Serum biomarkers for liver fibrosis

Clinical Policy ID: CCP.1079

Recent review date: 1/2020

Next review date: 5/2021

Policy contains: FIBROSpect® II (PROMETHEUS Laboratories, San Diego, California); FibroSURE® (LABCORP®, Burlington, North Carolina); chronic hepatitis C virus infection.

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Coverage policy

HCV FibroSURE is clinically proven and, therefore, medically necessary for the pre-treatment identification of clinically significant, advanced liver fibrosis (e.g., Metavir stages ≥ 3) in members with chronic hepatitis C virus infection when both criteria are met (American Association for the Study of Liver Diseases and Infectious Diseases Society of America, 2018; LabCorp, 2019; Houot, 2016):

- The test results will impact treatment decisions.
- The test is performed only in Clinical Laboratory Improvement Amendments-certified, validated reference laboratories.

The following tests are investigational and, therefore, not medically necessary:

- NASH FibroSURE.
- ASH FibroSURE.
- FIBRO*Spect* II.

Limitations

All other uses of FIBRO*Spect* II or FibroSURE are not medically necessary, including population screening, disease monitoring, or treatment monitoring.

HCV FibroSURE is not medically necessary:

- When used in combination with other serum liver fibrosis biomarkers (e.g., fibrosis-4 index or the aspartate aminotransferase-platelet ratio index) (Koksal, 2018; Thiele, 2018; Voican, 2017).
- In members with conditions that may affect test accuracy, for example (Nguyen, 2011):
  - Acute hemolysis.
  - Gilbert's disease.
  - Extrahepatic cholestasis.
  - Post transplantation state.
  - Renal insufficiency.
  - Increased α2-macroglobulin and haptoglobin from systemic or hepatic inflammation.
- In members with no or cured hepatitis C virus infection.
- In members with clinically evident cirrhosis.

Alternative covered services

- Alanine transaminase test.
- Aspartate aminotransferase test.
- Computed tomography.
- Magnetic resonance imaging.
- Fibrogen test.
- Haptoglobin test.
- Liver biopsy.
- Total bilirubin test.
- Transient elastography (Fibroscan®; Echosens Co., Paris, France).
- Ultrasound.

Background

In the United States, an estimated 150,000 persons are diagnosed annually with chronic liver disease, and nearly 30,000 have cirrhosis at initial presentation (Thein, 2008). The development and progression of hepatic fibrosis can mediate disease-related complications of cirrhosis. The progression of hepatic fibrosis is a nonlinear, discontinuous process that is greatly influenced by factors such as age, sex, race, alcohol exposure, and obesity. Obtaining further information about the degree of liver injury from hepatitis C is an important factor in deciding to pursue or defer antiviral therapy (Thein, 2008).

An accurate assessment of hepatic fibrosis is an important prognostic indicator of hepatitis C virus disease progression and clinical outcomes. Individuals with severe fibrosis require surveillance monitoring for liver cancer, esophageal varices, and hepatic function, and may require a longer duration of anti-viral treatment.

The clinical standard for diagnosis and therapy planning is histopathological examination of a percutaneous liver biopsy, but it is an invasive procedure that often requires multiple passes, has a small but significant risk for procedure-related complications, and is subject to inter- and intra-observer variability in biopsy interpretation (Nguyen, 2011). Inaccurate staging from sampling error is estimated to occur in up to 25 percent of cases, and substantial discordance in fibrosis stage involving the right and left liver lobes in the same patient may cause sampling variability. Finally, patients may be reluctant to undergo invasive testing (Nguyen, 2011).

A variety of serum markers have been developed to identify patients who are at risk for clinically significant hepatic fibrosis (defined by Metavir stages F2 to F4). These markers are classified as direct (representing components of extracellular matrix) or indirect (reflecting hepatic inflammation and function). Indirect markers may be used alone or combined with direct markers to form panels. The practical advantages of these blood

tests include their noninvasiveness, potential for widespread availability, and reproducibility when serial examinations are performed using the same laboratory.

Two indirect serum biomarkers marketed in the United States are FibroSURE (known as Fibrotest in Europe) and FIBRO*Spect*® II. FibroSURE consists of a six-biomarker panel (alpha-2-macroglobulin, haptoglobin, gamma-globulin, apolipoprotein A1, gamma-glutamyl transferase, and total bilirubin) that provides Metavir fibrosis staging and necroinflammatory grading to monitor liver status in patients with chronic liver disease (LabCorp, 2019). FibroSURE can be performed using a variety of components in assays and analyzers. To ensure reproducibility, FibroSURE can only be performed in Clinical Laboratory Improvement Amendments-certified, validated reference laboratories (e.g., LabCorp) as opposed to local outpatient or hospital-based labs where other testing is typically performed (LabCorp, 2019; Nguyen, 2011).

