Noninvasive Tests for Hepatic Fibrosis

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Medical Coverage Policy

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Description

Chronic liver disease (CLD) is an overarching term that includes numerous conditions that contribute to the progressive destruction of liver tissue. CLD can be used to describe both diseases that affect liver cells (hepatocellular) and conditions that affect liver structures and function (eg, cholestatic). Examples of hepatocellular liver conditions include, but may not be limited to, alcohol-associated liver disease (ALD), metabolic dysfunction-associated steatotic liver disease (MASLD [also known as nonalcoholic fatty liver disease or NAFLD])[8] and infections with either hepatitis B virus (HBV) or hepatitis C virus (HCV). Cholestatic conditions include, but may not be limited to, diseases such as primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC).[1,2]

If CLD is left untreated, it can result in hepatic fibrosis, cirrhosis, and, eventually, liver failure. Hepatic fibrosis is the excessive accumulation of fibrotic connective tissue resulting from prolonged inflammation and progressive scarring of the liver. Increased fibrosis causes a corresponding increase in liver stiffness

and, thus, reduces blood flow through the liver. This can lead to hardening of the tissue and death of liver cells.

Liver biopsy is considered the gold standard for definitive diagnosis of fibrosis. However, it is an invasive procedure that may result in complications. For that reason, noninvasive tests, both imaging-based and blood-based, have been developed to diagnose and stage hepatic fibrosis. Examples of these tests include, but may not be limited to:

Elastography

Elastography is a noninvasive, imaging-based method for measuring liver stiffness utilizing ultrasound and low frequency elastic waves. Examples of elastography techniques include, but may not be limited to:

- **Acoustic radiation forced impulse (ARFI) elastography** utilizes ultrasound to measure the tissue displacement that results when a high-intensity acoustic pulse (also referred to as a push pulse) is applied. This technique purportedly provides single one-dimensional measures of tissue elasticity. However, the area can also be positioned on a two-dimensional B mode image. The measurements are expressed as meters per second (m/s), which supposedly indicates the shear wave speed traveling perpendicular to the shear wave source. The Acuson S2000 and S3000 are examples of ARFI devices approved by the US Food & Drug Administration (FDA). **(Refer to Coverage Limitations section)**

- **Magnetic resonance elastography (MRE)** uses wave propagation and tissue deformation analysis to assess changes to tissue viscoelasticity caused by disease. MRE is based on principles similar to vibration-controlled transient elastography and ARFI. This form of imaging involves placing a probe against the individual's back which emits low frequency vibrations that pass through the liver and can reportedly be measured by the MRI spin echo sequence. MRE assesses wave propagation and tissue displacement in three dimensions rather than one dimension. Additionally, MRE interrogates a much larger portion of the liver than ultrasound-based elastography methods.

- **Shear wave elastography (SWE)** is an ultrasound-based technique that utilizes the propagation of shear waves to measure liver stiffness. There are several methods for performing SWE. Each method is unique based on how the shear wave is generated and how the measurements are taken. These methods include:

    - **Real-time SWE**, which may also be known as 2D-SWE, uses ARFI technology to interrogate multiple areas of the liver in rapid succession. This produces a very fast (5,000 frames per second) signal transmission and acquisition sequence to measure the propagation speed of the shear waves. Supposedly, this allows real-time SWE to simultaneously generate the shear waves through a volume of tissue, produce an image and calculate the velocity of the waves. The Aixplorer and the Aplio are examples of FDA-approved SWE devices. **(Refer to Coverage Limitations section)**

    - **Point-SWE (pSWE)**, like real-time SWE, also uses ARFI technology to generate the shear waves. However, unlike real-time SWE, pSWE only measures shear wave speeds through one small area of tissue.[53] **(Refer to Coverage Limitations section)**

- **Vibration-controlled transient elastography (VCTE [also known as transient elastography or TE])** uses a single-element ultrasound transducer with a mechanical vibration source. When it is lightly pressed into the skin between the ribs on the right side of the body, an elastic shear wave is propagated through the liver.[53,54] The stiffness is proportional to the square of the velocity of the shear wave, which is measured in kilopascals (kPa). There are approximately 5 to 10 readings taken and the median is used as the final value. The FibroScan is an example of an FDA-approved VCTE device.

