Bright HealthCare™

Medical Policy

Liver Fibrosis Serum Testing	
MEDICAL POLICY NUMBER	MED_Clin_Ops_039
CURRENT VERSION EFFECTIVE DATE	March 1, 2023
APPLICABLE PRODUCT AND MARKET	*Individual Family Plan:* All Plans *Small Group*: All Plans *Medicare Advantage:* All Plans

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PURPOSE

The purpose of this policy is to provide background and for exclusion of serum panel testing for evaluation and long-term monitoring of liver fibrosis.

POLICY/CRITERIA

The use of liver fibrosis serum panel testing (e.g., FibroSure or Siemens ELF™) for the evaluation and monitoring of liver fibrosis is **investigational** as there is insufficient peer-reviewed evidence to indicate effectiveness.

BACKGROUND

Fibrosis of the liver occurs as a result of continuous inflammation and injury from a variety of causes such as hepatitis B, hepatitis C, alcohol or non-alcoholic fatty liver disease (NAFLD). Some individuals with NAFLD can develop nonalcoholic steatohepatitis (NASH) which is an aggressive form of fatty liver disease marked by liver inflammation and may progress to cirrhosis and liver failure. NASH is the second most common indication for liver transplant in 2019, and the fastest increasing indication for liver transplantation.[3]

Fibrosis is a wound healing response in which damaged regions are encapsulated by an extracellular matrix or scar. It develops in almost all patients with chronic liver injury at variable rates depending in part upon the cause of liver disease and host factors. In contrast, for unclear reasons, patients with self-limited injury (such as fulminant hepatitis) do not develop scarring despite an abundance of fibrogenic stimuli, unless they go on to develop chronic injury. The composition of the hepatic scar is similar regardless of the cause of injury. Furthermore, hepatic fibrosis represents a paradigm for wound healing in other tissues, including skin, lung, and kidney, since it involves many of the same cell types and mediators. Fibrosis occurs earliest in regions where injury is most severe, particularly in chronic inflammatory liver disease due to alcohol or viral infection. As an example, pericentral injury is a hallmark of alcoholic hepatitis; the development of pericentral fibrosis (also known as sclerosing hyaline necrosis or perivenular fibrosis) is an early marker of likely progression to panlobular cirrhosis.

The development of fibrosis usually requires several months to years of ongoing injury. Two exceptions in adults are veno-occlusive disease and mechanical biliary obstruction, in which (for unclear reasons) fibrosis can progress more rapidly.

While fibrosis is reversible in its initial stages, progressive fibrosis can lead to cirrhosis. The exact point when fibrosis becomes irreversible is incompletely understood. However, increasing evidence suggests that even early stages of cirrhosis may be reversible. Furthermore, an understanding of the molecular mechanisms involved in fibrogenesis has a number of clinical implications, including the development of interventions designed to impede or reverse hepatic fibrosis, some of which are already available. Despite significant advances in understanding hepatic fibrosis and defining targets of therapy, there are no antifibrotic drugs yet approved for clinical use in patients with advanced liver disease. (Source: UpToDate[1])

> “Chronic liver diseases are major global health problems causing approximately 800,000 deaths per year worldwide. Liver fibrosis is the common pathologic process of all chronic liver diseases, regardless of the cause, which results from excessive accumulation of extracellular matrix. Liver fibrosis may progress to cirrhosis and eventually death. However, increasing evidence suggests that even advanced fibrosis is reversible, although end-stage cirrhosis is irreversible and affected patients can only survive with a liver transplant. Estimating the current degree of fibrosis is crucial for determining whether the fibrosis could be reversed with treatment.
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> Liver fibrosis evaluation methods can be divided into those that are invasive and those that are non-invasive. Liver biopsy is an invasive method that has long been regarded as the ‘gold standard’ for staging liver fibrosis. Biopsy allows physicians to obtain diagnostic information not only on fibrosis, but also on many other liver-injuring processes, such as inflammation, necrosis, steatosis and hepatic deposits of iron or copper. However, several issues prevent the routine use of liver biopsy as a clinical tool, including risk of injury to the patient, variable accessibility of the damaged section of the liver, high cost, sampling errors and inaccuracy due to inter- and intra-observer variability of pathologic interpretations.
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> Non-invasive methods include serum and genetic tests, and imaging techniques. In recent years, interest in identifying and describing liver fibrosis using molecular serum markers has been on the rise. Serum markers offer a cost-effective alternative to liver

biopsy for both patients and clinicians. In addition to being less invasive, there is a low risk of sampling error and small observer-related variability. Moreover, measurements may be performed repeatedly over time, allowing for ongoing monitoring of fibrosis. However, there are many limitations for serum biomarkers. They are not liver-specific and have a tendency to be more elevated in the presence of inflammation. In addition, serum marker readings may be falsely high due to their low clearance rates, which are influenced by dysfunction of endothelial cells, impaired biliary excretion or renal function. Until now, most serum biomarkers have only been used as investigative, rather than diagnostic, parameters in the clinic."[2]

