [cited 05/17/2013]; Available from: http://www.gastro.org/journals-publications/gastroenterology/NAFLD_Guideline_6-12.pdf
34. Ghany, MG, Strader, DB, Thomas, DL, Seeff, LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology*. 2009 Apr;49(4):1335-74. PMID: 19330875
35. Prevention and Management of Gastroesophageal Varices and Variceal Hemorrhage in Cirrhosis. Published 2007 [cited 04/2014]; Available from: http://www.aasld.org/practiceguidelines/pages/default.aspx
36. BlueCross BlueShield Association Medical Policy Reference Manual "Multianalyte Assays with Algorithmic Analysis for the Evaluation and Monitoring of Patients with Chronic Liver Disease." Policy No. 2.04.41

CROSS REFERENCES

None

CODES	NUMBER	DESCRIPTION
CPT	0001M	HCV FibroSURE™, LabCorp, Infectious disease, HCV, 6 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	ASH FibroSURE™, LabCorp, Liver disease, 10 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)

CODES	NUMBER	DESCRIPTION
	0003M	NASH FibroSURE™, LabCorp , Liver disease, 10 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 non-alcoholic steatohepatitis (NASH)
	81599	Multianalyte assay with algorithmic analysis
	83520	Immunoassay, analyte, quantitative; not otherwise specified] tissue inhibitor of metalloproteinase (TIMP-1)
	83883	Alpha-2 macroglobulin– Nephelometry, each analyte not elsewhere specified
	84999	Unlisted chemistry procedure
HCPCS	None	