- **Spleen stiffness measurement (SSM)** is a technique that reportedly expands capabilities of assessing liver fibrosis. Purportedly, measuring SSM, along with liver stiffness using elastography, may aid in the diagnosis and monitoring of fibrosis, as well as portal hypertension (PH) and risk of esophageal varices. PH is an increase in the pressure within the portal vein, which is caused by a blockage in the blood flow to the liver. This increased pressure can cause varices (enlarged veins) to develop across the esophagus and stomach. The FibroScan 630 Expert is an example of a SSM device. **(Refer to Coverage Limitations section)**

Quantitative magnetic resonance for analysis of tissue composition (eg, LiverMultiScan) has been developed for noninvasive liver evaluation. The system uses multiparametric magnetic resonance imaging (mpMRI) to reportedly quantify liver tissue. Post-processing software via a cloud-based service is also utilized to reportedly provide quantitative measures of liver fat and correlates of iron, fibrosis and inflammation in nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) to aid in the diagnosis. **(Refer to Coverage Limitations section)**

Liver Fibrosis Serum Tests

Blood-based tests for hepatic fibrosis have been developed to aid in the diagnosis and staging of fibrosis in individuals with liver disease. These tests include both nonproprietary assessments based on routine laboratory tests and proprietary panels that use complex algorithms in conjunction with more specialized laboratory testing. Examples of these blood-based tests include, but may not be limited to:

- **Enhanced liver fibrosis (ELF) test** reportedly assesses the risk of progression to cirrhosis in NAFLD by measuring the following 3 markers: hyaluronic acid (HA), tissue inhibitor of matrix metalloproteinase 1 (TIMP-1) and procollagen III amino-terminal peptide (PIIINP). The ELF test is also purportedly being utilized to assess the likelihood of progression to cirrhosis and liver-related clinical events due to NASH using a generated proprietary algorithm. **(Refer to Coverage Limitations section)**

- The **Fibrosis-4 index (FIB-4)** combines 3 routinely used serum markers (platelet count, AST, and alanine transaminase [ALT]) with an individual's age using a nonproprietary calculation. The resulting score corresponds with the level of fibrosis or cirrhosis present. While not typically used as a stand-alone test for hepatic fibrosis, the FIB-4 index is especially effective as an initial risk assessment tool due to its wide availability and its utility in guiding additional testing or treatment.

- **FibroMeter** is utilized to measure liver fibrosis in individuals with NAFLD. It measures platelet count, prothrombin index, AST, ALT, blood urea nitrogen, HA and age. Using a proprietary algorithm, the results of the measurements are converted into a score to determine an individual's fibrosis score. **(Refer to Coverage Limitations section)**

- **FibroSpect II** measures 3 markers for liver fibrosis: serum HA, TIMP-1 and alpha2-macroglobulin (A2M). Using a proprietary algorithm, the results of the measurements are converted into a score to determine an individual's fibrosis score. **(Refer to Coverage Limitations section)**

- **FibroSure (also known as FibroTest)** measures several markers for liver fibrosis and uses a proprietary algorithm to determine liver fibrosis severity. There are 3 variations of the FibroSure test:

  - **ASH FibroSure** is utilized to reportedly assess liver fibrosis in an individual with alcoholic liver disease. It consists of 10 serum biomarkers including ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, gamma glutamyl transpeptidase (GGT), haptoglobin, AST, glucose, total cholesterol and triglycerides. The resulting score purportedly reflects a quantitative measurement of the severity of fibrosis, steatosis and alcoholic steatohepatitis that may be present. **(Refer to Coverage Limitations section)**

