Clinical Policy Title: Serum biomarkers for liver fibrosis

Clinical Policy Number: CCP.1079

Effective Date: June 1, 2014
Initial Review Date: December 18, 2013
Most Recent Review Date: January 81, 2019
Next Review Date: January 20 20

Related policies:
CCP.1118  Liver elastography

ABOUT THIS POLICY: Prestige Health Choice has developed clinical policies to assist with making coverage determinations. Prestige Health Choice’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Prestige Health Choice when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Prestige Health Choice’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Prestige Health Choice’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Prestige Health Choice will update its clinical policies as necessary. Prestige Health Choice’s clinical policies are not guarantees of payment.

Coverage policy

Prestige Health Choice considers the use of HCV FibroSURE to be 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, 2017; Houot, 2016):

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

Prestige Health Choice considers the following tests to be investigational and, therefore, not medically necessary:
- NASH FibroSURE.
- ASH FibroSURE.
Limitations:

Coverage determinations are subject to benefit limitations and exclusions as delineated by the state Medicaid authority. The Florida Medicaid website may be accessed at [http://ahca.myflorida.com/Medicaid/](http://ahca.myflorida.com/Medicaid/).

All other uses of FIBROspec 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).

**Serum biomarkers:**

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 FIBROSpect® 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, 2017). 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, 2017; 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, 2017):
- 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) posttreatment 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.

FIBROSure 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).

**Searches**

Prestige Health Choice searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality.
- The Centers for Medicare & Medicaid Services.

We conducted searches on October 17, 2018. Search terms were: “liver cirrhosis” (MeSH) and “chronic hepatitis” (MeSH), crossed with “biomarkers” (MeSH), “Fibrotest,” “FibroSURE,” and “FIBROSure.”

We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

We identified six systematic reviews for this policy. No economic analyses were identified.
For the FIBROSpec 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). FIBROSpec 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 FIBROSpec 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 (Chou, 2013; Cholongitas, 2010; Smith, 2009; Shaheen, 2008; Shaheen, 2007). 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 FIBROSpec 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 (Moyer, 2013; Centers for Disease Control and Prevention, 2013; Rockey, 2009; Ghany, 2009; Mofenson, 2009).

**Policy updates:**

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 previous 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 FIBROspect 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, updated 2017), 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 2016, 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 change 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) 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 FibroSpect 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; Terrault, 2018; Horowitz, 2017). 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, Prestige Health Choice determined a finding of medical necessity for HCV FibroSURE for fibrosis staging in treatment-naïve persons with chronic hepatitis C virus.

Policy ID changed from CP# 01.01.01 to CCP.1079.

