

Serologic Testing for Liver Fibrosis

Policy MP-069

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1. Policies are subject to change in accordance with State and Federal notice requirements.
2. Policies outline coverage determinations for U of U Health Plans Commercial, Healthy U (Medicaid) and Advantage U (Medicare) plans. Refer to the "Policy" section for more information.
3. **This Medical Policy does not guarantee coverage or payment of the service. The service must be a benefit in the member's plan and the member must be eligible for coverage at the time of service. Additional payment guidelines may be applied that are not included in this policy.**

Description:

Hepatic fibrosis occurs in response to chronic liver injury. It includes collapse of hepatic lobules, formation of fibrous septae, and hepatocyte regeneration with nodule formation. Extracellular matrix components accumulate in the liver as a result of imbalances in their production, deposition, and degradation. This diffuse process is now recognized as a dynamic process with the potential for significant resolution. However, there is still concern of hepatic fibrosis ultimately progressing into cirrhosis.

Conventional biochemical and serological tests, when examined alone, are of little value for the assessment of fibrosis. As a result, histopathological examination of a liver biopsy specimen is the gold standard for staging hepatic fibrosis. However, liver biopsy is an invasive procedure which can have associated complications and is generally not welcomed by patients. Also, only being able to sample a small portion of the liver may create susceptible to sampling variation and inter- and intra-observer variability. These issues have led to the development of noninvasive means to estimate the amount of hepatic fibrosis present.

Due the invasive nature of liver biopsies alternative testing has been developed to assess for hepatic fibrosis/cirrhosis. There are two general categories of noninvasive tests for fibrosis: serologic panels of tests and radiologic tests.

Radiologic studies commonly performed include hepatic elastography (Fibroscan) or magnetic resonant (MR) elastography. Elastography estimates liver stiffness by applying mechanical waves and measuring their propagation speed through tissue using imaging.

Serologic testing is more widely available. However, while tremendous progress has been made in improving the accuracy of serum markers of hepatic fibrosis, they cannot yet supplant direct histologic analysis. When available, radiologic measurement of elasticity can be used alone or in combination with serologic testing. Transient elastography is the most commonly used imaging test because it is widely available and has been validated in large populations. Other imaging methods for assessing hepatic fibrosis include magnetic resonance elastography (MRE), acoustic radiation force impulse imaging (ARFI), and cross-sectional imaging.

All the serum tests have limitations:

- They typically reflect the rate of matrix turnover, not deposition, and thus tend to be more elevated when there is high inflammatory activity. By contrast, extensive matrix deposition can go undetected if there is minimal inflammation;
- None of the markers are liver-specific, and concurrent sites of inflammation or fibrosis may contribute to serum levels;
- Serum levels are affected by clearance rates, which may be impaired either due to cellular dysfunction or impaired biliary excretion;
- They are surrogates, not biomarkers.

Overall, studies of the various panels suggest that they have good ability to differentiate patients with significant fibrosis (F2 to F4) from those without significant fibrosis (F0 to F1). A disadvantage of these panels is that they are not able to reliably differentiate between the different stages of fibrosis, and indeterminate outcomes are common (up to 50 percent with the FibroTest). No panel has yet emerged as the standard of care, and the choice of panel is often dictated by local availability.

Policy Statement and Criteria

1. Commercial Plans

U of U Health Plans does NOT cover serum marker tests of hepatic fibrosis, used to produce a predictive score indicating the probability of liver fibrosis, as they are considered investigational and not medically necessary in the diagnosis and monitoring of individuals with chronic liver disease, including but not limited to hepatitis C, hepatitis B, and nonalcoholic fatty liver disease (NAFLD).

The following proprietary algorithm-based serum markers for liver fibrosis are considered investigational/not medically necessary for any indication (*this may not be an all-inclusive list*):

- ASH FibroSURE® (Laboratory Corporation of America, Burlington, NC)
- Enhanced Liver Fibrosis™ (ELF™, Siemens Healthcare Laboratory, LLC., Malvern, PA)
- FibroMeter™ (ARUP Laboratories, Salt Lake City, UT)
- FIBROSpect HCV® (Prometheus Biosciences, Inc., San Diego, CA)
- FIBROSpect NASH® (Prometheus Biosciences, Inc., San Diego, CA)

- FibroTest-ActiTest™ (BioPredictive S.A.S., Paris, France)
- HCV FibroSure® (Laboratory Corporation of America, Burlington, NC)
- LIVERFAST™ (Fibronostics, Orlando, FL)
- NASH FibroSURE® (Laboratory Corporation of America, Burlington, NC)

2. Medicaid Plans

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website at:

<http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

CPT/HCPCS codes covered by Utah State Medicaid may still require further evaluation to determine medical necessity for coverage.