The literature indicates ongoing research into the value, effectiveness and appropriateness for non-invasive serum markers as a tool to better manage the increasing impact of liver disease and progressive fibrosis. These tests will need to be evaluated on an ongoing basis to determine when they meet the threshold for generally accepted medical practice and included in evidence-based clinical practice guidelines. The large costs in both economic and human suffering of liver fibrosis is highlighted by the following; "In an analysis of data from the Scientific Registry of Transplant Recipients (2002 through 2019), we found NASH to be the second most common indication for liver transplant in 2019, and the fastest increasing indication. In 2019, NASH was the leading indication for liver transplantation among women without hepatocellular carcinoma."[3]

DEFINITIONS

Acronyms:

- Enhanced Liver Fibrosis (ELF)
- Hepatitis C virus (HCV)
- Non-alcoholic fatty liver disease (NAFLD)
- Non-alcoholic steatohepatitis (NASH)

CODING

Applicable CPT® codes:

0001M HCV FibroSure & FibroTest-ActiTest: 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
0002M AHS FibroSure 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)
0003M NASH FibroSure 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)
0014M - Enhanced Liver Fibrosis (ELF) test: Liver disease, analysis of 3 biomarkers (hyaluronic acid [HA], procollagen III amino terminal peptide [PIIINP], tissue inhibitor of metalloproteinase 1 [TIMP-hyphen1]), using immunoassays, utilizing serum, prognostic algorithm reported as a risk score and risk of liver fibrosis and liver-hyphenrelated clinical events within 5 years
81596: Multianalyte Assays with Algorithmic Analyses HCV FibroSure - Assessment of liver status following a diagnosis of HCV. Baseline determination of liver status before initiating HCV therapy. Posttreatment assessment of liver status six months after completion of therapy. Noninvasive assessment of liver status in patients who are at increased risk of complications from a liver biopsy.
81599: Multianalyte Assays with Algorithmic Analyses

EVIDENCE BASED REFERENCES

1. Bright Health Summary of Research on Liver Fibrosis Serum
2. UpToDate: Pathogenesis of hepatic fibrosis. Author: Scott L Friedman, MD Section Editor: Bruce A Runyon, MD Deputy Editor: Kristen M Robson, MD, MBA, FACG Literature review current through: Dec 2020. | This topic last updated: Jan 29, 2020.
3. Liu T, Wang X, Karsdal MA, Leeming DJ, Genovese F. Molecular serum markers of liver fibrosis. Biomark Insights. 2012;7:105-117. doi:10.4137/BMI.S10009
4. Zobair M. Younossi, Maria Stepanova, Janus Ong, Greg Trimble, Saleh AlQahtani, Issah Younossi, Aijaz Ahmed, Andrei Racila, Linda Henry, Nonalcoholic Steatohepatitis Is the Most Rapidly Increasing Indication for Liver Transplantation in the United States, Clinical Gastroenterology and Hepatology, 2020, ISSN 1542-3565, https://doi.org/10.1016/j.cgh.2020.05.064.
5. https://www.siemens-healthineers.com/laboratory-diagnostics/assays-by-diseases-conditions/liver-disease/elf-test
6. NICE Guidelines: NICE Guidelines: Non-Alcoholic Fatty Liver Disease: assessment and management.
7. Inadomi C, Takahashi H, Ogawa Y, et al. Accuracy of the enhanced liver fibrosis (ELF) test and combination of ELF and noninvasive tests for the diagnosis of advanced liver fibrosis in patients with nonalcoholic fatty liver disease. Hepatol Res. 2020. [Epub ahead of print].

POLICY HISTORY

This policy has been approved by the approval body listed below or has received other necessary approval pursuant to Bright HealthCare's policies on clinical criteria and policy development.

Original Effective Date	February 18, 2021
Revision	*Version History:* V2: February 25, 2022 Annual review – no changes V3: March 01, 2023 Adopted by MA UM Committee (no policy revisions made)