Three FibroSURE tests are available, and the parameters of each FibroSURE testing panel are specific to the liver disease for which it was developed (LabCorp, 2019):

- HCV FibroSURE for: 1) assessment of liver status following a diagnosis of hepatitis C virus; 2) baseline determination of liver status before initiating anti-viral therapy; 3) post-treatment assessment of liver status six months after completion of therapy; and 4) noninvasive assessment of liver status in patients who are at increased risk of complications from a liver biopsy.
- NASH FibroSURE for noninvasive assessment of liver status in patients with nonalcoholic fatty liver disease.
- ASH FibroSURE for noninvasive assessment of liver status in patients with suspected alcoholic liver disease.

FIBRO*Spect* uses a quantitative analysis of hyaluronic acid, tissue inhibitor of metalloproteinase and α2-macroglobulin, which applies an algorithm to predict the likelihood of liver fibrosis in patients with hepatitis C with no indeterminate results (PROMETHEUS, 2017). PROMETHEUS Laboratories Inc. is Clinical Laboratory Improvement Amendments-certified and accredited by the College of American Pathologists. This test is only offered at PROMETHEUS Laboratories (PROMETHEUS, 2017).

Findings

We identified six systematic reviews for this policy. No economic analyses were identified.

For the FIBRO*Spect* test, two systematic reviews with overlapping literature found insufficient evidence to determine either its efficacy for detecting fibrosis or disease severity in hepatitis C virus-infected populations (Chou, 2013; Smith, 2009). FIBRO*Spect* has a significant false-negative rate, indicating that it fails to detect cases of clinically significant fibrosis detected by biopsy. Studies generally enrolled populations with a high prevalence of clinically significant fibrosis, which may overestimate accuracy estimates, and used a variety of gold standards. Thus, its “true” discriminative ability has not been tested adequately. Finally, there is a lack of evidence of the effect of FIBRO*Spect* testing on patient management or patient outcomes.

For FibroSURE, five systematic reviews with overlapping literature found insufficient evidence to determine either its efficacy for detecting fibrosis or disease severity or impact on patient outcomes in hepatitis C virus-infected populations (Cholongitas, 2010; Chou, 2013; Shaheen, 2007, 2008; Smith, 2009). Test scores at the extremes of the fibrosis measures (e.g., Fibrotest < 0.20 or > 0.60), which are seen in approximately 50 percent of patients, have acceptable predictive values (80 percent range), but test scores with intermediate values are not accurate enough to replace liver biopsy. False-positive results may be attributed to decreases in haptoglobin from hemolysis, increases in total bilirubin from conditions such as Gilbert's syndrome and cholestasis, and increases in α2-macroglobulin and haptoglobin from systemic or hepatic inflammation (Nguyen, 2011).

Overall, variability in methods and poor interobserver agreement for histological staging limit the diagnostic efficacy of noninvasive biomarkers such as FIBRO*Spect* and FibroSURE. Noninvasive biomarkers produce continuous scores that are then correlated with categorical variables (i.e., the stage scores), which are only descriptive categories of fibrosis. There are differences among the various histological scoring systems, and they lack an arithmetical progression. Quantitative measurement of liver fibrosis would be a more appropriate comparator to these test scores, but the relationship between clinical correlations and quantitative measurement of liver fibrosis has not been extensively evaluated (Cholongitas, 2010).

The National Institutes of Health (2002) issued a consensus statement on the management of hepatitis C that considered the use of noninvasive tests for assessing liver fibrosis. It concluded noninvasive tests were not adequate substitutes for liver biopsy, as they were not widely available or well validated; no single test or panel of serologic markers can provide an accurate assessment of intermediate stages of hepatic fibrosis. Since then, several organizations have issued evidence-based recommendations and arrived at similar conclusions, despite wider availability of these tests (Centers for Disease Control and Prevention, 2013; Ghany, 2009; Mofenson, 2009; Moyer, 2013; Rockey, 2009).

In 2015, one systematic review update (Selph, 2014) of a previously included review (Chou, 2013), one cost-effectiveness analysis (Crossan, 2015), and one guideline (American Association for the Study of Liver Diseases, 2014) were added to the policy. The new information does not change the previous findings or the clinical policy. Therefore, no changes to the policy are warranted.

In a previously included systematic review, Chou (2013) had omitted a significant number of published studies from summary estimates, because they provided insufficient information to calculate diagnostic accuracy. Selph (2014) obtained the unpublished data and recalculated diagnostic accuracy estimates. The additional data had no appreciable impact on diagnostic accuracy estimates for diagnostic tests for hepatic fibrosis.

Crossan (2015) assessed the diagnostic accuracy and cost-effectiveness of noninvasive liver tests in adults with chronic liver disease from the perspective of current practice in the United Kingdom. Fibrotest was the most widely assessed commercial test, and FIBRO*Spect* was studied only in hepatitis C virus populations for the stages of interest in their models. Noninvasive liver tests were compared with each other, sequential testing strategies, biopsy, and strategies including no testing. The overall robustness of included studies was poor, and the economic benefits of noninvasive liver tests varied according to the cause of the liver disease.

For persons with an active hepatitis C virus infection, the best option is to treat all regardless of stage of liver disease. For persons with hepatitis B e antigen (HBeAg)-negative chronic hepatitis B virus, this is also the case if the higher bound of the standard cost-effectiveness threshold is considered acceptable. These findings would apply in settings similar to the United Kingdom; however, in resource-poor settings, a treat-all strategy may not be possible. In this case, a noninvasive test may be a better diagnostic option than liver biopsy.

