PREMERA BLUE CROSS
An Independent Licensee of the Blue Cross Blue Shield Association

ROUTINE TEST MANAGEMENT POLICY – 15.01.013

Serum Testing for Hepatic Fibrosis in the Evaluation and Monitoring of Chronic Liver Disease

Ref. Policy:	G2110	
Effective Date:	**Feb. 6, 2026**	RELATED POLICIES:
Last Revised:	Oct. 14, 2025	15.01.042 Serum Tumor Markers for Malignancies
Replaces:	N/A	15.01.021 Gamma-glutamyl Transferase Testing in Adults

Select a hyperlink below to be directed to that section.

POLICY DESCRIPTION | INDICATIONS | RELATED INFORMATION

CODING | EVIDENCE REVIEW | REFERENCES | HISTORY

Clicking this icon returns you to the hyperlinks menu above.

Policy Description

Chronic liver disease (CLD) refers to a wide range of liver pathologies that include inflammation (chronic hepatitis), liver cirrhosis, and hepatocellular carcinoma.

Hepatic fibrosis is associated with a cycle of extracellular matrix deposition and degradation. Biomarkers of extracellular matrix turnover are used to directly assess fibrosis and, theoretically, to monitor progression or regression (Valva et al., 2016). These markers include several glycoproteins, members of the collagen family, collagenases and their inhibitors, and several cytokines involved in the fibrogenic process (Valva et al., 2016). The markers may be utilized individually, as well as in panel combinations (Parikh et al., 2017).

Indications

1. For individuals with hepatitis C, hepatitis B, metabolic dysfunction-associated steatotic liver disease (MASLD) (including metabolic dysfunction-associated steatohepatitis [MASH]), or alcoholic hepatitis, the use of the following multianalyte assays with algorithmic analysis to distinguish hepatic cirrhosis from non-cirrhosis is considered **reimbursable** once every 6 months:

    a. ELF(ELFTM).

   b. FibroTest.
   c. HBV FibroSURE.
   d. HCV FibroSURE.

2. For individuals with hepatitis C, hepatitis B, MASLD, or alcoholic hepatitis, the use of other multianalyte assays with algorithmic analysis (e.g., ASH FibroSURE, LIVERFAStTM, NASH FibroSURE) is **not reimbursable**.
3. For individuals with liver disease not meeting the above criteria, the use of multianalyte assays with algorithmic analysis is **not reimbursable**.

The following is **not reimbursable** due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

4. Except as previously described, the use of the following serum biomarkers in immunoassays and/or immunohistochemistry assays is **not reimbursable**:

   a. Signal-induced proliferation-associated 1 like 1 (SIPA1L1)
   b. microRNA (miRNA or miR) analysis, including but not limited to, the following:

      - microRNA-21 (miRNA-21 or miR-21)
      - miRNA-29a (miR-29a)
      - miRNA-122 (miR-122)
      - miRNA-221 (miR-221)
      - miRNA-222 (miR-222)

   c. Chitinase 3-like 1 (CHI3L1)
   d. Hyaluronic acid
   e. Type III procollagen (PCIII)
   f. Type IV collagen
   g. Laminin
   h. Plasma caspase-generated cytokeratin-18
   i. Micro-fibrillar associated glycoprotein 4 (MFAP4)

Coding

Code	Description
CPT	
81517	Liver disease, analysis of 3 biomarkers (hyaluronic acid [HA], procollagen III amino terminal peptide [PIIINP], tissue inhibitor of metalloproteinase 1 [TIMP-1]), using

Code	Description
	immunoassays, utilizing serum, prognostic algorithm reported as a risk score and risk of liver fibrosis and liver-related clinical events within 5 years
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 Proprietary test: HCV FibroSURE™, FibroTest™ Laboratory/Manufacturer: BioPredictive S.A.S
88341	Immunohistochemistry or immunocytochemistry, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)
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) Proprietary test: ASH FibroSURE™ Laboratory/Manufacturer: BioPredictive S.A.S
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) Proprietary test: NASH FibroSURE™ Laboratory/Manufacturer: BioPredictive S.A.S
0166U	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 Proprietary test: LiverFASt™ Lab/Manufacturer: Fibronostics

Related Information

Table of Terminology

Term	Definition
AAFP	American Academy of Family Physicians
AASLD	American Association for the Study of Liver Diseases

Term	Definition
AFP	Alpha-fetoprotein
AGA	American Gastroenterological Association
ALT	Alanine aminotransferase
ALT	Alanine transaminase
AST	Aspartate aminotransferase-to-platelet ratio index
AUC	Area under the curve
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CHBV	Chronic hepatitis B virus
CHC	Chronic hepatitis C
CHCV	Chronic hepatitis C virus infection
CK-18	Cytokeratin-18 fragments
CLD	Chronic liver disease
CMS	Centers for Medicare and Medicaid Services
EASD	European Association for the Study of Diabetes
EASL	European Association for the Study of Obesity
GGT	Gamma-glutamyl transferase
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
IDSA	Infectious Diseases Society of America
LDTs	Laboratory developed tests
MASH	Metabolic dysfunction-associated steatohepatitis
MASLD	Metabolic dysfunction-associated steatotic liver disease
MFAP4	Microfibrillar-associated protein 4
miRNA	Micro ribonucleic acid
MTX	Methotrexate
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NICE	National Institute for Health and Care Excellence
NILTS	Non-invasive fibrosis tests

Term	Definition
NIT	Non-invasive test
PT/INR	Prothrombin time/elevated international normalized ratio
SC	Standard care
SIPA1L1	Signal-induced proliferation-associated 1 like 1
SWE	Shear-wave elastography
TACE	Trans-arterial chemoembolization
TE	Transient elastography
US	Ultrasonography
USPSTF	United States Preventive Services Task Force
VCTE	Vibration controlled transient elastography
WHO	World Health Organization

Evidence Review

Scientific Background

Fibrosis is a wound healing response in which damaged regions are encapsulated by an extracellular matrix. This is common in individuals with chronic liver injury but may be seen in other organs such as the kidneys or lungs. Chronic liver injury may be caused by numerous conditions, such as hepatitis or metabolic dysfunction-associated steatotic liver disease (MASLD) (formerly known as nonalcoholic fatty liver disease [NAFLD]), including metabolic dysfunction-associated steatohepatitis (MASH) (formerly known as nonalcoholic steatohepatitis [NASH]) (EASL, 2023), and progressive fibrosis may lead to cirrhosis (Friedman, 2024). Liver biopsy remains the gold standard for evaluation of chronic liver disease to monitor treatment and disease progression. However, this invasive procedure has several drawbacks including pain, bleeding, inaccurate staging due to sampling error, and variability of biopsy interpretation (Chin et al., 2016).

Serum biomarkers, such as the aspartate aminotransferase (AST) to platelet ratio (APRI), have been proposed as measures of hepatic fibrosis assessment, and numerous panels exist (Curry & Afdhal, 2024). These markers (and corresponding panels) may be categorized as “direct” or “indirect.” Direct markers of fibrosis evaluate extracellular matrix turnover, and indirect markers signify changes in hepatic function. Direct biomarkers may be further subdivided by markers associated with matrix deposition, matrix degradation, or cytokines (and chemokines) associated with fibrogenesis. Procollagen I peptide, procollagen III peptide, type I collagen, type IV collagen, YKL-40 (chondrex), laminin, and hyaluronic acid, MMP-2, TIMP-1, -2, TGF-beta, TGF-alpha, and PDGF have all been proposed as direct measures of fibrosis. Indirect markers include serum aminotransferase levels, platelet count, coagulation parameters, gamma-glutamyl transferase (GGT), total bilirubin, alpha-2-macroglobulin, and alpha-2-globulin (haptoglobin) (Curry & Afdhal, 2024). Other markers have been investigated to be used independently or as part of these panels. The human microfibrillar-associated protein 4 (MFAP4) is located in extracellular matrix fibers and plays a role in disease-related tissue remodeling. Bracht et al. (2016) evaluated the "potential" of MFAP4 as a biomarker for hepatic fibrosis. A total of 542 patients were included, and the authors focused on differentiation of no to moderate (F0–F2) and severe fibrosis stages and cirrhosis (F3 and F4). In the "leave-one-out cross validation," a sensitivity of 85.8% and specificity of 54.9% was observed and the multivariate model yielded 81.3 % sensitivity and 61.5 % specificity. The authors suggested that "the combination of MFAP4 with existing tests might lead to a more accurate non-invasive diagnosis of hepatic fibrosis and allow a cost-effective disease management in the era of new direct acting antivirals" (Bracht et al., 2016).

