CLINICAL MEDICAL POLICY	
Policy Name:	Liver Fibrosis Assessment Biomarkers
Policy Number:	MP-137-MD-PA
Responsible Department(s):	Medical Management
Provider Notice/Issue Date:	09/01/2025
Effective Date:	10/01/2025
Next Annual Review:	07/2026
Revision Date:	07/16/2025
Products:	Highmark Wholecare℠ Medicaid
Application:	All participating hospitals and providers
Page Number(s):	1 of 6

Policy History

Date	Action
10/01/2025	Provider Effective date
08/11/2025	PARP Approval
07/16/2025	QI/UM Committee review
07/16/2025	Policy initially developed

Disclaimer

Highmark Wholecare℠ medical policy is intended to serve only as a general reference resource regarding coverage for the services described. This policy does not constitute medical advice and is not intended to govern or otherwise influence medical decisions.

Policy Statement

Highmark Wholecare℠ will not coverage under the laboratory testing benefits of the Company's Medicaid products for non-invasive, multianalyte assays that utilize proprietary algorithms for the screening, diagnosis or monitoring of liver fibrosis, as these tests are considered experimental/investigational.

This policy is designed to address medical necessity guidelines that are appropriate for the majority of individuals with a particular disease, illness or condition. Each person's unique clinical circumstances warrant individual consideration, based upon review of applicable medical records.

(Current applicable Pennsylvania HealthChoices Agreement Section V. Program Requirements, B. Prior Authorization of Services, 1. General Prior Authorization Requirements.)

Definitions

Prior Authorization Review Panel (PARP) – A panel of representatives from within the PA Department of Human Services who have been assigned organizational responsibility for the review, approval and denial of all PH-MCO Prior Authorization policies and procedures.

Proprietary Laboratory Analyses (PLA) Codes - alpha-numeric CPT codes with a corresponding descriptor for labs or manufacturers that want to more specifically identify their test. Tests with PLA codes must be performed on human specimens and must be requested by the clinical laboratory or the manufacturer that offers the test. The codes consist of four numbers ending in a capital U.

Fibrosis – the development of fibrous connective tissue as a reparative response to injury or damage. Fibrosis may refer to the connective tissue deposition that occurs as part of normal healing or to the excess tissue deposition that occurs as a pathological process.

Non-alcoholic fatty liver disease (NAFLD) - also known as metabolic dysfunction-associated steatotic liver disease (MASLD), is a condition in which excess fat builds up in the liver. The build-up is not caused by heavy alcohol consumption. The two types of NAFLD are non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). NAFL occurs when an individual has fat in the liver but little or no inflammation or liver damage complications.

Non-alcoholic steatohepatitis (NASH) - also referred to as metabolic dysfunction-associated steatohepatitis (MASH), is a form of NAFLD in which an individual experiences inflammation of the liver and liver damage, in addition to fat in the liver. The inflammation and liver damage can cause fibrosis of the liver. NASH may lead to cirrhosis and liver cancer.

Metabolic dysfunction-associated steatotic liver disease (MASLD) - a condition where there is a buildup of fat in the liver in individuals with diabetes, obesity, high blood pressure, or high cholesterol and drink little to no alcohol. MASLD is part of the metabolic syndrome characterized by diabetes, or pre-diabetes (insulin resistance), being overweight or obese, elevated blood lipids such as cholesterol and triglycerides, as well as high blood pressure.

Procedures

1. A single HCV FibroSURE® /FibroTest™ (CPT code 81596) multianalyte assay is considered medically necessary for the initial evaluation of individuals with chronic liver disease.

2. Multiple multianalyte assays in an individual's lifetime are considered not medically necessary, and therefore not covered, because the safety and/or efficacy of the testing's use in monitoring individuals with chronic liver disease cannot be established by review of available peer-reviewed publications.

3. Noninvasive, multianalyte assays that utilize proprietary algorithms for the screening, diagnosis or monitoring of liver fibrosis are considered experimental/investigational and, therefore, not covered

for any indications because the safety and/or efficacy of this testing cannot be established by review of available peer-reviewed publications. These test include, but are not limited to, the following:

- LIVERFASt™
- Enhanced Liver Fibrosis (ELF) test
- NASHnext™ (NIS4T™)
- NASH FibroSURE®
- ASH FibroSURE®
- FibroSpect®

4. This policy does not apply to biomarker tests that are performed individually or as part of a non-proprietary scoring system (e.g., FIB-4 or NAFLD Fibrosis Score), or tests performed on tissue obtained from a liver biopsy.

5. Post-payment Audit Statement
   The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Highmark Wholecare℠ at any time pursuant to the terms of your provider agreement.

Summary of Literature

HCV FibroSure®/FibroTest™
FibroSURE/FibroTest is a non-invasive option to diagnose liver fibrosis. The test combines five biochemical assays: alpha2-macroglobulin, haptoglobin, apolipoprotein A1, gamma glutamyl transpeptidase (GGT) and total bilirubin. The tests results combine a person's gender, height, age and weight to reach an algorithmic score from 0-1. The scores are then assigned a corresponding Ishak stage, and a METAVIR stage. It is considered the most widely validated of the non-invasive commercial tests.

