



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Serum Markers for Liver Disease

Effective Date 3/15/2011
Next Review Date 3/15/2012
Coverage Policy Number 0296

Table of Contents

General Background	1
Coding/Billing Information	12
References	12
Policy History	17

Hyperlink to Related Coverage Policies

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2011 CIGNA

CIGNA does not cover serum marker panels for the diagnosis or clinical management of liver disease, including hepatitis C, because they are considered experimental, investigational or unproven (this list may not be all inclusive):

- ASH FibroSURE™
- FibroMAX™
- FIBROSpect II®
- HCV FibroSURE™ or FibroTest + ActiTest
- HepaScore™
- NASH FibroSURE™

General Background

Liver fibrosis results from chronic damage to the liver. Although fibrosis in the liver may be a progressive process leading to cirrhosis, fibrosis is a potentially reversible process in the early stages. The main causes of liver fibrosis include chronic hepatitis C virus (HCV) infection, alcohol abuse, and nonalcoholic steatohepatitis. Liver biopsy is considered the gold standard for assessing fibrosis and inflammation of the liver, but its sampling error (10–40%), intraobserver and interobserver variability for staging fibrosis (60–90% and 70–90%, respectively), imperfect accuracy (mean rate of false negative results of 24%) and adverse event risk limit its utility. Given the limitations of the liver biopsy, there is interest in developing noninvasive markers of hepatic fibrosis. Noninvasive serum markers, noninvasive diagnostic or imaging tests (e.g., ultrasonography, positron

emission tomography, transient elastography and magnetic resonance imaging) and genetic studies for assessing fibrosis have been evaluated (Ray and Thomas, 2009; Rossi, et al., 2007; Halfon, et al., 2006; Grigorescu, 2006; Bataller and Brenner, 2005).

The ideal liver fibrosis marker has not been identified. The properties of an ideal fibrosis marker test include a high sensitivity and specificity, pose low risk for the patient, and are convenient to perform with reproducible and easily interpreted results. High sensitivity and specificity is needed to avoid failing to initiate therapy in a patient despite the presence of significant fibrosis or necroinflammatory activity or, conversely, initiating treatment without the presence of significant liver damage. Most current serum markers are not liver specific, or may represent hepatic clearance affected by inflammation. Coexisting pathologies such as hemolysis or rheumatoid arthritis are associated with changes in levels of serum markers (Rossi, et al., 2007; Crockett, et al., 2006).

The receiver-operator curve (ROC) is a technique used to assist in identifying the accuracy of a diagnostic test. ROCs are used to compare the relative accuracies of different tests by comparing the areas under the curve (AUC) for each test. The test with the greater area under the curve would be considered more accurate. This is also referred to as the area under the receiver operating characteristic curve (AUROC). An ideal biomarker would have an AUC of 1.0; this translates to 100% sensitivity and specificity. The majority of biochemical markers studied have an AUC between 0.80–0.85 and have value not for staging the disease, but for differentiating insignificant (F0–F1) from significant fibrosis (F2–F4 Metavir). Indeterminate results occur mainly in patients who have F1–F2 disease. The value of a biomarker is validated against the liver biopsy, which has an accuracy of about 80%. Therefore it is improbable that a biomarker has a better performance than a liver biopsy for staging fibrosis (Grigorescu, 2006). Recent textbook literature addressing noninvasive markers of hepatic fibrosis states that the diagnostic accuracies of various marker panels vary across studies. When compared to the liver biopsy, the accuracy or AUROC rarely exceeds 0.8–0.9 (Ray and Thomas, 2009).

Numerous individual markers of liver fibrosis have been studied (e.g., hyaluronic acid, matrix metalloproteinases, YKL-40, and others) but have been found to have limited accuracy in predicting hepatic fibrosis. The individual markers are useful for establishing the presence, but not absence, of fibrosis. Due to the limitations of individual markers to assess liver fibrosis, algorithms or indices combining the results of panels of markers have been studied which reportedly improve diagnostic accuracy. The serum marker panels have been proposed as an alternative to liver biopsy (Crockett, et al., 2006; Castera and Pawlotsky, 2005).

