FibroTest/FibroSURE

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

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<th>Procedures addressed by this guideline</th>
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<td>ASH Fibrosure</td>
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What is FibroTest/FibroSURE

Definition

Liver fibrosis is a condition that can lead to cirrhosis, liver failure, and portal hypertension; it is defined by the accumulation of excess proteins such as collagen, which leads to the buildup of scar tissue.¹

- There are many disease pathways that can lead to fibrosis, such as hepatitis B and C viruses (HBV and HCV, respectively), heavy alcohol use, and metabolic disease. Such diseases cause the liver cells (hepatocytes) to function improperly, which leads to the excess buildup of protein.

- Evaluating the extent of liver fibrosis is an important factor for clinicians making treatment decisions for patients with hepatitis B and C. Liver biopsy is currently considered to be the gold standard for evaluating liver fibrosis; however, obtaining a liver biopsy involves invasive surgery. As a result, several non-invasive alternatives have been developed, including FibroTest.

- FibroTest uses indirect markers to estimate the extent of fibrosis.¹ FibroTest (licensed in the United States as FibroSURE) was developed as an alternative to liver biopsy in the assessment of liver fibrosis. The remainder of this guideline will refer to the test as FibroSURE.

- FibroSURE is a combination of five biochemical assays: alpha2-macroglobulin, haptoglobin, apolipoprotein A1, gamma glutamyl transpeptidase (GGT) and total bilirubin. An additional component – alanine aminotransferase (ALT) – is infrequently used to test for necroinflammatory lesions. This addition is known as ActiTest. The results of these assays are factored together, along with patient age,
gender, height, and weight to produce a final FibroSURE score and/or ActiTest stage.²

- FibroSURE is intended for patients with chronic viral hepatitis B or C, alcoholic liver disease, and non-alcoholic steatohepatitis (NASH). Under the broad brand name of FibroMax, there are five distinct test panels: FibroSURE, ActiTest, SteatoTest, NashTest and AshTest.²

**Test information**

- FibroSURE™ is a serum biomarker test that is designed to assess liver fibrosis in patients with chronic viral hepatitis B or C, alcoholic liver disease, and metabolic steatohepatitis (for those who are overweight, have diabetes, or hyperlipidemia).
- This test uses serum or plasma from a blood sample, preferably from a patient who has fasted or had a light meal prior to blood draw.
- The specific assays performed are as follows:
  - Alpha-2-macroglobulin
  - Haptoglobin
  - Apolipoprotein A1
  - Gamma-glutamyl transpeptidase (GGT)
  - Total bilirubin
  - ALT (an additional component that, when performed, deems the panel ActiTest)
- The FibroSURE score ranges from 0-1 and is proportional to the severity of fibrosis. FibroSURE scores have been assigned a corresponding METAVIR stage, as well as a Knodell and Ishak stage. Results are displayed using a three-color severity scheme along with the numeric score (green=absent/minimal, orange=moderate, and red=significant).

**Guidelines and evidence**

**American Association for the Study of Liver Disease**

The American Association for the Study of Liver Disease published a practice guideline (2018) stating:³

- “Liver stiffness measurements (elastography) are more accurate than serum fibrosis panels (e.g. aspartate aminotransferase [AST] to platelet ratio index or FIB-4) in predicting significant or advanced fibrosis. (123,124) Noninvasive methods overestimate fibrosis if high levels of necroinflammation, as reflected by elevated ALT, are present.”
- “Liver biopsy offers the only means of assessing both fibrosis and inflammation.”
• Of alternate/non-invasive methods, elastography is preferred.

**World Health Organization**

The WHO has published documents on several liver-related diseases.

• Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection (2018):4
  
  o “In resource-limited settings, WHO recommends that the assessment of liver fibrosis should be performed using non-invasive tests (e.g. aspartate/platelet ratio index (APRI) score or FIB-4 test, see existing recommendations, p. xvii). This can determine if there is cirrhosis before initiation of treatment.”

• Guidelines for the care and treatment of persons diagnosed with chronic hepatitis B virus infection (2015):5
  
  o “Aspartate aminotransferase (AST)-to-platelet ratio index (APRI) is recommended as the preferred non-invasive test (NIT) to assess for the presence of cirrhosis (APRI score >2 in adults) in resource-limited settings. Transient elastography (e.g., FibroScan) or FibroTest may be the preferred NITs in settings where they are available and cost is not a major constraint. (Conditional recommendation, low quality of evidence)”

**World Gastroenterology Organisation**

The World Gastroenterology Organisation has published documents on several liver-related diseases.

• Hepatitis C (2017)6
  
  o The extent of hepatic fibrosis should be checked using noninvasive measures:
    
    ▪ “Studies have demonstrated that FibroScan is a sensitive alternative to liver biopsy. The amount of fibrosis can be quantified very easily and reliably in more than 95% of the patients [45]. A correct interpretation of transient elastography must have an interquartile range/median values of < 30% and serum ALT < 5 × upper limit of normal. There should be no ongoing excessive alcohol intake, and the patient’s BMI should be taken into account. If the BMI is over 30 kg/m2, using extralarge (XL) probes may be considered.”
    