  - **HCV FibroSure** uses 6 serum biomarkers, in addition to age and gender, to supposedly measure the degree of hepatic fibrosis and necroinflammation in individuals with HCV. The biomarkers utilized in this test include alpha-2 macroglobulin, haptoglobin, GGT, ALT and apolipoprotein A1. **(Refer to Coverage Limitations section)**

  - **NASH FibroSure** is utilized in individuals with MASLD/NAFLD. It includes the same 10 serum biomarkers that are used in the ASH FibroSure test. However, the NASH FibroSure uses a different algorithm to purportedly quantify the degree of fibrosis, steatosis, and/or steatohepatitis present. **(Refer to Coverage Limitations section)**

  - **ActiTest** refers to the addition of ALT to the various FibroSure algorithms. This addition supposedly allows the test to quantify inflammatory activity as well as fibrosis. **(Refer to Coverage Limitations section)**

- **HepaScore** measures 4 markers for liver fibrosis: bilirubin, GGT, HA, A2M and applies the results to a proprietary algorithm, combined with an individual's age and sex, to determine a liver fibrosis score. **(Refer to Coverage Limitations section)**

- **LiverFASt** combines 10 biomarkers along with a proprietary algorithm that reportedly measures fibrosis as well as inflammatory activity and steatosis. The biomarkers included in the test are A2M, ALT, haptoglobin, AST, apolipoprotein, fasting glucose, total bilirubin, triglyceride, GGT and total cholesterol. **(Refer to Coverage Limitations section)**

- **NIS4** is an emerging test that is designed to reportedly identify the presence of at-risk NASH. Supposedly, an individual who is determined to be at-risk for NASH could face increased likelihood of progression to more severe complications such as cirrhosis or cancer. The test purportedly uses a multimarker-based proprietary algorithm that integrates the following biomarkers: miR-34a-5p, A2M, YKL-40 and HbA1c. **(Refer to Coverage Limitations section)**

- **OWLiver test** for fatty liver disease is a noninvasive test that combines 28 biomarkers (metabolites) from a blood sample that are analyzed together in 2 proprietary algorithms to reportedly determine or approximate an individual's liver status regarding fibrosis. **(Refer to Coverage Limitations section)**

Artificial Intelligence Technologies

Artificial intelligence (AI) combines computer systems, databases and advanced algorithms to imitate human abilities, such as decision-making and problem-solving. Common everyday uses include customer service, facial and voice recognition, and recommendation/search engines. AI is also being explored for many clinical uses, such as its ability to reportedly detect hepatic fibrosis. **(Refer to Coverage Limitations section)**

Coverage Determination

FIB-4

Humana members may be eligible under the Plan for **Fibrosis-4 Index** testing for the detection and staging of hepatic fibrosis.

VCTE/TE

Humana members may be eligible under the Plan for **vibration-controlled transient elastography (also known as transient elastography)** when the following criteria are met:

- Initial diagnosis and staging of hepatic fibrosis in an individual with chronic liver disease[2,13,30,41]; **OR**
- Follow-up assessment in an individual with a FIB-4 test result that is either inconclusive or greater than or equal to 1.3[4,19]; **OR**
- Follow-up assessment in an individual with a FIB-4 test result that is less than 1.3 when **ONE** of the following risk factors are present:
    - Diagnosis of type II diabetes mellitus or pre-diabetes; **OR**
    - Radiologic confirmation of hepatic steatosis; **OR**
    - Two or more metabolic risk factors[4,19]; **OR**
- Prior to the use of Hemgenix (etranacogene dezaparvovec-drib) for treatment of hemophilia B (congenital factor IX deficiency); **OR**
- Prior to the use of Roctavian (valoctocogene roxaparvovec-rvox) for the treatment of hemophilia A (congenital factor VIII deficiency); **OR**
- Treatment-related evaluation for hepatic fibrosis in ANY of the following scenarios:
    - Annual monitoring for individuals undergoing treatment for HBV[67]; **OR**
    - Six months after successful completion of treatment in individuals with autoimmune hepatitis[5];

AND ALL of the following:

- Testing for hepatic fibrosis (eg, liver biopsy, MRE) has not been performed within the previous 6 months; **AND**
- VCTE/TE performed no more frequently than **ONCE** every 6 months

MRE

Humana members may be eligible under the Plan for **magnetic resonance elastography** when the following criteria are met:

- Diagnosis of chronic liver disease[2,13,30,41]; **OR**
- Follow-up assessment for hepatic fibrosis in an individual with a FIB-4 test result that is either inconclusive or greater than or equal to 1.3[4,19]; **OR**
- Follow-up assessment for hepatic fibrosis in an individual with a FIB-4 test result that is less than 1.3 when **ONE** of the following risk factors are present:
  - Diagnosis of type II diabetes mellitus or pre-diabetes; **OR**
  - Radiologic confirmation of hepatic steatosis; **OR**
  - Two or more metabolic risk factors[4,19];

AND ALL of the following:

- Absence of contraindications to magnetic resonance imaging (eg, pacemaker, metal implants)[14]; **AND**
- Absence of documented moderate to severe hepatic iron overload (eg, hemochromatosis)[40]; **AND**
- Successful testing for hepatic fibrosis (eg, liver biopsy, MRE, VCTE) has not been performed within the previous 6 months; **AND**
- VCTE/TE is not available, inconclusive or contraindicated due to clinical factors that would affect accuracy of the test (eg, ascites)[2]

Coverage Limitations

Humana members may **NOT** be eligible under the Plan for **VCTE/TE or MRE** for any indications other than those listed above.

This is considered experimental/investigational as it is not identified as widely used and generally accepted for any other proposed use as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for any other **noninvasive tests for hepatic fibrosis** for any indications other than those listed above including:

- ARFI (eg, Virtual Touch Imaging – Acuson S2000-3000); **OR**
- Artificial intelligence technologies
- Proprietary liver fibrosis serum panels (eg, ASH FibroSure, ELF test, FibroMeter, FibroSpect, FibroSure, FibroTest-ActiTest panel, HCV FibroSure, HepaScore, LiverFASt, NASH FibroSure, NIS4, OWLiver); **OR**
- Quantitative magnetic resonance for analysis of tissue composition (eg, LiverMultiScan); **OR**
- Real-time shear wave elastography (eg, Aixplorer MACH 20-30, Aplio); **OR**
- Spleen stiffness measurements (eg, FibroScan 630 Expert)

These are considered experimental/investigational as they are not identified as widely used and generally accepted for any other proposed uses as reported in nationally recognized peer-reviewed medical literature published in the English language.

Coding Information

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
76391	Magnetic resonance (eg, vibration) elastography	**Not Covered**
76498	Unlisted magnetic resonance procedure (eg, diagnostic, interventional)	**Not Covered if used to report noninvasive tests for hepatic fibrosis**
76981	Ultrasound, elastography; parenchyma (eg, organ)	**Not Covered**
76982	Ultrasound, elastography; first target lesion	**Not Covered**

76983	Ultrasound, elastography; each additional target lesion (List separately in addition to code for primary procedure)	**Not Covered**
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	**Not Covered**
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	**Not Covered**
81599	Unlisted multianalyte assay with algorithmic analysis	**Not Covered if used to report noninvasive tests for hepatic fibrosis**
82172	Apolipoprotein, each	**Not Covered if used to report noninvasive tests for hepatic fibrosis**
82247	Bilirubin; total	**Not Covered if used to report noninvasive tests for hepatic fibrosis**
82977	Glutamyltransferase, gamma (GGT)	**Not Covered if used to report noninvasive tests for hepatic fibrosis**
83010	Haptoglobin; quantitative	**Not Covered if used to report noninvasive tests for hepatic fibrosis**
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified	**Not Covered if used to report noninvasive tests for hepatic fibrosis**
83883	Nephelometry, each analyte not elsewhere specified	**Not Covered if used to report noninvasive tests for hepatic fibrosis**
84450	Transferase; aspartate amino (AST) (SGOT)	
84460	Transferase; alanine amino (ALT) (SGPT)	
84999	Unlisted chemistry procedure	**Not Covered if used to report noninvasive tests for hepatic fibrosis**
85049	Blood count; platelet, automated	