Some of the available serum marker panels include HCV FibroSURE™ (LabCorp, Burlington, NC), ASH FibroSURE™ (LabCorp, Burlington, NC), NASH FibroSURE™ (LabCorp, Burlington, NC), FIBROSpect II® (Prometheus Lab., San Diego, CA), Hepascore, Forns' score/index, aspartate aminotransferase (AST)-platelet ratio index (APRI), SHASTA index and the European Liver Fibrosis Group (ELFG) algorithm. Some panels are commercially available with proprietary bundled assays and patented formulas. Other panels and indices have been published and are freely available. The most widely studied serum marker panel is the FibroTest™ (FT) (Shaheen, et al., 2008; Crockett, et al., 2006).

Serum Marker Panels/Models

HCV FibroSURE™: HCV FibroSURE or FibroSURE™ combines FibroTest (FT) and ActiTest (AT) (Biopredictive, Paris, France). FT and HCV FibroSURE are identical tests marketed under different names in the United States and Europe. According to the manufacturer, this noninvasive blood test is intended to replace liver biopsy, thus avoiding the risk of biopsy-related adverse events, as well as avoiding limitations of liver biopsy, such as sampling errors and inter- and intra-pathologist variability. HCV FibroSURE has been proposed as an alternative to liver biopsy for the assessment of liver status following a diagnosis of HCV, baseline determination of liver status before initiating HCV therapy, post-treatment assessment of liver status six months after completion of therapy, noninvasive assessment of liver status in patients who are at increased risk of complications from a liver biopsy (LabCorp, 2006c).

HCV FibroSURE combines the quantitative results of six serum biochemical markers [i.e., alpha2-macroglobulin, haptoglobin, apolipoprotein A1, total bilirubin, gamma glutamyl transpeptidase (GGT), and alanine aminotransferase (ALT)]. Additionally, the patient's age and gender are factored in a patented algorithm to generate a measure of fibrosis and necroinflammatory activity in the liver (LabCorp, 2006c).

HCV FibroSURE is a continuous, linear biochemical assessment of fibrosis stage. It provides a numerical quantitative estimate of liver fibrosis ranging from 0.00–1.00, corresponding to the well- established Metavir scoring system of stages F0–F4 (LabCorp, 2006c).

Metavir Scoring Stage

- Fibrosis Stage (FT)
 - F0–fibrosis < 0.21
 - F0–F1 0.21–0.27
 - F1–portal fibrosis 0.27–0.31
 - F1–F2 0.31–0.48
 - F2–bridging fibrosis with few septa 0.48–0.58
 - F3–bridging fibrosis with many septa 0.58–0.72
 - F3–F4 0.72–0.74
 - F4–cirrhosis > 0.74

In addition, the test provides a numerical quantitative estimate of necroinflammatory activity ranging from 0.00–1.00, corresponding to the Metavir scoring system of grades A0–A3 (LabCorp, 2006c).

- Activity Grade (AT)
 - A0–no activity < 0.17
 - A0–A1 0.17–0.29
 - A1–minimal activity 0.29–0.36
 - A1–A2 0.36–0.52
 - A2–moderate activity 0.52–0.60
 - A2–A3 0.60–0.62
 - A3–severe activity > 0.62

HCV FibroSURE is not recommended for patients during combined interferon/ribavirin therapy since ribavirin may induce hemolysis and falsely elevate fibrosis and activity scores (LabCorp, 2006c).

FIBROSpect II™: FIBROSpect II is another proposed noninvasive approach to evaluating liver fibrosis. FIBROSpect II may help to distinguish the stage of fibrosis and assists in the treatment decisions for patients with HCV. This panel of markers does not measure necroinflammatory activity in chronic HCV patients. FIBROSpect II uses a combination of three markers, including tissue inhibitors of metalloproteinases (TIMP-1), alpha-2 macroglobulin, and hyaluronic acid (Mukherjee and Sorrell, 2006). According to the FIBROSpect II product description detail, “FIBROSpect II testing can aid physicians in differentiating no/mild liver fibrosis from moderate-to-severe liver fibrosis in patients with hepatitis C, and may help reduce the number of liver biopsies required. Due to sampling error and the relative risk of biopsy, PROMETHEUS FIBROSpect II testing is useful for initial patient evaluation and when biopsy is contraindicated or refused.”