Plasma caspase-generated cytokeratin-18 fragments (CK-18) have been proposed as a biomarker in the diagnosis and staging of nonalcoholic steatohepatitis (NASH). Cusi et al. (2014) studied the clinical value of CK-18. The authors studied the adipose tissue, liver, and muscle insulin resistance of 424 patients as well as liver fat (n = 275) and histology (n = 318). The authors found that median CK-18 levels were elevated in patients with verses without nonalcoholic fatty liver disease (NAFLD) (209 U/L vs. 122 U/L) or with verses without NASH (232 U/L vs. 170 U/L). The CK-18 area under curve to predict NAFLD, NASH, or fibrosis were 0.77, 0.65, and 0.68, respectively. The overall sensitivity/specificity for NAFLD, NASH and fibrosis were 63%/83%, 58%/68% and 54%/85%, respectively. CK-18 correlated most strongly with ALT (r=0.57) and adipose tissue IR (insulin-suppression of FFA: r=-0.43), but not with ballooning, body mass index, metabolic syndrome, or type 2 diabetes. The authors concluded, "Plasma CK-18 has a high specificity for NAFLD and fibrosis, but its limited sensitivity makes it inadequate as a screening test for staging NASH. Whether combined as a diagnostic panel with other biomarkers or clinical/laboratory tests may prove useful requires further study" (Cusi et al., 2014).

Likewise, Chitinase 3-like 1 (CHI3L1) has been proposed to be a better serum biomarker than hyaluronic acid, type III procollagen, type IV collagen, and laminin. CHI3L1 is preferentially expressed in hepatocytes over any other body tissue. Huang et al. (2015) investigated CHI3L1 in 98 patients with hepatitis B. The authors reported that CHI3L1 can be used to differentiate between early stages of liver fibrosis (S0-S2) from late stages (S3-S4) "with areas under the ROC curves (AUCs) of 0.94 for substantial (S2, S3, S4) fibrosis and 0.96 for advanced (S3, S4) fibrosis"

(Huang et al., 2015). Wang et al. (2018) also report that CHI3L1 is a useful marker for the assessment of liver fibrosis before treatment and can also be used to monitor change during therapy.

MicroRNA (miRNA) sequences have also been proposed as a marker of liver function. MiRNA sequences often have roles in gene regulation and other cellular processes, so changes in these sequences may indicate a liver condition (Tendler, 2022). For example, Abdel-Al et al. (2018) investigated miRNA's association with Hepatitis C virus (HCV) patients. Forty-two patients with HCV and early-stage fibrosis, 45 patients with HCV and late-stage fibrosis, and 40 healthy controls were examined and the expression patterns of five miRNA sequences (miR-16, miR-146a, miR-214-5p, miR-221, and miR-222) were measured. The authors found miRNA-222 to have the highest sensitivity and specificity for both fibrosis groups, and all mi-RNA sequences except miRNA-214-5p were significantly upregulated in fibrosis. MiRNA-221 was also found to have significant positive correlations with miRNA-16 and miRNA-146a. The authors concluded that "the high sensitivity and specificity of miRNA-222 and miRNA-221 in late-stage fibrosis indicate promising prognostic biomarkers for HCV-induced liver fibrosis (Abdel-Al et al., 2018).

Multiple biomarkers may be combined into a panel. Panels may include a combination of direct markers, indirect markers, or markers from both categories. The most studied panels are the aspartate aminotransferase (AST) to platelet ratio (APRI), FibroTest/FibroSure, and Hepascore, although many more exist. FibroTest/FibroSure incorporates alpha-2-macroglobulin, alpha-2-globulin (haptoglobin), gamma globulin, apolipoprotein A1, GGT, and total bilirubin, age, and sex. HepaScore measures bilirubin, GGT, hyaluronic acid, alpha-2-macroglobulin, age, and sex. These panels have demonstrated some promising results, but Curry and Afdhal (2024) note that indeterminate outcomes are common. Furthermore, they state that no singular panel has emerged as the standard of care (Curry & Afdhal, 2024). Another test, known as the LIVERFAStTM by Fibronostics, utilizes a blood sample to measure 10 biomarkers; algorithm technology is used "to determine the fibrosis, activity and steatosis stages of the liver" (Fibronsotics, 2020). OWLiver® by CIMA Sciences, LLC, evaluates 28 metabolites from a blood sample. Relative concentrations of those biomarkers are analyzed together with two algorithms to generate a final OWLiver® score, which "indicates the probability of approximation of the patient's liver status to a healthy liver / steatosis stage, a non-alcoholic steatohepatitis (NASH *) stage, or NASH and significant-advanced fibrosis (≥F2) stage" (CIMA Sciences, 2023).

Many combinations of biomarkers, and even combinations of panels, exist. For example, FibroMax combines FibroTest, SteatoTest, NashTest, ActiTest, and AshTest on the same result sheet and provides a more comprehensive estimation of the liver injury. This test measures 10 biomarkers which are as follows: GGT, total bilirubin, alpha-2-macroglobulin, apolipoprotein A1, haptoglobin, alanine aminotransferase (ALT), AST Transaminase, triglycerides, cholesterol, and fasting glucose (BioPredictive, 2019). Fouad et al. (2013) analyzed samples from 44 patients and found that FibroMax results were positively correlated with viral load by quantitative polymerase chain reaction and histopathological findings. Further, body mass index was significantly higher in steatotic patients and was significantly associated with the results on FibroMax (Fouad et al., 2013).

Clinical Utility and Validity

Berends et al. (2007) performed a study assessing FibroTest's (known as FibroSure in the United States) ability to detect methotrexate (MTX)-induced hepatic fibrosis. Twenty-four psoriasis patients that underwent a liver biopsy were included, and FibroTest identified 83 percent of the patients who had significant fibrosis. The authors suggested FibroTest may be used as part of monitoring MTX-induced fibrosis (Berends et al., 2007).

Kwok et al. (2014) performed a meta-analysis of non-invasive assessments of NASH. The authors identified nine studies for transient elastography (TE) and 11 for cytokeratin-18 (CK-18). The pooled sensitivities and specificities for TE to diagnose F ≥ 2, F ≥ 3, and F4 disease were 79% and 75%, 85% and 85%, and 92% and 92%, respectively. CK-18 was found to have a pooled sensitivity of 66% and specificity of 82% in diagnosing NASH. The authors concluded that "At present, serum tests and physical measurements such as TE come close as highly accurate non-invasive tests to exclude advanced fibrosis and cirrhosis in NAFLD patients. CK18 has moderate accuracy in diagnosing NASH, while other biomarkers have not been extensively studied" (Kwok et al., 2014).

Gao et al. (2018) compared aspartate amino transferase–to-platelet ratio index (APRI), the Fibrosis-4 index (FIB-4), transient elastography (TE), and two-dimensional (2D) shear-wave elastography (SWE). A total of 402 patients with chronic hepatitis B were included. 2D-SWE was found to have the highest area under the curve (AUC), with 0.87 compared to APRI's 0.70, TE's 0.80, and FIB-4's 0.73 (Gao et al., 2018).

Dong et al. (2018) compared the performance of several biomarkers (serum hyaluronan (HA), procollagen type III N-terminal peptide (PIIINP), type IV collagen (IVC), laminin (LN), ALT, AST) to transient elastography (FibroScan). Seventy patients with hepatitis B underwent a liver biopsy. Fibrosis was found in 24 patients. The correlation of serum levels with fibrosis stage are as follows: 0.468 (HA), 0.392 (PIIINP), 0.538 (IVC), 0.213 (LN), 0.350 (ALT), 0.375 (AST). The authors found that the combination of all five biomarkers yielded a superior diagnostic performance (area under curve: 0.861) compared to all five alone (Dong et al., 2018).