FibroSure has been studied in populations with viral hepatitis, NAFLD, and ALD. In a meta-analysis of fibrosis (16 studies) or cirrhosis (13 studies) involving adults with chronic hepatitis B and using liver biopsy as the sole comparator, the authors concluded that FibroTest had suboptimal accuracy (Salkic et al, 2014).

LIVERFASt™
LIVERFASt is a proprietary test that combines 10 biochemical assay results with age, height, weight and gender to render a combination of three scores which are correlated to the degree of liver damage, including fibrosis, necroinflammation and steatosis. Each score is then reported on a scale of 0.00-1.00, with interpretive comments such as "minimal activity" or "significant fibrosis".

There are no sufficient high-quality studies evaluating LIVERFASt. A 2022 study evaluated LIVERFASt in persons with metabolic associated fatty liver disease (MAFLD) which found that non-invasive, baseline testing (liver stiffness measurement, FIB-4 and LIVERFASt) can predict global and liver-related mortality and morbidity in persons with MAFLD (Decraecker et al, 2022).

Enhanced Liver Fibrosis (ELF) test
The purpose of the ELF test is to assess the risk of MASLD progression and is utilized most frequently among persons with, or at high risk for developing, MASLD. This test measures hyaluronic acid (HA), Type

III procollagen peptide (PIIINP) and tissue inhibitor of matrix metalloproteinase 1 (TIMP-1) analytes. An algorithm is then applied to calculate a specific risk score. The two main algorithms used are the Guha algorithm and the Siemens algorithm. The results are highly correlated with an equation available to convert between the two. There is some variation among studies as to the suggested decision thresholds for interpreting the risk score (Vali et al, 2020).

In a systematic review and meta-analysis, the ELF test had an area under the receiver operator characteristic curve (AUROC) of 0.83 (95% CI 0.71-0.90) for detecting advanced fibrosis, which is defined as F $\geq$ 3 on the fibrosis scale. The included studies displayed high heterogeneity with regards to disease severity to study populations, disease prevalence, test result thresholds, and the time interval between biopsy and blood test results. Pathologist review was also highly variable (Vali et al, 2020).

The ELF test clinical utility has not been established. Available studies do not address whether these tests can reduce the need for liver biopsy, improve health outcomes, or guide therapy.

NASHnext™ (NIS4™)

NASHnext is a non-invasive blood test that can predict the risk of MASH by combining the results of four different MASH-associated biomarkers: HbA1c, a2-macroglobin, miR34a, and CH13L1/YKI40.

ASH/NASH FibroSURE®

The test features the same components as the HCV FibroSure, with the algorithm created for individuals suspected of having NAFLD. Separate scores are provided as indicators of the degree of fibrosis, steatosis, and MASH.

In a systematic review and meta-analysis, the NASH FibroSURE/FibroTest used for MASLD/MASH delivered a sub-par performance in detecting fibrosis, but did show promise in detecting cirrhosis. This study demonstrated a wide range of fibrosis and diabetes prevalence and some of the studies were thought to have a high risk of bias (Vali et al, 2021).

FibroSpect®

FibroSpect HCV is a blood test that assist in the detection, staging, and monitoring of the severity of liver fibrosis in persons with the hepatitis C virus (HCV). Test results provide a quantitative fibrosis score to assess and monitor disease risk based on three biomarkers (tissue inhibitor of metalloprotienase-1, hyaluronic acid, and α2-macroglobulin). The test can differentiate between F0-F1 and F2-F4 liver fibrosis.

FibroSpect NASH is a blood test which uses the same biomarkers as the HCV version and assists in the detection, staging, and monitoring of liver fibrosis for MASH. The MASH-specific algorithm seeks to differentiate F0-F2 from F3-F4 liver fibrosis resulting from MASH.

A single-center prospective study comparing the results of FibroSpect to liver biopsy in populations with hepatitis C and a prevalence of fibrosis of 36% demonstrated a PPV of 60.9% and NPV of 82.3% (Zaman et al, 2007). A similar study showed the test to have favorable operating characteristics, but the histologic assessment was poor and the prevalence of fibrosis was 77% (Patel et al, 2008). A retrospective study of individuals undergoing gastric bypass reported the FibroSpect had a high negative predictive value of F2

for greater fibrosis, but a low positive predictive value in the study population which had a fibrosis prevalence of 30.9% (Guajardo-Salinas et al, 2010).

Coding Requirements

Procedure Code

CPT Code	Description
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 (HCV FibroSURE® / FibroTest™)

Non-covered Procedure Codes

These procedure codes will not be reimbursed without Medical Director approval.

CPT Code	Description
0002M	Liver disease, ten biochemical assays (ALT, A2-macroglobulin, apolipoprotein A1, 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 A1, 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®)
0016U	Liver disease, 10 biochemical assays (α2- 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™)
0468U	Hepatology (nonalcoholic steatohepatitis [NASH]), miR-34a-5p, alpha 2-macroglobulin, YKL40, HbA1c, serum and whole blood, algorithm reported as a single score for NASH activity and fibrosis (NASHnext™ [NIS4™])
81517	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] test)
81599	Miscellaneous multianalyte algorithmic assays for non-invasive liver fibrosis assessment
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified

	(FibroSpect®)

Reimbursement

Participating facilities will be reimbursed per their Highmark Wholecare℠ contract.

Reference Sources

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