The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (2014), in collaboration with the International Antiviral Society–USA, recommend assessing the degree of hepatic fibrosis, using liver biopsy, imaging, and/or noninvasive markers to determine the urgency for treatment. Indirect serum markers, direct serum markers, and vibration-controlled transient elastography may be considered. However, no single method has sufficiently high accuracy, and each test must be interpreted carefully. Based on the results of Selph (2014), these tests are, at best, only moderately useful for identifying clinically significant fibrosis or cirrhosis. The most efficient approach to fibrosis assessment is to combine direct biomarkers and vibration-controlled transient elastography. A biopsy should be considered for any patient who has discordant results between the two modalities that would affect clinical decision making.

In 2017, we added one new systematic review/meta-analysis of studies that directly compared Fibrotest, aspartate aminotransferase-platelet ratio index, the fibrosis-4 index, and transient elastography to biopsy (Houot, 2016). The analysis applied a novel Bayesian approach to compare and rank the area under the receiver

operating curve of each test based on etiology (persons with hepatitis C virus, hepatitis B virus, or hepatitis C virus and hepatitis B virus co-infection).

Combined results for all etiologies revealed that the aspartate aminotransferase-platelet ratio index had the lowest test performance for identifying advanced fibrosis, and Fibrotest had the highest. For identifying cirrhosis, the aspartate aminotransferase-platelet ratio index had the lowest test performance compared to either transient elastography or fibrosis-4 index, with no significant differences between the remaining test comparisons. There were no differences in test performances for either cirrhosis or fibrosis based on specific etiology. This analysis provides new information on the relative performance of the four most common noninvasive tests for liver fibrosis. The impact of this test on patient management and outcomes, particularly for individuals with intermediate stages of fibrosis, is yet to be determined. While encouraging, these results do not changed previous conclusions. Therefore, no policy changes are warranted.

In 2018, we added one joint guideline on testing, managing, and treating hepatitis C virus disease (American Association for the Study of Liver Diseases and Infectious Diseases Society of America, 2017, update of 2014) and one guideline by the American Association for the Study of Liver Diseases on the diagnosis and management of nonalcoholic fatty liver disease (Chalasani, 2017). While both guidelines discuss the value of noninvasive assessment of liver fibrosis using transient elastography, aspartate aminotransferase-platelet ratio index, or the fibrosis-4 index score, neither specifically mentions Fibrotest/FibroSURE or Fibro*Spect* in their testing algorithms. These results do not change previous conclusions, and no policy changes are warranted.

In 2019, we added two guideline updates from the American Association for the Study of Liver Diseases (Chalasani, 2018, update of 2017; Terrault, 2018) and one guideline from the American College of Radiology (Horowitz, 2017). Liver biopsy remains the clinical standard for evaluating the presence of fibrosis, and cross-sectional imaging and transient elastography are recommended for noninvasive evaluation (Chalasani, 2018; Horowitz, 2017; Terrault, 2018). Guidelines increasingly support a role for noninvasive alternatives for assessing liver disease severity to reduce the need for liver biopsy and inform treatment decisions, although the clinical value of combining noninvasive options is inconclusive (Koksal, 2018; Thiele, 2018; Voican, 2017). Guidelines make no specific recommendations for optimal testing sequence. FibroSURE, fibrosis-4, and the aspartate aminotransferase-platelet ratio index are among the most extensively studied serum liver fibrosis biomarkers (Nguyen, 2011).

The strongest evidence supports HCV FibroSURE for pre-treatment identification of patients with chronic hepatitis C virus who have a higher likelihood of advanced liver fibrosis (Metavir stage ≥ 3), when the information could impact treatment strategy and determine the need for initiating additional measures for cirrhosis management (e.g., hepatocellular carcinoma monitoring) (American Association for the Study of Liver Diseases and Infectious Diseases Society of America, 2018). The evidence supporting a clinical role for FibroSURE in persons with other liver diseases is inconclusive (Chalasani, 2018; Terrault, 2018). Taking into account the existing uncertainties and evolving clinician and patient preferences for noninvasive options, we determined a finding of medical necessity for HCV FibroSURE for fibrosis staging in treatment-naïve persons with chronic hepatitis C virus. The policy ID was changed from CP# 01.01.01 to CCP.1079.

In 2020, we added a meta-analysis (Xu, 2019) that addressed noninvasive staging of liver fibrosis in people with chronic hepatitis B virus infection. The results are consistent with previous policy findings, and no policy changes are warranted.

References

On October 2, 2019, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “liver cirrhosis” (MeSH) and “chronic hepatitis”

(MeSH), crossed with “biomarkers” (MeSH), “Fibrotest,” “FibroSURE,” and “FIBROSpect.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

12/2013: initial review date and clinical policy effective date: 6/2014

6/2015: Policy references updated.

1/2017: Policy references updated.

1/2018: Policy references updated.

1/2019: Policy references updated and policy ID changed. Coverage for HCV FibroSURE changed to medically necessary.

1/2020: Policy references updated.