3. Medicare Plans

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicare policies and coverage, please visit their search website at:

<http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or [the manual website](#)

Clinical Rationale

Chou et al., in 2013 published a systematic review related to noninvasive serologic testing available at the time. This review noted that when use in identifying clinically significant fibrosis, the platelet count, age-platelet index, aspartate aminotransferase-platelet ratio index (APRI), FibroIndex, FibroTest, and Forns index had median positive likelihood ratios of 5 to 10 at commonly used cutoffs and areas under the receiver-operating characteristic curve (AUROCs) of 0.70 or greater (range, 0.71 to 0.86). For identifying cirrhosis, the platelet count, age-platelet index, APRI, and Hepascore had median positive likelihood ratios of 5 to 10 and AUROCs of 0.80 or greater (range, 0.80 to 0.91). The Göteborg University Cirrhosis Index and the Lok index had slightly lower positive likelihood ratios (4.8 and 4.4, respectively). In direct comparisons, the APRI was associated with a slightly lower AUROC than the FibroTest for identifying fibrosis and a substantially higher AUROC than the aspartate aminotransferase-alanine aminotransferase ratio for identifying fibrosis or cirrhosis. The authors note limitations of their findings included that only English-language articles were included, and most studies had methodological limitations, including failure to describe blinded interpretation of liver biopsy specimens and inadequate description of enrollment methods.

Houot et al, also completed a systematic review with a metaanalysis directly comparing biomarkers for diagnosing fibrosis in chronic hepatitis C and B. Their review observed APRI had lower performances than FIB-4, TE and FibroTest. TE had lower performance than FibroTest for identifying advanced fibrosis in All-CB, without significant difference for identifying cirrhosis in all groups.

In 2015, Xiao et al completed another systematic review comparing the diagnostic accuracy of aspartate aminotransferase to platelet ratio index and fibrosis-4 index for detecting liver fibrosis in adult patients with chronic hepatitis B virus infection. This systemic review and meta-analysis included 16 articles of APRI only, 21 articles of APRI and FIB-4 and two articles of FIB-4 for detecting different levels of liver fibrosis. Their meta-analysis suggested that APRI and FIB-4 can identify hepatitis B-related fibrosis with only moderate sensitivity and accuracy.

In a study by Leroy et al published in 2006, they assessed the Overall diagnostic performance of scores determined by AUROCs ranged from 0.86 for Fibrometer to 0.78 for Forns' score (NS) for discriminating F0F1 versus F2F3F4. For discriminating F0F1F2 versus F3F4, AUROCs ranged from 0.91 for Fibrometer to 0.78 for Forns' score ($p < 0.02$). Significant or extensive fibrosis was predicted in 10-86% of patients with positive predictive value (PPV) ranging from 55% to 94%. Using logistic regression, statistical independence was demonstrated for MP3, Fibrotest and APRI. They observed the best combinations could select one-third of patients for whom either absence of significant fibrosis or presence of extensive fibrosis could be predicted with more than 90% of certainty.

Ragazzo et al in a study published in 2017 evaluated the accuracy of transient elastography-FibroScan®, acoustic radiation force impulse (ARFI), enhanced liver fibrosis (ELF), the aspartate aminotransferase-to-platelet ratio index (APRI), and the FIB-4 index compared with liver biopsy in hepatitis C. A total of 107 patients were included in the study. This study confirmed transient elastography remained the most effective method for evaluating all degrees of fibrosis. The accuracy of all methodologies was best at F4.

There are a number of publications addressing multiple scoring systems including multicenter, retrospective cohort studies, systematic reviews and meta-analyses. The scoring systems were found to have low diagnostic accuracy therefore resulting in poor prediction of fibrosis (Bhat, 2017; Mansoor, 2015; Xiao, 2015; Xiao, 2017; Xu, 2019).

Several Societies have also weighed in on serologic testing in the assessment of hepatic fibrosis. In a clinical care pathway (Kanwal, 2017) on the screening and evaluation of hepatitis C, the American Gastroenterological Association (AGA) recommends “In the absence of clinically apparent cirrhosis, there is the need to assess degree of liver fibrosis. Such assessment can be done noninvasively via elastography (usually “vibration-controlled” or Fibroscan®), serum biomarkers (FIB4 or aspartate aminotransferase to platelet ratio index), or various proprietary markers...The results of non-invasive studies provide helpful information to patient and clinician regarding fibrosis stage, though all may suffer from occasional false readings and must be tempered by clinical judgment.”