ASH FibroSURE™: ASH FibroSURE is a noninvasive assessment of liver status for patients with alcoholic liver disease (ALD). ALD covers a wide range of manifestations from simple fatty infiltration to extensive fibrosis, cirrhosis, and/or hepatocellular carcinoma. ASH FibroSURE testing is not recommended for patients with other liver diseases. Quantitative results of ten biochemicals including alpha2-macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, GGT, ALT, AST, total cholesterol, triglycerides, and fasting glucose, in combination with age, gender, height, and weight, are analyzed, using a proprietary algorithm, to provide quantitative surrogate markers for liver fibrosis, hepatic steatosis, and alcoholic steatosis (ASH) (LabCorp, 2006a).

ASH FibroSURE includes a quantitative surrogate fibrosis marker (0.00–1.00), corresponding to the Metavir F0–F4 fibrosis staging. ASH FibroSURE provides a quantitative surrogate marker (0.00–1.00) for hepatic steatosis grade S0–S3 corresponding to 0% to > 66%. The ASH FibroSURE test also provides a quantitative surrogate marker (0.00–1.00) for alcoholic steatohepatitis grade (ASH 0–ASH 3) (LabCorp, 2006a).

NASH FibroSURE™: NASH FibroSURE is a noninvasive assessment of liver status for patients with nonalcoholic fatty liver disease (NAFLD). It is recommended that NASH FibroSURE be used for patients with

suspected NAFLD. NAFLD covers a spectrum of liver disease from simple fatty infiltration (steatosis) to progressive fibrosis. Quantitative results of ten biochemicals, including alpha2-macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, GGT, ALT, AST, total cholesterol, triglycerides, and fasting glucose, in combination with age, gender, height, and weight, are analyzed, using a proprietary algorithm, to provide quantitative surrogate markers for liver fibrosis, hepatic steatosis, and nonalcoholic steatohepatitis (NASH) (LabCorp, 2006b).

NASH FibroSURE includes a quantitative surrogate fibrosis marker (0.00–1.00), corresponding to the Metavir F0–F4 fibrosis staging. NASH FibroSURE provides a quantitative surrogate marker (0.00–1.00) for hepatic steatosis grade S0–S3 corresponding to 0% to > 66%. The NASH FibroSURE test also provides a diagnostic assessment of the presence of NASH using three broad categories N0–N2 corresponding to “Not NASH,” “Borderline NASH,” and “NASH” per the Kleiner classification (LabCorp, 2006b).

It is recommended that none of the FibroSURE tests be used for patients with Gilbert disease, acute hemolysis, acute viral hepatitis, drug-induced hepatitis, genetic liver disease, autoimmune hepatitis, and/or extrahepatic cholestatic. Any of these clinical situations may lead to inaccurate quantitative predictions of fibrosis (LabCorp, 2006b).

FibroMAX™: FibroMAX (Biopredictive, Paris, France) is a method of concomitant calculation of five fibrosis-related tests in a single procedure. The tests include: FT for the quantitative assessment of fibrosis; SteatoTest™ (Biopredictive, Paris, France) for the quantitative assessment of steatosis; AT for the quantitative assessment of necroinflammatory activity in HCV and hepatitis B (HBV); NashTest for the categorical diagnosis of nonalcoholic steatohepatitis; and AsthTest for the quantitative assessment of alcoholic steatohepatitis. These tests are also known as HCV FibroSURE, HBV FibroSURE™, ASH FibroSURE and NASH FibroSURE (Morra, et al., 2007).

HepaScore™: The HepaScore is based on serum levels of alpha-2 macroglobulin, hyaluronic acid, GGT, and total bilirubin. HepaScore is a score from 0.00–1.00 calculated from the results of these four analyses and the age and sex of the patient. This test is meant as a screening tool to avoid unnecessary biopsies in patients with HCV. The lowest and highest scores may obviate the need for a biopsy, while intermediary scores should be interpreted in the overall clinical context of the individual patient (Rossi, et al., 2007; Quest Diagnostics, 2010).