A pilot study of the FM-fibro index was performed with 400 patients enrolled, and the FM-fibro index, CA-fibro index, and European Liver Fibrosis panel (ELF) were compared with respect to estimating prognosis of patients with NAFLD. Three separate biomarkers comprise the FM-fibro index: type IV collagen 7S, hyaluronic acid, and vascular cell adhesion molecule-1. The area under the curve was 0.7093 for the CA-fibro index, 0.7245 for ELF, and 0.7178 (type IV collagen 7S)/0.7095 (hyaluronic acid)/0.7065 (vascular cell adhesion molecule-1) (Itoh et al., 2018). The sensitivity and specificity of the FM-fibro index for predicting NASH-related fibrosis was 0.5359/0.5210/0.4641 and 0.8333/0.8182/0.8788, respectively (Itoh et al., 2018). The accuracy of the FM-fibro index was not significantly different from that of the CA-fibro index and the ELF panel.

Patel et al. (2018) performed a retrospective study focusing on fibrosis scoring systems to identify NAFLD. A total of 329 patients (296 NAFLD, 33 controls) were included. The following indices were studied: "NAFLD fibrosis score (NFS), fibrosis-4 calculator (FIB-4), aspartate aminotransferase-to-alanine aminotransferase ratio (AST/ALT ratio), AST-to-platelet ratio index (APRI), and body mass index, AST/ALT ratio, and diabetes (BARD) score by age groups" (Patel et al., 2018). NFS and FIB-4 were found to best predict advanced fibrosis with areas under curve of 0.71-0.76 and 0.62-0.80 respectively. However, the authors concluded that "While NFS and FIB-4 scores exhibit good diagnostic accuracy, FIB-4 is optimal in identifying NAFLD advanced fibrosis in the VHA. Easily implemented as a point-of-care clinical test, FIB-4 can be useful in directing patients that are most likely to have advanced fibrosis to GI/hepatology consultation and follow-up" (Patel et al., 2018).

Kim et al. (2017) evaluated the "association between plasma miR-122 [microRNA-122] and treatment outcomes following transarterial chemoembolization (TACE) in hepatocellular carcinoma patients." A total of 177 patients were included, and miR-122 levels were measured; the researchers found that 112 patients exhibited TACE refractoriness. Multivariate analyses showed that tumor number (hazard ratio [HR], 2.51) and tumor size (HR, 2.65) can independently predict overall TACE refractoriness. High miR-122 expression (> 100) was associated with early TACE refractoriness (within 1 year; HR, 2.77; 95% CI,) together with tumor number (HR, 22.73) and tumor size (HR, 4.90). Univariate analyses showed that high miR-122 expression tends to be associated with poor liver transplantation-free survival (HR, 1.42). However, this was statistically insignificant in multivariate analysis. The authors concluded that "High expression levels of plasma miR-122 are associated with early TACE refractoriness in HCC patients treated with TACE" (Kim et al., 2017).

Suehiro et al. (2018) performed a study analyzing "the importance of serum exosomal miRNA expression levels in hepatocellular carcinoma (HCC) patients that underwent transarterial chemoembolization (TACE)." Seventy-five patients underwent TACE. Exosomal miR-122 expression levels significantly decreased after TACE. The expression levels of exosomal miR-122 before TACE were shown to correlate significantly with AST ($r=0.31$) and ALT ($r=0.33$) levels. According to the median relative expression of miR-122 after TACE/before TACE (miR-122 ratio) in liver cirrhosis patients ($n=57$), the patients with a higher miR-122 ratio had significantly longer disease-specific survival compared with that of the patients with the lower miR-122 ratio. A lower exosomal miR-122 ratio (HR 2.720) was associated with the disease-specific survival. The authors concluded that "the exosomal miR-122 level alterations may represent a predictive biomarker in HCC patients with liver cirrhosis treated with TACE" (Suehiro et al., 2018).

Kar et al. (2019) analyzed the performance of biomarkers implicated in hepatic inflammation. The authors enrolled 52 patients with NAFLD/NASH and evaluated the following biomarkers: IL-6, CRP, TNFα, MCP-1, MIP-1β, eotaxin, and VCAM-1. Serum IL-6 was found to be increased in patients with advanced fibrosis (2.71 pg/mL in fibrosis stages 3 and 4 compared to 1.26 pg/mL in stages 1-2 and 1.39 pg/mL in stage 0), but there were no other significant differences in CRP, TNFα, MCP-1, MIP-1β. VCAM-1 was noted to have increased by 55% over the mild fibrosis group and 40% over the no fibrosis group. VCAM-1 was also observed to have an area under curve of 0.87. The authors suggested that the "addition of biomarkers such as IL-6 and VCAM-1 to panels may yield increased sensitivity and specificity for staging of NASH" (Kar et al., 2019).

Srivastava et al. (2019) performed a cost-benefit analysis of non-invasive fibrosis tests (NILTS) for nonalcoholic fatty liver disease (NAFLD). The authors compared the current standard of care, FIB-4, and the Enhanced Liver Fibrosis (ELF) panel. The simulations consisted of 10000 NAFLD patients. Standard care (SC) was compared to the following four scenarios: "FIB-4 for all patients followed by ELF test for patients with indeterminate FIB-4 results; FIB-4 followed by fibroscan for indeterminate FIB-4; ELF alone; and fibroscan alone." The authors identified the following observations: "Introduction of NILT increased detection of advanced fibrosis over one year by 114, 118, 129 and 137% compared to SC in scenarios 2, 3, 4 and 5 respectively with reduction in unnecessary referrals by 85, 78, 71 and 42% respectively. Total budget spend [sic] was reduced by 25.2, 22.7, 15.1 and 4.0% in Scenarios 2, 3, 4 and 5 compared to £670 K at baseline." The authors suggested that the "use of NILT in primary care can increase early detection of advanced liver fibrosis and reduce unnecessary referral of patients with mild disease and is cost efficient" (Srivastava et al., 2019).

Weis et al. (2019) evaluated miRNA expression's ability to distinguish between HCC and cirrhosis. Sixty patients with chronic hepatitis C (CHC) were divided into three groups; 20 with fibrosis stages 0-2, 20 with cirrhosis, and 20 with cirrhosis and HCC. A total of 372 miRNA sequences were measured. The authors found that a theoretical panel consisting of miRNA-122-5p, miRNA-486-5p, and miRNA-142-3p distinguished HCC from cirrhosis (area under the curve [AUC]= 0.94; sensitivity = 80%, specificity = 95%) outperforming alpha-fetoprotein (AFP) (AUC = 0.64). Another theoretical panel of miRNA-122-5p and miRNA-409-3p distinguished cirrhosis from mild disease (AUC = 0.80; sensitivity = 85%, specificity = 70%). The authors concluded that "MicroRNAs have great potential as diagnostic biomarkers in CHC, particularly in HCC where they outperform the only currently-used biomarker, AFP" (Weis et al., 2019).

Both Parikh et al. (2017) and Kaswala et al. (2016) performed studies evaluating the diagnostic accuracy of non-invasive markers for liver conditions. Parikh et al. (2017) focused on chronic hepatitis B virus (HBV) infections while Kaswala et al. (2016) studied nonalcoholic fatty liver. Tables detailing their summarized findings are listed below:

Table 1. Diagnostic accuracy of most commonly used non-invasive fibrosis (≥F2) tests in chronic HBV infection from (Parikh et al., 2017)

Test	Cut-off	AUROC	Sensitivity (%)	Specificity (%)
Indirect markers				
FIB-4 index (high cut-off)	3.25	N/A	16.2	73.6
FIB-4 index (low cut-off)	1.45–1.62	0.78	65	77
APRI (low cut-off)	0.5	0.79	84	41
APRI (high cut-off)	1.5		49	84
Forns index (low cut-off)	3.11	0.68	91.4	31.5
Forns index (high cut-off)	5.11	N/A	42.5	75
Direct markers				
Hyaluronic acid	113–203	0.73	63–80	78–94
Hepascore	0.32	0.75	74	69
Fibrotest	0.38	0.77	65	78
Fibrometer	0.47	0.84	73	80
ELF	8.75	0.8	N/A	N/A