In 2017, the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) published a clinical practice guideline for the diagnosis and treatment of NAFLD in children. The guideline noted the accuracy of currently marketed fibrosis biomarker tests in children, and markers such as AST to platelet ratio and hyaluronic acid (and their optimal cutoffs), remain to be determined.

The 2019 American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) have also made recommendations for testing, managing, and treating hepatitis C include statements addressing both adult and pediatric care. The AASLD concludes the evidence shows benefit in adults but the pediatric population requires additional study for serum fibrosis markers. The evidence for these conclusions was rated Class I, Level A-Evidence and/or general agreement; data derived from multiple randomized clinical trials, meta-analyses, or equivalent for appropriate decision making for HCV treatment strategies and determining the need for initiating additional measures for cirrhosis management, but felt insufficient to support a recommendation for this testing in pediatric populations. The guidelines did not differentiate between radiological and serologic noninvasive testing.

The AASLD in conjunction with the AGA and the American College of Gastroenterology (ACG) published a practice guidance document (Chalasan, 2018) on the diagnosis and management of nonalcoholic fatty liver disease (NAFLD). The guideline does not recommend screening (including higher-risk individuals with diabetes or obesity) given significant gaps in knowledge regarding the diagnosis, natural history, and treatment of NAFLD, as well as uncertainties around which diagnostic test to use (since liver enzyme levels may be normal in individuals with NAFLD). The guideline notes Liver biopsy should be considered in patients with NAFLD who are at increased risk of having SH (steatohepatitis) and/or advanced fibrosis. It also notes, the presence of MetS, NFS or FIB-4, or liver stiffness measured by VCTE or MRE may be used for identifying patients who are at risk for SH and/or advanced fibrosis.

In a 2018 update on the prevention, diagnosis, and treatment of chronic hepatitis B (Terrault, 2018), the AASLD notes liver biopsy offers the only means of assessing both fibrosis and inflammation. If the biopsy specimen shows moderate or severe inflammation (A2 or A3) or significant fibrosis (F2), treatment is recommended. Alternative methods to assess fibrosis are elastography (preferred) and liver fibrosis biomarkers (e.g., FIB-4 or FibroTest). If these noninvasive tests indicate significant fibrosis (F2), treatment is recommended.

Applicable Coding

CPT Codes

Not Covered:

- 81599** Unlisted multianalyte assay with algorithmic analysis
- 82977** Glutamyltransferase, gamma (GGT)
- 83520** Immunoassay, analyte, quantitative; not otherwise specified (no specific code for FIBROSpect)
- 83883** Nephelometry, each analyte not elsewhere specified (no specific code for FIBROSpect)
- 88342** Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure
- 0002M** Liver disease, ten biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, haptoglobin, AST, glucose, total cholesterol and triglycerides) utilizing serum, prognostic algorithm reported as quantitative scores for fibrosis, steatosis and alcoholic steatohepatitis (ASH) (**ASH FibroSURE™**)
- 0003M** Liver disease, ten biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, haptoglobin, AST, glucose, total cholesterol and triglycerides) utilizing serum, prognostic algorithm reported as quantitative scores for fibrosis, steatosis and nonalcoholic steatohepatitis (NASH) (**NASH FibroSURE™**)
- 0014M** Liver disease, analysis of 3 biomarkers (hyaluronic acid [HA], procollagen III amino terminal peptide [PIIINP], tissue inhibitor of metalloproteinase 1 [TIMP-1]), using immunoassays, utilizing serum, prognostic algorithm reported as a risk

score and risk of liver fibrosis and liver-related clinical events within 5 years
(Enhanced Liver Fibrosis™ [ELF™])

0166U Liver disease, 10 biochemical assays (a2-macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, GGT, ALT, AST, triglycerides, cholesterol, fasting glucose) and biometric and demographic data, utilizing serum, algorithm reported as scores for fibrosis, necroinflammatory activity, and steatosis with a summary interpretation (**LiverFAST®**)

81596 Infectious disease, chronic hepatitis C virus (HCV) infection, 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 (**FibroSURE™**)

84999 Unlisted chemistry procedure

HCPCS Codes

No applicable codes

ICD-10 Codes

K70.0-K77 Liver diseases code range (fibrosis is K74.0)

R94.5 Abnormal results of liver function tests

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