Miscellaneous Serum Marker Panels: Additional serum marker panels found in the literature include AST-platelet ratio index (APRI), Forns' index (i.e., age, GGT, cholesterol and platelets), SHASTA index (i.e., hyaluronic acid, AST and albumin), European Liver Fibrosis Group (ELFG) panel (i.e., age, hyaluronic acid, tissue inhibitor of matrix metalloproteinase 1 [TIMP 1], aminoterminal peptide of pro-collage III (P3NP), Enhanced Liver Fibrosis panel (ELF) (i.e., same as ELFG panel minus age), MP3 (i.e., P3NP, matrix metalloproteinase MMP-1), FibrometerA (prothrombin index, alpha-2 macroglobulin, HA, and age) (Naveau, et al. 2009; Guha, et al., 2008; Shaheen, et al., 2008; Rossi, et al., 2007; Leroy, et al., 2007).

Literature Review

HCV FibroSURE/ FibroTest (FT) and ActiTest (AT): In a cohort study, Bourliere et al. (2006) assessed the diagnostic accuracy of noninvasive indexes in comparison with liver histology performed in HCV infected patients (n=235). FT, aspartate aminotransferase to platelet ratio index (APRI), and Forns score were assessed with liver histology performed on the same day. The authors reported that performing all the tests, and liver biopsy, improved the diagnostic accuracy (96%) for liver fibrosis in HCV patients without comorbidities. The authors state that any single test could not be a gold standard. The combination of all tests without liver biopsy allowed 81.3% of the patients to be correctly classified. Liver biopsy was mandatory in 18.7% of the patients. The authors reported one of the weaknesses of their study is the distribution of liver fibrosis in the cohort, with 42% of patients with significant fibrosis, reflecting the fact that most centers were referral centers for liver disease. This is a limitation of this study, since noninvasive markers of fibrosis may have different diagnostic accuracy depending on the prevalence of significant fibrosis in the studied population.

In a multicenter prospective study, Halfon et al. (2006) studied 504 patients with chronic HCV to determine the validity of FT and AT. Diagnostic accuracies were assessed by receiver operating characteristics analysis. Liver biopsy and biochemical markers were taken on the same day. The median biopsy size was 15 mm (range: 2–58), with 9 portal tracts (1–37) and 1 fragment (1–12). Forty-six percent (230/504) were classified F2–F4 in fibrosis and 39% A2–A3 in activity. FT area AUROC for diagnosis of activity (A2–A3), significant fibrosis (F2–F4), and severe fibrosis (F3–F4) were 0.73 (0.69–0.77), 0.79 (0.75–0.82), and 0.80 (0.76–0.83), respectively.

Among the 92 patients (18%) with 2 fibrosis stages of discordance between FT and biopsy, the discordance was attributable to FT in 5%, to biopsy in 4%, and undetermined in 9%. The FT threshold giving the highest sensitivity and specificity was 0.36: sensitivity of 73% (66–78), specificity of 72% (67–78), negative predictive value of 76%, and positive predictive value of 69%. For the diagnosis of severe fibrosis, the FT threshold giving the highest sensitivity and specificity was 0.44: sensitivity of 76% (67–83), specificity of 70% (65–74), negative predictive value of 90%, and positive predictive value of 44%. The most frequent failures attributable to markers were false positives due to Gilbert's disease and inflammation, and false negatives due to inflammation. The most frequent failures attributable to biopsy were false negatives due to small biopsy size.

Summary of the Diagnostic Values of FT and AT for the Staging of Hepatic Fibrosis and the Grading of Hepatic Activity (Halfon, et al., 2006)