Table 2. Diagnostic accuracy of most commonly used non-invasive fibrosis tests in nonalcoholic fatty liver (NAFL) from (Kaswala et al., 2016)

Test	Cut-off	AUROC	Sensitivity (%)	Specificity (%)
AST/ALT ratio	1	0.83	21	90
AST to platelet ratio index (low cutoff)	0.45	0.67–0.94	30	93
AST to platelet ratio index (high cutoff)	1.5			
BAAT score	2	0.84	71	80
BARD	2	0.8	86.8	32.5
ELF test	8.5–11.35	0.82–0.90	80	90
FibroMeter (low cutoff)	F3: 0.61	0.90–0.94	81	84
FibroMeter (high cutoff)	0.71			
FibroTest (low cutoff)	0.3	0.81–0.92	15–77	77–90
FibroTest (high cutoff)	0.7			
FIB-4 (low cutoff)	1.3–1.92	0.88	26–74	71–98
FIB-4 (high cutoff)	3.25			
Hepascore	0.37	0.81	75.5	84.1
	0.7	0.9	87	89
NAFLD (low cutoff)	−1.45	0.81	51	96
NAFLD (high cutoff)	0.67	0.83	21	90

AST- aspartate aminotransferase; APRI- AST to platelet ratio; BAAT- body mass index (BMI), age, alanine aminotransferase (ALT), triglycerides; BARD- BMI, AST/ALT ratio, diabetes; ELF- Enhanced Liver Fibrosis panel; FIB-4- Fibrosis-4 index; NAFLD – Nonalcoholic fatty liver disease

Bril et al. (2019) assessed the performance of the FibroTest, along with other tests which measure steatosis, necrosis, and inflammation (the SteatoTest, ActiTest, NashTest), in a cohort of patients with type 2 diabetes. A total of 220 diabetic patients participated in this study. Plasma samples from each participant were used for the FibroTest. The researchers note that "Regarding the FibroTest score, its performance to identify patients with moderate or advanced fibrosis was 0.67" (Bril et al., 2019). The authors concluded that "Non-invasive panels for the diagnosis of steatosis, NASH and/or fibrosis, which were developed and validated in non-diabetic cohorts, underperformed when applied to a large cohort of patients with T2DM [type 2 diabetes mellitus]" (Bril et al., 2019)

In a metanalysis, seven studies reported the accuracy of FibroTest in nonalcoholic fatty liver disease (NAFLD) patients. The mean AUC was 0.77, mean sensitivity was 0.72, and mean specificity was 0.69. Due to poor AUC, sensitivity, and specificity values, FibroTest did not meet the minimally acceptable performance level in detecting significant, advanced, or any fibrosis. However, diagnostic accuracy of FibroTest was more promising in detecting cirrhosis, with an AUC of 0.92. The author states that in primary care settings which have a low disease prevalence, FibroTest can have a high negative predictive value, based on sensitivities between 0.90 and 0.98, demonstrating its ability to rule out advanced fibrosis in NAFLD patients. However, the test does have low specificity, leading to a considerable number of false positive results, which can lead to invasive and expensive follow-up tests. Overall, "this analysis showed that by optimizing sensitivity to values above 0.90, the test could result in high NPVs (>90%) in settings with low prevalence of disease, such as primary and secondary care settings, but with relatively low PPVs (11–61%)" (Vali et al., 2021).

Chow et al. (2023) conduced a systematic review of society guidelines to compare recommendations for screening, diagnosis, and assessment of NAFLD. Two researchers independently extracted key information from 20 guidelines published between 2015 and 2022. "No guidelines recommended routine screening for NAFLD, while 14 guidelines recommended case finding in high-risk groups," but guidelines differed on cutoffs and interpretations of high-risk results. Overall, the authors concluded that "despite their differences, all guidelines recognize the utility of NITs and recommend their incorporation into the clinical assessment of NAFLD" (Chow et al., 2023).

Vali et al. (2023) studied the diagnostic accuracy of non-invasive biomarkers in detecting NASH and clinically significant fibrosis in patients with NAFLD. The researchers studied 17 biomarkers and multimarker scores. A total of 1430 participants with NAFLD were included from 13 countries in Europe. "For people with NASH and clinically significant fibrosis, no single biomarker or multimarker score significantly reached the predefined AUC 0·80 acceptability threshold." For the detection of advanced fibrosis, SomaSignal (AUC 0·90), ADAPT (AUC 0·85), and FibroScan liver stiffness measurement (AUC 0·83) all reached acceptable accuracy. "With 11 of 17 markers, histological screen failure rates could be reduced to 33% in trials if only people who were marker positive had a biopsy for evaluating eligibility." The authors concluded that “none of the single markers or multimarker scores achieved the predefined acceptable AUC for replacing biopsy in detecting people with both NASH and clinically significant fibrosis. However, several biomarkers could be applied in a prescreening strategy in clinical trial recruitment” (Vali et al., 2023).

Guidelines and Recommendations

American Academy of Family Physicians (AAFP)

The 2019 AAFP guideline lists viral hepatitis, alcoholic liver disease, and nonalcoholic steatohepatitis as the most common causes of cirrhosis. They state that “common serum and ultrasound-based screening tests to assess fibrosis include the aspartate transaminase to platelet ratio index score, Fibrosis 4 score, FibroTest/FibroSure, nonalcoholic fatty liver fibrosis score, standard ultrasonography, and transient elastography. Generally noninvasive tests are most useful in identifying patients with no to minimal fibrosis or advanced fibrosis. Chronic liver disease management includes directed counseling, laboratory testing, and ultrasound monitoring” (AAFP, 2019).

In regards to the monitoring of patients post-diagnosis and staging, “For patients with cirrhosis, a basic metabolic panel, liver function tests, complete blood count, and PT/INR should be completed every six months to recalculate Child-Pugh and Model for End-Stage Liver Disease scores” (AAFP, 2019).

American Association for the Study of Liver Diseases (AASLD)

The 2015 AASLD and Infectious Diseases Society of America (IDSA) recommendations for testing, managing, and treating adults infected with hepatitis C virus stated that “Recently, noninvasive tests to stage the degree of fibrosis in patients with chronic HCV infection include models incorporating indirect serum biomarkers (routine tests such as aspartate transaminase, alanine transaminase [ALT], and platelet count), direct serum biomarkers (components of the extracellular matrix produced by activated hepatic stellate cells), and vibration-controlled transient liver elastography. No single method is recognized to have high accuracy alone, and the results of each test must be interpreted carefully.” The guidelines further stated that “although liver biopsy is the diagnostic standard, sampling error and observer variability limit test performance, particularly when inadequate sampling occurs. In addition, the test is invasive and minor complications are common, limiting patient and practitioner acceptance. Serious complications such as bleeding, although rare, are well recognized.” The guidelines further recommend that for patients who fail to achieve a sustained virological response, “disease progression assessment every 6 months to 12 months with a hepatic function panel, complete blood count, and international normalized ration” (AASLD-IDSA, 2015).

The 2018 AASLD and Infectious Diseases Society of America (IDSA) recommendations for HCV testing stated that "evaluation for advanced fibrosis using liver biopsy, imaging, and/or noninvasive markers is recommended for all persons with HCV infection, to facilitate an appropriate decision regarding HCV treatment strategy and to determine the need for initiating additional measures for the management of cirrhosis (eg, hepatocellular carcinoma screening). Rating: Class I, Level A" (AASLD-IDSA, 2019).

The 2018 AASLD update (Terrault et al., 2018) on prevention, diagnosis, and treatment of chronic hepatitis B states that:

For monitoring patients with a chronic HBV infection, who are not currently on treatment, "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."

The 2018 AASLD practice guidelines (Chalasani et al., 2017) on the diagnosis and management of nonalcoholic fatty liver disease recommend:

- "In patients with NAFLD, metabolic syndrome predicts the presence of steatohepatitis, and its presence can be used to target patients for a liver biopsy."
- "NFS or FIB-4 index are clinically useful tools for identifying NAFLD patients with higher likelihood of having bridging fibrosis (stage 3) or cirrhosis (stage 4)."
- "Vibration controlled transient elastography or magnetic resonance elastography are clinically useful tools for identifying advanced fibrosis in patients with NAFLD. "

The AASLD does not mention miRNA for assessment in liver disease.