88342	Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure	**Not Covered if used to report noninvasive tests for hepatic fibrosis**
91200	Liver elastography, mechanically induced shear wave (eg, vibration), without imaging, with interpretation and report	
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)	**Not Covered**
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)	**Not Covered**
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	**Not Covered** **Deleted Code Effective 12/31/2023**
0166U	Liver disease, 10 biochemical assays (╬▒2-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	**Not Covered**
0344U	Hepatology (nonalcoholic fatty liver disease [NAFLD]), semiquantitative evaluation of 28 lipid markers by liquid chromatography with tandem mass spectrometry (LC-MS/MS), serum,	**Not Covered**
CPT® Category III Code(s)	**Description**	**Comments**
0648T	Quantitative magnetic resonance for analysis of tissue composition (eg, fat, iron, water content), including multiparametric data acquisition, data preparation and transmission, interpretation and report, obtained without diagnostic MRI examination of the same anatomy (eg, organ, gland, tissue, target structure) during the same session; single organ	**Not Covered**

0649T	Quantitative magnetic resonance for analysis of tissue composition (eg, fat, iron, water content), including multiparametric data acquisition, data preparation and transmission, interpretation and report, obtained with diagnostic MRI examination of the same anatomy (eg, organ, gland, tissue, target structure); single organ (List separately in addition to code for primary procedure)	**Not Covered**
0697T	Quantitative magnetic resonance for analysis of tissue composition (eg, fat, iron, water content), including multiparametric data acquisition, data preparation and transmission, interpretation and report, obtained without diagnostic MRI examination of the same anatomy (eg, organ, gland, tissue, target structure) during the same session; multiple organs	**Not Covered**
0698T	Quantitative magnetic resonance for analysis of tissue composition (eg, fat, iron, water content), including multiparametric data acquisition, data preparation and transmission, interpretation and report, obtained with diagnostic MRI examination of the same anatomy (eg, organ, gland, tissue, target structure); multiple organs (List separately in addition to code for primary procedure)	**Not Covered**
0723T	Quantitative magnetic resonance cholangiopancreatography (QMRCP) including data preparation and transmission, interpretation and report, obtained without diagnostic magnetic resonance imaging (MRI) examination of the same anatomy (eg, organ, gland, tissue, target structure) during the same session	**Not Covered**
0724T	Quantitative magnetic resonance cholangiopancreatography (QMRCP) including data preparation and transmission, interpretation and report, obtained with diagnostic magnetic resonance imaging (MRI) examination of the same anatomy (eg, organ, gland, tissue, target structure) (List separately in addition to code for primary procedure)	**Not Covered**
HCPCS Code(s)	**Description**	**Comments**
No code(s) identified		

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Appendix

Appendix A
Chronic Liver Disease
Chronic liver disease is defined by the presence of **ANY** of the following:

- Persistence of positive hepatitis B surface antigen and antibody (HBsAg) tests for greater than 6 months[48,67]; **OR**
- Positive HCV RNA testing[7,37,59]; **OR**
- Sustained elevation of liver function tests (LFTs) for 6 months or more[25]

Appendix B
Metabolic Risk Factors[31,39]
An individual is considered to be at increased risk of metabolic syndrome based on the presence of **ANY** of the following risk factors:

- Abdominal obesity (waist circumference greater than 40 inches in men or 35 inches in women)
- Blood pressure greater than or equal to 130/85
- Fasting glucose level greater than or equal to 110 mg/dL
- Serum high-density lipoprotein (HDL) level less than 40 mg/dL in men or less than 50 mg/dL in women
- Serum triglyceride level greater than or equal to 150 mg/dL

Change Summary

- 04/25/2024 Annual Review, Coverage Change.