    ▪ “In resource limited regions, and in places where FibroScan is not readily available, scores such as the fibrosis 4 index (FIB4), AST to platelet ratio index (APRI), and acoustic radiation force impulse (ARFI) can be used. An APRI score ≥ 2 can be used to predict the presence of cirrhosis. At its cut-off point, the ARFI score has a sensitivity of 48% but a specificity of 94% for predicting cirrhosis. It can also be used to predict the presence of significant fibrosis (stages 2–4). Using a cut-off value of 1.5, the sensitivity is 37% and the specificity is 95% for significant fibrosis [46,47].”
• Hepatitis B (2015)\(^7\)
  o “Measurement of liver fibrosis by serological testing, FibroScan (transient elastography), or liver biopsy.”
  o Determination of the severity of liver disease:
    ▪ “Laboratory tests for inflammation (ALT), hepatic function (bilirubin, albumin, coagulation factors and viral load (HBV DNA), if available”
    ▪ “Hepatic ultrasound examination”
    ▪ “Non-invasive methods to assess fibrosis (serum panels, transient elastography)”
  o Liver biopsy "can help exclude other coexistent causes of liver disease and clarify the diagnosis when ALT and HBV DNA levels are discordant."

• Esophageal Varices (2014)\(^8\)
  o In recommendations on “Esophageal varices”, the WGO states that the “predictive accuracy is still unsatisfactory” for noninvasive markers such as FibroSURE.

**European Association for the Study of the Liver**

The European Association for the Study of the Liver (EASL) (2015) published a guideline entitled “Non-invasive test for evaluation of liver disease severity and prognosis”. In this document the EASL discusses the pros and cons of serum biomarkers of liver disease, stating that “further validation is warranted”.\(^9\)

**British HIV Association**

In a 2013 document the Association states:\(^10\)

• “The Writing Group suggests hepatic transient elastography (TE) (FibroScan™ or Acoustic Radiation Force Impulse [ARFI]) as the non-invasive investigation of choice (2B) but if unavailable, or when reliable TE readings are not obtained, a blood panel test (aspartate transaminase to platelet ratio index [APRI], FIB-4, enhanced liver fibrosis [ELF], Fibrometer™, Forns Index, FibroTest™) as an alternative (2C).”

**Peer Reviewed Literature**

• Several systematic reviews evaluating evidence of FibroSURE have pooled results of multiple studies; one review found the area under the receiver-operating curve (AUROC, an index of overall test sensitivity and specificity) was in the range of 0.75 to 0.84 for fibrosis; from 0.81-0.92 for cirrhosis in patients with HCV; 0.72-0.90 for detecting fibrosis; and from 0.75-0.92 for detecting cirrhosis in patients with HBV.\(^11\) Another systematic review reported a hierarchical summary receiver-operating
characteristic (HSROC) of 0.84 for fibrosis, and 0.87 for cirrhosis in patients with HBV.\textsuperscript{12} A pooled meta-analysis estimated a sensitivity of 71.2\% and a specificity of 81.4\% in patients with HBV.\textsuperscript{12} In patients with ALD, the sensitivity for detecting fibrosis was 85\% and specificity was 66\%; for detecting cirrhosis, sensitivity rose to 91\% and specificity to 87\%.\textsuperscript{13} Different analysis methods resulted in different AUROCs for diagnosing NAFLD; a weighting method produced an AUROC of 0.85, while a random effects model yielded an AUROC of 0.72.\textsuperscript{14} In a prospective study of nearly 300 patients with alcohol-related liver disease, while FibroTest showed accuracy in predicting advanced fibrosis, it was outperformed by Enhanced Liver Fibrosis (ELF) test and elastography.\textsuperscript{15}

- Despite many different types of studies and analysis methods, the diagnostic accuracy of FibroSURE generally seems to fall within a consistent, albeit moderate range. FibroSURE also generally seems to perform better in diagnosing cirrhosis than fibrosis.

- FibroSURE is intended as an alternative to liver biopsy, which is currently considered the gold standard for staging liver fibrosis and cirrhosis. As a blood-based test, FibroSURE is an appealing alternative to the invasive nature of a biopsy. However, the evidence as a whole is insufficient and does not yet fully support using FibroSURE as a stand-alone test.\textsuperscript{11-20} Furthermore, several guideline organizations have published evidence-based recommendations regarding the treatment of liver disease and do not definitively recommend FibroSURE as a first-line choice; instead, they recommend the test as an alternative after other preferred tests, or in settings where resources are not constrained.

Criteria

- This test is considered investigational and/or experimental.
  
  o Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.
  
  o In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.
References