A 2019 update from the AASLD and IDSA states that "Noninvasive tests using serum biomarkers or imaging allow for accurate diagnosis of cirrhosis in most individuals" and frequently used noninvasive methods to estimate liver disease severity include "serum fibrosis marker panels" (AASLD-IDSA, 2019). Further, regarding recommendations for counseling persons with an active HCV infection, the guideline recommend that "Evaluation for advanced fibrosis using noninvasive markers or liver biopsy, if required, is recommended for all persons with HCV infection to facilitate an appropriate decision regarding HCV treatment strategy, and to determine the need for initiating additional measures for cirrhosis management (e.g., hepatocellular carcinoma screening)" (AASLD-IDSA, 2019).

In a 2021 update, AASLD discussed changes in liver biochemistry during normal pregnancy. AASLD states that an "elevation in aminotransferases, bilirubin, or bile acids in pregnancy is abnormal and requires investigation. Evaluation in pregnant patients must include a thorough history (including travel, environmental, and drug exposures), physical examination, and focused serologic testing. Hepatic ultrasonography (US) is the favored initial imaging modality. Diagnosis can usually be determined without liver biopsy" (Sarkar et al., 2021).

In 2023, the AASLD and IDSA stated "For initial HCV testing, the Guidance Panel recommends HCV antibody screening with reflex HCV RNA testing to establish the presence of active infection (as opposed to spontaneous or treatment-induced viral clearance)" (Bhattacharya et al., 2023).

American Gastroenterological Association (AGA)

The 2017 guidelines (Lim et al., 2017) on the Role of Elastography in the Evaluation of Liver Fibrosis state that:

- "In patients with chronic hepatitis C, the AGA recommends vibration controlled transient elastography, if available, rather than other nonproprietary, noninvasive serum tests (APRI, FIB-4) to detect cirrhosis."
- "In patients with chronic hepatitis B, the AGA suggests vibration controlled transient elastography (VCTE) rather than other nonproprietary noninvasive serum tests (ie, APRI and FIB-4) to detect cirrhosis."
- "The AGA makes no recommendation regarding the role of VCTE in the diagnosis of cirrhosis in adults with NAFLD."

In 2023, the AGA released an expert review of the role of noninvasive biomarkers in the evaluation and management of nonalcoholic fatty liver disease (Wattacheril et al., 2023). The AGA recommends:

- "NITs can be used for risk stratification in the diagnostic evaluation of patients with NAFLD.
- A Fibrosis 4 Index score <1.3 is associated with strong negative predictive value for advanced hepatic fibrosis and may be useful for exclusion of advanced hepatic fibrosis in patients with NAFLD.
- A combination of 2 or more NITs combining serum biomarkers and/or imaging-based biomarkers is preferred for staging and risk stratification of patients with NAFLD whose Fibrosis 4 Index score is >1.3.
- Use of NITs in accordance with manufacturer's specifications (e.g., not in patients with ascites or pacemakers) can minimize risk of discordant results and adverse events.
- NITs should be interpreted with context and consideration of pertinent clinical data (e.g., physical examination, biochemical, radiographic, and endoscopic) to optimize positive predictive value in the identification of patients with advanced fibrosis.
- Liver biopsy should be considered for patients with NIT results that are indeterminate or discordant; conflict with other clinical, laboratory, or radiologic findings; or when alternative etiologies for liver disease are suspected.

- Serial longitudinal monitoring using NITs for assessment of disease progression or regression may inform clinical management (i.e., response to lifestyle modification or therapeutic intervention).
- Patients with NAFLD and NITs results suggestive of advanced fibrosis (F3) or cirrhosis (F4) should be considered for surveillance of liver complications (e.g., hepatocellular carcinoma screening and variceal screening per Baveno criteria). Patients with NAFLD and NITs suggestive of advanced hepatic fibrosis (F3) or (F4), should be monitored with serial liver stiffness measurement; vibration controlled transient elastography; or magnetic resonance elastography, given its correlation with clinically significant portal hypertension and clinical decompensation."

World Health Organization (WHO)

In March 2015, the WHO released Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection. In the section titled "Non-invasive Assessment of Liver Disease Stage at Baseline and during Follow up," the following is noted: 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 (WHO, 2015). In 2024, the WHO added a new recommendation for non-invasive test thresholds to establish the presence of significant fibrosis (≥F2) or cirrhosis (F4): "Evidence of significant fibrosis (≥F2) should be based on an APRI score of >0.5 or transient elastography value of >7.0 kPa, and cirrhosis (F4) should be based on clinical criteria (or an APRI score of >1.0 or transient elastography (FibroScan®) value of >12.5 kPa a)." The clinical features of decompensated cirrhosis are: "portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy), coagulopathy, or liver insufficiency (jaundice). Other clinical features of advanced liver disease/cirrhosis may include: hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema or oedema" (WHO, 2024).

In 2018, the WHO also published guidelines for management of patients with Hepatitis C. In it, they suggest "that aminotransferase/platelet ratio index (APRI) or FIB-4 be used for the assessment of hepatic fibrosis rather than other non-invasive tests that require more resources such as elastography or FibroTest." However, they do note that "FibroScan, which is more accurate than APRI and FIB-4, may be preferable in settings where the equipment is available and the cost of the test is not a barrier to testing."

The WHO does not mention miRNA as a tool for assessment of hepatitis (WHO, 2018).

United States Preventive Services Task Force (USPSTF)

The USPSTF published their final recommendation statement on Hepatitis C screening in adolescents and adults in 2020. THE USPSTF recommends "screening for hepatitis C virus (HCV) in adults aged 18 to 79" (grade B recommendation) (USPSTF, 2020).

National Institute for Health and Care Excellence (NICE)

NICE has released guidelines regarding chronic liver conditions. They note that the enhanced liver fibrosis test (ELF) may be considered in patients with NAFLD to test for advanced liver fibrosis. The ELF test should be offered to adults every three years and to children and young people every two years. (NICE, 2016).

European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity

These joint guidelines include recommendations for fibrosis, mentioning ELF, FibroTest, NFS, and FIB-4. Their recommendations include the following:

- "Biomarkers and scores of fibrosis, as well as transient elastography, are acceptable non-invasive procedures for the identification of cases at low risk of advanced fibrosis/cirrhosis (A2[1,5]). The combination of biomarkers/ scores and transient elastography might confer additional diagnostic accuracy and might save a number of diagnostic liver biopsies (B2[2,5])."
- "Monitoring of fibrosis progression in clinical practice may rely on a combination of biomarkers/scores and transient elastography, although this strategy requires validation (C2[3,5])."
- "The identification of advanced fibrosis or cirrhosis by serum biomarkers/scores and/or elastography is less accurate and needs to be confirmed by liver biopsy, according to the clinical context (B2[2,5])."
- The guidelines observe that due to non-invasive tests' high negative predictive values, they "may be confidently used for first-line risk stratification to exclude severe disease." Still, they state that "There is no consensus on thresholds or strategies for use in clinical practice when trying to avoid liver biopsy. Some data suggest that the combination of elastography and serum markers performs better than either method alone. Importantly, longitudinal data correlating changes in histological severity and in non-invasive measurements are urgently needed."
- For nonalcoholic steatohepatitis (NASH), the guidelines state that "to date, non-invasive tests are not validated for the diagnosis of NASH" and addresses CK-18 as a proposed biomarker.

- For monitoring of NAFLD, the guidelines state that "Monitoring should include routine biochemistry, assessment of comorbidities and non-invasive monitoring of fibrosis" (EASL et al., 2016).

[1]Grade A Evidence Quality- High: Further research is very unlikely to change our confidence in the estimate of effect

[2]Grade B Evidence Quality- Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

[3]Grade C Evidence Quality- Low or very low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate effect. Any estimate of effect is uncertain.

[4]Grade 1 Recommendation- Strong: Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost.

[5]Grade 2 Recommendation- Weak: Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption.