Stage/Grade Studied	AUC [95%CI]	Cut-off	Sensitivity (%) [95%CI]	Specificity (%) [95%CI]	NPV (%)	PPV (%)	Youden Index*
F0F1 vs F2F4	0.79 [0.75–0.82]	0.10	97 [94–99]	27 [22–33]	91	53	0.240
		0.30	77 [71–82]	65 [59–71]	77	65	0.420
		0.36±	73 [66–78]	72 [67–78]	76	69	0.449
		0.60	44 [38–51]	91 [87–94]	66	81	0.355
		0.80	20 [15–26]	98 [96–99]	59	90	0.169
F0F2 vs F3F4	0.80 [0.76–0.83]	0.10	99 [95–100]	21 [17–25]	99	28	0.200
		0.30	87 [79–92]	56 [51–61]	93	38	0.427
		0.44±	76 [67–83]	70 [65–74]	90	44	0.456
		0.60	56 [47–65]	85 [81–88]	86	53	0.404
		0.80	29 [21–38]	97 [94–98]	81	73	0.258
A0A1 vs A2A3	0.73 [0.69–0.77]	0.10	98 [94–99]	16 [12–20]	91	43	0.132
		0.30	79 [73–85]	56 [50–62]	81	54	0.355
		0.32±	78 [71–83]	60 [54–66]	81	56	0.379
		0.60	41 [34–48]	85 [80–89]	69	63	0.255
		0.80	16 [11–22]	94 [91–96]	63	63	0.100

*Youden index evaluates the diagnostic efficacy of a test. If the index is equal to or below zero, the diagnostic efficacy of the test is poor. The closer the index is to one, the higher the diagnostic value.

± Fibrotest cut off giving the best diagnostic values, corresponding to the highest Youden index value.

Ratzu et al. (2006) conducted a prospective study to determine the diagnostic utility of noninvasive markers for fibrosis (FT) in patients with NAFLD. One hundred seventy patients with suspected NAFLD were prospectively included in a reference center (Group 1), 97 in a multicenter study (Group 2), and 954 blood donors as controls. Fibrosis was assessed on a five-stage histological scale: F0 none, F1 perisinusoidal or periportal, F2 perisinusoidal and portal/periportal, F3 bridging, and F4 cirrhosis. Histology and the biochemical measurements were blinded to any other characteristics. The AUROC, sensitivity, specificity, and positive and negative predictive values were assessed. In both groups, FT has elevated and not different AUROCs for the diagnosis of advanced fibrosis (F2F3F4): 0.86 versus 0.75, and for F3F4: 0.92 versus 0.81 in Group1 and Group 2, respectively. When the two groups were pooled together, an FT cutoff of 0.30 had a 90% negative predictive value for advanced fibrosis (sensitivity 77%); and an FT cutoff of 0.70 had a 73% positive predictive value for advanced fibrosis (specificity 98%).

Diagnostic value of FT for predicting fibrosis in all patients (Ratzu, et al., 2006)

Stage	Cutoff	Sensitivity	Specificity	PPV	NPV
F2F3F4				Prevalence 0.27	

	0.30	0.77 (55/71)	0.77 (150/196)	0.54 (55/101)	0.90 (150/166)
	0.70	0.15 (11/71)	0.98 (192/196)	0.73 (11/15)	0.76 (192/252)
F3F4				Prevalence 0.13	
	0.30	0.92 (33/36)	0.71 (163/231)	0.33 (33/101)	0.98 (163/169)
	0.70	0.25 (9/36)	0.97 (225/252)	0.60 (9/15)	0.89 (225/252)

Rosenthal-Allieri et al. (2005) evaluated the analytical variability of the FT proteins (i.e., haptoglobin, apolipoprotein A1 and alpha 2 macroglobulin). The researchers concluded that inter-technique analytical variability of the FT parameters remains an issue, stating that national and international quality control programs would be useful to monitor analytical performance of protein assays.