**Summary of clinical evidence:**
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<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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| Chalasani (2018) for the American Association for the Study of Liver Diseases | **Key points:**  
- Routine screening in high-risk groups in primary care, diabetes, or obesity clinics is not recommended due to knowledge gaps in diagnosis and treatment.  
- Noninvasive testing may identify those at low or high risk for advanced fibrosis (bridging fibrosis or cirrhosis) when there is a high index of suspicion for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis in patients with type 2 diabetes.  
- Clinical decision aids such as the nonalcoholic fatty liver disease Fibrosis Score, fibrosis-4 index, or vibration controlled transient elastography are clinically useful tools for identifying patients with higher likelihood of having bridging fibrosis (stage 3) or cirrhosis (stage 4).  
- No recommendation for or against Fibrotest. |
| Terrault (2018) for the American Association for the Study of Liver Diseases | **Key points:**  
- The presence of hepatitis B surface antigen establishes the diagnosis of hepatitis B.  
- Follow-up of patients not currently on antiviral treatment require regular monitoring to assess the need for future therapy.  
- Liver biopsy offers the only means of assessing both fibrosis and inflammation.  
- Elastography (preferred) and liver fibrosis biomarkers (e.g., fibrosis-4 or Fibrotest) are alternatives to liver biopsy for assessing histological disease severity in patients who have achieved hepatitis B surface antigen loss spontaneously or with therapy (resolved chronic hepatitis B or functional cure), especially those > 40 years old who were infected at a young age (i.e., long duration of infection). |
| American Association for the Study of Liver Diseases and Infectious Diseases Society of America (2018) | **Key points:**  
- Recommends evaluation for advanced fibrosis using liver biopsy, imaging, and/or noninvasive markers for all persons with active hepatitis C virus infection, to facilitate hepatitis C virus treatment decisions and determine additional management decisions (e.g., hepatocellular carcinoma screening) based on data derived from multiple randomized controlled trials, meta-analyses, or equivalent, and/or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective.  
- The most efficient approach to fibrosis assessment is to combine direct biomarkers (not available in the U.S. market) and transient elastography. Consider a biopsy for discordant results that would affect clinical decision making.  
- If direct biomarkers or transient elastography are not available, the aspartate aminotransferase to platelet ratio index or fibrosis-4 index can prove helpful, but neither is sensitive enough to rule out substantial fibrosis.  
- No recommendation for or against Fibrotest.  
- Consider biopsy when more accurate fibrosis staging would impact treatment decisions.  
- Individuals with clinically evident cirrhosis do not require additional staging (biopsy or noninvasive assessment). |
| Horowitz (2017) | **Key points:**  
- Imaging options to diagnose cirrhosis include assessment for morphologic features on cross sectional imaging (e.g., ultrasonography, computed tomography, and magnetic resonance imaging), and elastography is used to diagnose liver fibrosis and cirrhosis.  
- Noninvasive assessment of liver fibrosis using serologic tests is not reliable because of
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| Houot (2016) | **Key points:**  
  - Systematic review and meta-analysis of 71 direct comparisons of Fibrotest, aspartate aminotransferase-platelet ratio index, fibrosis-4 index, or transient elastography to biopsy, in persons with either advanced fibrosis or cirrhosis.  
  - Overall quality: good (four studies), fair (53 studies), and poor (14 studies).  
  - Area under the receiver operating curve (AUROC) (median, credibility interval):  
    - Grouping all hepatitis C and B virus, identifying advanced fibrosis favored Fibrotest versus transient elastography (0.06, 0.02 to 0.09), Fibrotest versus aspartate aminotransferase to platelet ratio index (0.05, 0.03 to 0.07).  
    - For identifying cirrhosis transient elastography versus aspartate aminotransferase-platelet ratio index (0.07, 0.02 to 0.13) and fibrosis-4 versus aspartate aminotransferase-platelet ratio index (0.04, 0.02 to 0.05), but no significant differences found for the remaining comparisons.  
    - Similar rankings were observed in chronic hepatitis C and B virus etiologies. |
| Chou (2013) for the Agency for Healthcare Research and Quality | **Key points:**  
  - Systematic review of 40 studies of diagnostic accuracy in screened populations: Fibrotest versus liver biopsy (20 studies); FIBROspect versus liver biopsy (four studies); aspartate aminotransferase-platelet ratio index versus Fibrotest (16 studies).  
  - Quality of evidence: Fibrotest versus liver biopsy (high); FIBROspect versus liver biopsy (low); aspartate aminotransferase-platelet ratio index versus Fibrotest (moderate). Studies generally enrolled a broad spectrum of patients with varying severity of fibrosis and other markers of hepatitis C virus infection severity; results are likely applicable to a screening population.  
  - Fibrotest: the median AUROC = 0.79 (range 0.70 to 0.89) (Metavir F2 – F4, Ishak 3 – 6, or equivalent); FIBROspect: median AUROC=0.86 (range 0.82 to 0.90) (Metavir F2 – F4, Ishak 3 – 6, or equivalent).  
  - Comparison of aspartate aminotransferase-platelet ratio index and Fibrotest showed similar AUROC estimates.  
  - Results were robust to changes in biopsy specimen length and aminotransferase levels.  
  - Insufficient evidence to determine clinical outcomes associated with various testing strategies. |

**References**

**Professional society guidelines/other:**


**Peer-reviewed references:**


**Centers for Medicare & Medicaid National Coverage Determinations:**

No National Coverage Determinations identified as of the writing of this policy.

**Local Coverage Determinations:**

No Local Coverage Determinations identified as of the writing of this policy.

**Commonly submitted codes:**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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<td>Infectious disease, hcv, six biochemical assays (alt, a2-macroglobulin, apolipoprotein a-1, total bilirubin, ggt, and haptoglobin) utilizing serum, prognostic algorithm reported as scores for fibrosis and necroinflammatory activity in liver</td>
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