The EASL also released guidelines on management of Hepatitis C. In it, they recommend that "Fibrosis stage must be assessed by non-invasive methods initially, with liver biopsy reserved for cases where there is uncertainty or potential additional aetiologies (A1[1,4])" (grading scale same as the 2016 guideline above). Non-invasive methods include FibroScan, ARFI, Aixplorer, FibroTest, APRI, and FIB-4 (EASL, 2018).

Guidelines for Hepatitis B were also published. In it, EASL remarks that "the diagnostic accuracy of all non-invasive methods is better at excluding than confirming advanced fibrosis or cirrhosis." Non-invasive methods include assessment of serum biomarkers of liver fibrosis (EASL, 2017).

The EASL also published guidelines titled "Non-invasive tests for evaluation of liver disease severity and prognosis." In it, they state the following (grading scale same as the 2016 guideline above):

- "Serum biomarkers can be used in clinical practice due to their high applicability (>95%) and good interlaboratory reproducibility. However, they should be preferably obtained in fasting patients (particularly those including hyaluronic acid) and following the manufacturer's recommendations for the patented tests (A1[1,4])"
- "Serum biomarkers of fibrosis are well validated in patients with chronic viral hepatitis (with more evidence for HCV than for HBV and HIV/HCV coinfection). They are less well validated in NAFLD and not validated in other chronic liver diseases (A1[1,4])"
- "Their performances are better for detecting cirrhosis than significant fibrosis (A1[1,4])"

- "FibroTest, APRI and NAFLD fibrosis score are the most widely used and validated patented and nonpatented tests (A1[1,4])"
- "Among the different available strategies, algorithms combining TE and serum biomarkers appear to be the most attractive and validated one (A2[1,5])"
- "HCV patients who were diagnosed with cirrhosis based on non-invasive diagnosis should undergo screening for HCC and PH and do not need confirmatory liver biopsy (A1[1,4])"
- "Non-invasive assessment including serum biomarkers or TE can be used as first line procedure for the identification of patients at low risk of severe fibrosis/ cirrhosis (A1[1,4])"
- "The identification of significant fibrosis is less accurate with non-invasive tests as compared to liver biopsy and may necessitate, according to the clinical context, histological confirmation (A1[1,4])"
- "Follow-up assessment by either serum biomarkers or TE for progression of liver fibrosis should be performed among NAFLD patients at a 3 year interval (B1[2,4])" (EASL & ALEH, 2015).

[1]Grade A Evidence Quality- High: Further research is very unlikely to change our confidence in the estimate of effect

[2]Grade B Evidence Quality- Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

[3]Grade 1 Recommendation- Strong: Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost.

[4]Grade 2 Recommendation- Weak: Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption.

The EASL released guidelines on non-invasive tests for evaluation of liver disease severity and prognosis (EASL, 2020). The following recommendations were made (grading scale same as the 2016 guideline above):

- "Serum biomarkers can be used in clinical practice due to their high applicability (>95%) and good interlaboratory reproducibility. However, they should be preferably obtained in fasting patients (particularly those including hyaluronic acid) and following the manufacturer's recommendations for the patented tests (A1[1,4])"
- "TE and serum biomarkers have equivalent performance for detecting significant fibrosis in patients with untreated viral hepatitis (A1[1,4])"
- "In patients with viral hepatitis C, when TE and serum biomarkers results are in accordance, the diagnostic accuracy is increased for detecting significant fibrosis but not for cirrhosis. In cases of unexplained discordance, a liver biopsy should be performed if the results would change the patient management (A1[1,4])"

- "All HCV patients should be screened to exclude cirrhosis by TE if available. Serum biomarkers can be used in the absence of TE (A11,4)"(EASL, 2020).

In the 2021 update of the guidelines on non-invasive tests for evaluation of liver disease severity and prognosis (EASL, 2021), the EASL recommends the following for the general population:

- "Non-invasive fibrosis tests should be used for ruling out rather than diagnosing advanced fibrosis in low-prevalence populations (LoE 1, Strong recommendation).
- Non-invasive fibrosis tests should be preferentially used in patients at risk of advanced liver fibrosis (such as patients with metabolic risk factors and/or harmful use of alcohol) and not in unselected general populations (LoE 2, Strong recommendation).
- ALT, AST and platelet count should be part of the routine investigations in primary care in patients with suspected liver disease, so that simple non-invasive scores can be readily calculated (LoE 2, Strong recommendation).
- The automatic calculation and systematic reporting of simple non-invasive fibrosis tests such as FIB-4, in populations at risk of liver fibrosis (individuals with metabolic risk factors and/or harmful use of alcohol) in primary care, is recommended in order to improve risk stratification and linkage to care (LoE 2, Strong recommendation)."

The EASL recommends the following for the diagnosis of compensated advanced chronic liver disease (cACLD) and portal hypertension:

- "cACLD should be diagnosed using second line tests (patented serum tests or elastography) in a specialised setting (LoE 2, strong recommendation).
- Fibrotest or FibroMeter or ELF should be used to rule out cACLD if available (LoE 3, strong recommendation).
- LSM by TE should be used to rule-out and diagnose cACLD using the following cut-offs: <8-10 kPa to rule-out; >12-15 kPa to rule-in. Intermediate values require further testing (LoE 3 strong recommendation).
- pSWE and 2D-SWE should be used to rule-out and diagnose cACLD, with AUROCs >0.90 in the published meta-analyses (LoE 2, strong recommendation).
- Inter-system variability should be taken into account when interpreting the results of different elastography techniques, since values, ranges and cut-offs are not comparable (LoE 3, strong recommendation)" (EASL, 2021).

Centers for Disease Control and Prevention (CDC)

The CDC recommends that clinicians offer "medical evaluation (by either a primary care clinician or specialist for chronic liver disease, including treatment and monitoring)" to people who are diagnosed with HCV infection (CDC, 2023).

US Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the US Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

References

1. AAFP. (2019). Cirrhosis: Diagnosis and Management. American Family Physician. **https://www.aafp.org/pubs/afp/issues/2019/1215/p759.html** Accessed September 30, 2025.
2. AASLD-IDSA. (2015). Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology, 62(3), 932-954. **https://doi.org/10.1002/hep.27950** Accessed September 30, 2025.
3. AASLD-IDSA. (2019). HCV Testing and Linkage to Care. **https://www.hcvguidelines.org/evaluate/testing-and-linkage** Accessed September 30, 2025.
4. Abdel-Al, A., El-Ahwany, E., Zoheiry, M., Hassan, M., Ouf, A., Abu-Taleb, H., Abdel Rahim, A., El-Talkawy, M. D., & Zada, S. (2018). miRNA-221 and miRNA-222 are promising biomarkers for progression of liver fibrosis in HCV Egyptian patients. Virus Res, 253, 135-139. **https://doi.org/10.1016/j.virusres.2018.06.007** Accessed September 30, 2025.
5. Berends, M. A., Snoek, J., de Jong, E. M., Van Krieken, J. H., de Knegt, R. J., van Oijen, M. G., van de Kerkhof, P. C., & Drenth, J. P. (2007). Biochemical and biophysical assessment of MTX-induced liver fibrosis in psoriasis patients: Fibrotest predicts the presence and Fibroscan predicts the absence of significant liver fibrosis. Liver Int, 27(5), 639-645. **https://doi.org/10.1111/j.1478-3231.2007.01489.x** Accessed September 30, 2025.
6. Bhattacharya, D., Aronsohn, A., Price, J., Lo Re, V., III, & Panel, t. A. A. f. t. S. o. L. D. I. D. S. o. A. H. G. (2023). Hepatitis C Guidance 2023 Update: American Association for the Study of Liver Diseases– Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Clinical Infectious Diseases. **https://doi.org/10.1093/cid/ciad319** Accessed September 30, 2025.
7. BioPredictive. (2019). FibroMax. **https://www.biopredictive.com/products/fibromax/** Accessed September 30, 2025.
8. Bracht, T., Molleken, C., Ahrens, M., Poschmann, G., Schlosser, A., Eisenacher, M., Stuhler, K., Meyer, H. E., Schmiegel, W. H., Holmskov, U., Sorensen, G. L., & Sitek, B. (2016). Evaluation of the biomarker candidate MFAP4 for non-invasive assessment of hepatic fibrosis in hepatitis C patients. J Transl Med, 14(1), 201. **https://doi.org/10.1186/s12967-016-0952-3** Accessed September 30, 2025.
9. Bril, F., McPhaul, M. J., Caulfield, M. P., Castille, J. M., Poynard, T., Soldevila-Pico, C., Clark, V. C., Firpi-Morell, R. J., Lai, J., & Cusi, K. (2019). Performance of the SteatoTest, ActiTest, NashTest and FibroTest in a multiethnic cohort of patients with type 2 diabetes mellitus. J Investig Med, 67(2), 303-311. **https://doi.org/10.1136/jim-2018-000864** Accessed September 30, 2025.
10. CDC. (2023). Clinical Screening and Diagnosis for Hepatitis C. **https://www.cdc.gov/hepatitis-c/hcp/diagnosis-testing/** Accessed September 30, 2025.
11. Chalasani, N., Younossi, Z., Lavine, J. E., Charlton, M., Cusi, K., Rinella, M., Harrison, S. A., Brunt, E. M., & Sanyal, A. J. (2017). The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology, 67(1), 328-357. **https://doi.org/10.1002/hep.29367** Accessed September 30, 2025.
12. Chin, J. L., Pavlides, M., Moolla, A., & Ryan, J. D. (2016). Non-invasive Markers of Liver Fibrosis: Adjuncts or Alternatives to Liver Biopsy? Front Pharmacol, 7, 159. **https://doi.org/10.3389/fphar.2016.00159** Accessed September 30, 2025.