In a prospective study, Rossi et al. (2003) investigated the predictive value of the proprietary FT score to distinguish HCV patients whose liver biopsy revealed insignificant fibrosis from those with clinically significant fibrosis who would qualify for antiviral therapy. Prior to antiviral therapy, serum samples were obtained from 125 confirmed HCV patients. The samples were analyzed for haptoglobin, alpha2-macroglobulin, apolipoprotein A1, bilirubin and GGT activity, and the FT score was then computed. Liver biopsies were staged blindly, and fibrosis pathology was staged according to the Metavir scoring system on a scale of F0–F4. Patients with scores F0 or F1 were considered to have insignificant fibrosis, and those with scores of F2, F3 or F4 were considered to have clinically significant fibrosis that qualified for combination antiviral therapy. The results of the study showed that out of the 125 patients, 57 had FT scores either < 0.1 (no fibrosis) or > 0.6 (significant fibrosis). The researchers found that, although 33 of the 125 patients had FT scores < 0.1 and were, therefore, unlikely to have fibrosis, six (18%) had significant fibrosis. Conversely, of the 24 patients with scores > 0.6 who were likely to have significant fibrosis, five (21%) had mild fibrosis. Of the 125 patients in the cohort, 57 (46%) could have avoided liver biopsy, but discrepant results were recorded in 11 of those 57 (19%) patients. The authors noted that in clinical practice it has been suggested that the FT score might be applied to patients who either have contraindications or refuse liver biopsy for the management of their HCV. The authors found that FT scores could not accurately predict either the presence or absence of significant fibrosis and could not be reliably used to reduce the need for liver biopsy. This study did not address whether repeated determinations of FT scores might have utility in tracking the progression of fibrosis in individual patients.

Poynard et al. (2003) conducted a retrospective study to evaluate the usefulness of FT-AT as surrogate markers of histological features using the data from a recent randomized trial of combination peginterferon alfa-2b and ribavirin. A total of 352 patients were selected; each patient had two interpretable liver biopsies and stored a serum sample before and after treatment. In all, 208 patients received peginterferon alfa-2b 1.5 mcg/kg and ribavirin. A total of 144 patients received interferon alfa-2b MU three times a week and ribavirin for 48 weeks. A fibrosis and an activity index combining five and six biochemical markers (i.e., alpha-2 macroglobulin, haptoglobin, GGT, total bilirubin, apolipoprotein A1, and ALT) were assessed at baseline and at end of follow-up (24 weeks after treatment). The researchers found that, for the diagnosis of bridging fibrosis and/or moderate necroinflammatory activity, the AUROC of the activity index was 0.76 ± 0.03 at baseline and 0.82 ± 0.02 at end of follow-up. A cutoff of activity index at 0.30 (range: 0.00–1.00) had 90% sensitivity and 88% positive predictive value for the diagnosis of bridging fibrosis or moderate necroinflammatory activity. Sensitivity analyses with biopsy specimens of size greater than 15 mm suggest that part of the discordance between biochemical markers and histology was due to biopsy specimen sampling error. The researchers identified the fact that because ribavirin can induce hemolysis, and therefore a decrease of haptoglobin and an increase of unconjugated bilirubin, there is a risk of false-positive FT-AT during combination treatment.

FIBROSpect II: In a prospective study, Patel et al. (2009) compared HCV FibroSure and FIBROSpect II during interferon-based therapy. Ninety-five interferon-naïve patients with genotype 1 HCV were enrolled in a phase 2b, active-controlled study of albinferon alfa-2b/ribavirin for 48 weeks. Proprietary and simple biochemical marker panels were independently evaluated in serum before and during the study. Baseline liver biopsies were evaluated for METAVIR fibrosis. HCV FibroSURE and FIBROSpect II indicated sensitivity (1.00 and 0.95, respectively), specificity (0.61 and 0.66, respectively), and an area under the receiver operating characteristic curve (0.89 and 0.90, respectively). The reported limitations with this study include a small sample size and the absence of a second comparative biopsy during or after treatment. The authors reported that further evaluation of these serum markers to follow long-term changes in fibrosis is required.

In a prospective study, Zaman et al. (2007) assessed the validity of FIBROSpect II. Serum was obtained from HCV (15% with HCV/alcohol) patients (n=108) seen in a hepatology clinic at a single tertiary care center at the time of liver biopsy. The performance of FIBROSpect II in differentiating mild (F0–F1) from significant (F2–F4) fibrosis was assessed by comparing the panel results with performed liver biopsy. The prevalence of significant fibrosis in the study group was 36.1%. The diagnostic value of the serum marker panel to detect significant fibrosis as assessed by AUC of the ROC was 0.826. Performance characteristics are as follows: sensitivity 71.8%, specificity 73.9%, PPV 60.9%, NPV 82.3%, and overall accuracy of 73.1%. The authors noted that the FIBROSpect II assay is good at differentiating between advanced and minimal or no fibrosis but are poor at differentiating between the intermediate grades of fibrosis (i.e., F1–F3). The authors noted that due to the high NPV FIBROSpect II in low prevalence populations of F2–F4 fibrosis may allow providers to avoid a liver biopsy in certain situations, such as patients who refuse or have contraindication (e.g., hemophiliacs) to a liver biopsy. The authors noted the clinical utility of FIBROSpect II needs to be validated in a community setting with different relative prevalence of different stages of HCV.