13. Chow, K. W., Futela, P., Saharan, A., & Saab, S. (2023). Comparison of Guidelines for the Screening, Diagnosis, and Noninvasive Assessment of Nonalcoholic Fatty Liver Disease. J Clin Exp Hepatol, 13(5), 783-793. **https://doi.org/10.1016/j.jceh.2023.01.016** Accessed September 30, 2025.

14. CIMA Sciences. (2023). OWLiver: Test for Fatty Liver Disease. **https://cimasciences.com/owliver/** Accessed September 30, 2025.

15. Curry, M., & Afdhal, N. (2024). Noninvasive assessment of hepatic fibrosis: Overview of serologic and radiographic tests - UpToDate. In K. Robson (Ed.), UptoDate. **https://www.uptodate.com/contents/noninvasive-assessment-of-hepatic-fibrosis-overview-of-serologic-tests-and-imaging-examinations** Accessed September 30, 2025.

16. Cusi, K., Chang, Z., Harrison, S., Lomonaco, R., Bril, F., Orsak, B., Ortiz-Lopez, C., Hecht, J., Feldstein, A. E., Webb, A., Louden, C., Goros, M., & Tio, F. (2014). Limited value of plasma cytokeratin-18 as a biomarker for NASH and fibrosis in patients with non-alcoholic fatty liver disease. J Hepatol, 60(1), 167-174. **https://doi.org/10.1016/j.jhep.2013.07.042** Accessed September 30, 2025.

17. Dong, H., Xu, C., Zhou, W., Liao, Y., Cao, J., Li, Z., & Hu, B. (2018). The combination of 5 serum markers compared to FibroScan to predict significant liver fibrosis in patients with chronic hepatitis B virus. Clin Chim Acta, 483, 145-150. **https://doi.org/10.1016/j.cca.2018.04.036** Accessed September 30, 2025.

18. EASL. (2017). EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. **https://easl.eu/wp-content/uploads/2018/10/HepB-English-report.pdf** Accessed September 30, 2025.

19. EASL. (2018). Treatment of Hepatitis C **https://easl.eu/wp-content/uploads/2018/10/HepC-English-report.pdf** Accessed September 30, 2025.

20. EASL. (2020). EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis – 2020 update. **https://www.echosens.com/wp-content/uploads/2021/07/EASL-CPG-NITs-2021_Supplementary-1.pdf** Accessed September 30, 2025.

21. EASL. (2021). EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol, 75(3), 659-689. **https://doi.org/10.1016/j.jhep.2021.05.025** Accessed September 30, 2025.

22. EASL. (2023). Multinational liver societies announce new “Fatty” liver disease nomenclature that is affirmative and non-stigmatising. **https://easl.eu/news/new_fatty_liver_disease_nomenclature-2/** Accessed September 30, 2025.

23. EASL, & ALEH. (2015). EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol, 63(1), 237-264. https://doi.org/10.1016/j.jhep.2015.04.006

24. EASL, EASD, & EASO. (2016). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol, 64(6), 1388-1402. **https://doi.org/10.1016/j.jhep.2015.11.004** Accessed September 30, 2025.

25. Fibronsotics. (2020). LIVERFAst. **https://www.fibronostics.com/liverfast/** Accessed September 30, 2025.

26. Fouad, A., Sabry, D., Ahmed, R., Kamal, M., Allah, S. A., Marzouk, S., Amin, M., Abd El Aziz, R., El Badri, A., Khattab, H., & Helmy, D. (2013). Comparative diagnostic study of biomarkers using FibroMax™ and pathology for prediction of liver steatosis in patients with chronic hepatitis C virus infection: an Egyptian study. In Int J Gen Med (Vol. 6, pp. 127-134). **https://doi.org/10.2147/ijgm.s36433** Accessed September 30, 2025.

27. Friedman, S. L. (2024). Pathogenesis of hepatic fibrosis. **https://www.uptodate.com/contents/pathogenesis-of-hepatic-fibrosis** Accessed September 30, 2025.

28. Gao, Y., Zheng, J., Liang, P., Tong, M., Wang, J., Wu, C., He, X., Liu, C., Zhang, S., Huang, L., Jiang, T., Cheng, C., Meng, F., Mu, X., Lu, Y., Li, Y., Ai, H., Qiao, X., Xie, X. Y., Zheng, R. (2018). Liver Fibrosis with Two-dimensional US Shear-Wave Elastography in Participants with Chronic Hepatitis B: A Prospective Multicenter Study. Radiology, 172479. **https://doi.org/10.1148/radiol.2018172479** Accessed September 30, 2025.

29. Huang, H., Wu, T., Mao, J., Fang, Y., Zhang, J., Wu, L., Zheng, S., Lin, B., & Pan, H. (2015). CHI3L1 Is a Liver-Enriched, Noninvasive Biomarker That Can Be Used to Stage and Diagnose Substantial Hepatic Fibrosis. Omics, 19(6), 339-345. **https://doi.org/10.1089/omi.2015.0037** Accessed September 30, 2025.

30. Itoh, Y., Seko, Y., Shima, T., Nakajima, T., Mizuno, K., Kawamura, Y., Akuta, N., Ito, K., Kawanaka, M., Hiramatsu, A., Sakamoto, M., Harada, K., Goto, Y., Nakayama, T., Kumada, H., & Okanoue, T. (2018). The accuracy of noninvasive scoring systems for diagnosing nonalcoholic steatohepatitis-related fibrosis: multi-center validation study. Hepatol Res. **https://doi.org/10.1111/hepr.13226** Accessed September 30, 2025.

31. Kar, S., Paglialunga, S., Jaycox, S. H., Islam, R., & Paredes, A. H. (2019). Assay validation and clinical performance of chronic inflammatory and chemokine biomarkers of NASH fibrosis. PLoS One, 14(7), e0217263. **https://doi.org/10.1371/journal.pone.0217263** Accessed September 30, 2025.

32. Kaswala, D. H., Lai, M., & Afdhal, N. H. (2016). Fibrosis Assessment in Nonalcoholic Fatty Liver Disease (NAFLD) in 2016. Dig Dis Sci, 61(5), 1356-1364. **https://doi.org/10.1007/s10620-016-4079-4** Accessed September 30, 2025.

33. Kim, S. S., Nam, J. S., Cho, H. J., Won, J. H., Kim, J. W., Ji, J. H., Yang, M. J., Park, J. H., Noh, C. K., Shin, S. J., Lee, K. M., Cho, S. W., & Cheong, J. Y. (2017). Plasma micoRNA-122 as a predictive marker for treatment response following transarterial chemoembolization in patients with hepatocellular carcinoma. J Gastroenterol Hepatol, 32(1), 199-207. **https://doi.org/10.1111/jgh.13448** Accessed September 30, 2025.

34. Kwok, R., Tse, Y. K., Wong, G. L., Ha, Y., Lee, A. U., Ngu, M. C., Chan, H. L., & Wong, V. W. (2014). Systematic review with meta-analysis: non-invasive assessment of non-alcoholic fatty liver disease--the role of transient elastography and plasma cytokeratin-18 fragments. Aliment Pharmacol Ther, 39(3), 254-269. **https://doi.org/10.1111/apt.12569** Accessed September 30, 2025.

35. Lim, J. K., Flamm, S. L., Singh, S., & Falck-Ytter, Y. T. (2017). American Gastroenterological Association Institute Guideline on the Role of Elastography in the Evaluation of Liver Fibrosis. Gastroenterology, 152(6), 1536-1543. **https://doi.org/10.1053/j.gastro.2017.03.017** Accessed September 30, 2025.

36. NICE. (2016). Non-alcoholic fatty liver disease (NAFLD): assessment and management. **https://www.nice.org.uk/guidance/NG49/chapter/Recommendations#assessment-for-advanced-liver-fibrosis** Accessed September 30, 2025.

37. Parikh, P., Ryan, J. D., & Tsochatzis, E. A. (2017). Fibrosis assessment in patients with chronic hepatitis B virus (HBV) infection. Ann Transl Med, 5(3), 40. **https://doi.org/10.21037/atm.2017.01.28** Accessed September 30, 2025.

38. Patel, Y. A., Gifford, E. J., Glass, L. M., Turner, M. J., Han, B., Moylan, C. A., Choi, S., Suzuki, A., Provenzale, D., & Hunt, C. M. (2018). Identifying Nonalcoholic Fatty Liver Disease Advanced Fibrosis in the Veterans Health Administration. Dig Dis Sci. **https://doi.org/10.1007/s10620-018-5123-3** Accessed September 30, 2025.

39. Sarkar, M., Brady, C. W., Fleckenstein, J., Forde, K. A., Khungar, V., Molleston, J. P., Afshar, Y., & Terrault, N. A. (2021). Reproductive Health and Liver Disease: Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology, 73(1), 318-365. **https://doi.org/10.1002/hep.31559** Accessed September 30, 2025.

40. Srivastava, A., Jong, S., Gola, A., Gailer, R., Morgan, S., Sennett, K., Tanwar, S., Pizzo, E., O'Beirne, J., Tsochatzis, E., Parkes, J., & Rosenberg, W. (2019). Cost-comparison analysis of FIB-4, ELF and fibroscan in community pathways for non-alcoholic fatty liver disease. BMC Gastroenterol, 19(1), 122. **https://doi.org/10.1186/s12876-019-1039-4** Accessed September 30, 2025.

41. Suehiro, T., Miyaaki, H., Kanda, Y., Shibata, H., Honda, T., Ozawa, E., Miuma, S., Taura, N., & Nakao, K. (2018). Serum exosomal microRNA-122 and microRNA-21 as predictive biomarkers in transarterial chemoembolization-treated hepatocellular carcinoma patients. Oncol Lett, 16(3), 3267-3273. **https://doi.org/10.3892/ol.2018.8991** Accessed September 30, 2025.

42. Tendler, D. (2022). Pathogenesis of nonalcoholic fatty liver disease. **https://www.uptodate.com/contents/pathogenesis-of-nonalcoholic-fatty-liver-disease** Accessed September 30, 2025.

43. Terrault, N. A., Lok, A. S. F., McMahon, B. J., Chang, K. M., Hwang, J. P., Jonas, M. M., Brown, R. S., Jr., Bzowej, N. H., & Wong, J. B. (2018). Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology, 67(4), 1560-1599. **https://doi.org/10.1002/hep.29800** Accessed September 30, 2025.

44. USPSTF. (2020). Hepatitis C Virus Infection in Adolescents and Adults: Screening. **https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/hepatitis-c-screening** Accessed September 30, 2025.

45. Vali, Y., Lee, J., Boursier, J., Petta, S., Wonders, K., Tiniakos, D., Bedossa, P., Geier, A., Francque, S., Allison, M., Papatheodoridis, G., Cortez-Pinto, H., Pais, R., Dufour, J. F., Leeming, D. J., Harrison, S. A., Chen, Y., Cobbold, J. F., Pavlides, M., . . . Bossuyt, P. M. (2023). Biomarkers for staging fibrosis and non-alcoholic steatohepatitis in non-alcoholic fatty liver disease (the LITMUS project): a comparative diagnostic accuracy study. Lancet Gastroenterol Hepatol, 8(8), 714-725. **https://doi.org/10.1016/s2468-1253(23)00017-1** Accessed September 30, 2025.

46. Vali, Y., Lee, J., Boursier, J., Spijker, R., Verheij, J., Brosnan, M. J., Anstee, Q. M., Bossuyt, P. M., Zafarmand, M. H., & On Behalf Of The Litmus Systematic Review, T. (2021). FibroTest for Evaluating Fibrosis in Non-Alcoholic Fatty Liver Disease Patients: A Systematic Review and Meta-Analysis. Journal of clinical medicine, 10(11), 2415. **https://doi.org/10.3390/jcm10112415** Accessed September 30, 2025.

47. Valva, P., Rios, D. A., De Matteo, E., & Preciado, M. V. (2016). Chronic hepatitis C virus infection: Serum biomarkers in predicting liver damage. World J Gastroenterol, 22(4), 1367-1381. **https://doi.org/10.3748/wjg.v22.i4.1367** Accessed September 30, 2025.

48. Wang, L., Liu, T., Zhou, J., You, H., & Jia, J. (2018). Changes in serum chitinase 3-like 1 levels correlate with changes in liver fibrosis measured by two established quantitative methods in chronic hepatitis B patients following antiviral therapy. Hepatol Res, 48(3), E283-e290. **https://doi.org/10.1111/hepr.12982** Accessed September 30, 2025.

49. Wattacheril, J. J., Abdelmalek, M. F., Lim, J. K., & Sanyal, A. J. (2023). AGA Clinical Practice Update on the Role of Noninvasive Biomarkers in the Evaluation and Management of Nonalcoholic Fatty Liver Disease: Expert Review. Gastroenterology, 165(4), 1080-1088. **https://doi.org/10.1053/j.gastro.2023.06.013** Accessed September 30, 2025.

50. Weis, A., Marquart, L., Calvopina, D. A., Genz, B., Ramm, G. A., & Skoien, R. (2019). Serum MicroRNAs as Biomarkers in Hepatitis C: Preliminary Evidence of a MicroRNA Panel for the Diagnosis of Hepatocellular Carcinoma. Int J Mol Sci, 20(4). **https://doi.org/10.3390/ijms20040864** Accessed September 30, 2025.

51. WHO. (2015). WHO Guidelines Approved by the Guidelines Review Committee. In Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection. World Health OrganizationCopyright (c) World Health Organization 2015. **https://apps.who.int/iris/bitstream/handle/10665/154590/9789241549059_eng.pdf** Accessed September 30, 2025.

52. WHO. (2018). WHO Guidelines Approved by the Guidelines Review Committee. In Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection **https://apps.who.int/iris/bitstream/handle/10665/273174/9789241550345-eng.pdf** Accessed September 30, 2025.

53. WHO. (2024). Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection **https://iris.who.int/bitstream/handle/10665/376353/9789240090903-eng.pdf?sequence=1** Accessed September 30, 2025.

History

Date	Comments
11/01/25	New policy, approved October 14, 2025, effective for dates of service on or after February 6, 2026, following 90-day provider notification. Add to Routine Test Management Policy section. For individuals with hepatitis C, hepatitis B, metabolic dysfunction-associated steatotic liver disease (including metabolic dysfunction-associated steatohepatitis), or alcoholic hepatitis, ELF, FibroTest, HBV FibroSURE, or HCV FibroSURE are reimbursable once every 6 months to distinguish cirrhosis from non-cirrhosis; other multianalyte assays, use in other liver diseases, and serum biomarkers (e.g., SIPA1L1, miRNAs, CHI3L1, hyaluronic acid, procollagen, collagen, laminin, cytokeratin-18, MFAP4) are not reimbursable.