In a retrospective study, Snyder et al. (2007) reported that APRI is a simple biochemical index that has been shown to be useful and accurate in about 50% of patients with HCV. The authors studied if the combination of APRI and FIBROSpect II would further help distinguish mild from significant fibrosis in a group of patients with HCV. In an outpatient setting, 93 consecutive patients were studied who were undergoing staging liver biopsy for HCV who had a liver biopsy length ≥ 1.5 cm. All had blood drawn at the time of the biopsy. Liver biopsies were staged for fibrosis by the Batts Ludwig criteria (F0–F4). Patients with previous antiviral therapy, hepatocellular carcinoma, an organ transplant, or co-infection with HIV or hepatitis B were excluded. The AUROC for the APRI and FIBROSpect II were 0.887 and 0.879 respectively. Using cutoffs of ≤ 0.42 for mild fibrosis (F0–F1) and ≥ 1.2 for significant fibrosis, the APRI correctly estimated 19 of 20 patients with mild fibrosis for an NPV of 95.0%, and 31 of 33 patients with significant fibrosis for a PPV of 93.6%. The FIBROSpect II used cutoffs of ≤ 25 and ≥ 85 it correctly identified 18 of 18 patients with mild fibrosis and all 26 patients with significant fibrosis for an NPV and PPV of 100% for both. Among the 40 patients who could not be classified by the APRI, an additional 16 could be correctly classified using the FIBROSpect II with cutoffs of ≤ 25 and ≥ 85 . This lowered the indeterminate zone from 43.0 to 25.8%. By combining the APRI and the FIBROSpect II, the AUROC improved significantly to 0.931 ($p=0.013$).

In a retrospective study, Christensen et al. (2006) correlated FibroSpect II results with liver fibrosis scores to determine if the FibroSpect II test is sufficiently accurate to be a viable alternative to liver biopsy. FibroSpect II reports an index score ranging from 0.1–1.0, which corresponds to the probability of progressive liver fibrosis. The authors report that FibroSpect II was clinically useful in ruling out advanced HCV by identifying patients with mild disease in whom treatment could be deferred. The reported limitation of this test is decreased sensitivity and specificity in the middle of the test's reporting range between scores of 0.42–0.80.

The diagnostic performance characteristics of FIBROSpect II were established in a study population of 294 chronic HCV patients, and the algorithm was further validated in an external cohort of 402 patients. The predictive algorithm was designed to differentiate between no/mild (METAVIR F0–F1) and moderate/severe (F2–F4) fibrosis. At an index cutoff of > 0.36 and prevalence of 52% for F2–F4, results in all 696 patients indicated positive and negative predictive values of 74.3% and 75.8% with an accuracy of 75% (Patel, et al., 2004).

HepaScore: In a retrospective study, Bourliere et al. (2008) studied HepaScore as an alternative to liver biopsy and FT and the proposal of five optimized combination algorithms to improve diagnostic accuracy. The study included 467 patients with HCV. Hepascore AUC for $\geq F2$, F3F4 and F4 diagnosis were 0.82, 0.84 and 0.90 respectively, in the same range as FT. HepaScore and FT were concordant in 387/467 (82%) for fibrosis staging. Among these patients, 342/387 (88%) were concordant with liver biopsy. AUCs of AST to APRI and Forns for $\geq F2$ were 0.76 and 0.73 (0.65–0.79) respectively. The algorithm combining APRI and HepaScore had the highest rate of avoided liver biopsies (45%) with a high diagnostic accuracy (91%). The authors reported that Hepascore is an accurate non-invasive marker for $\geq F2$ and F4 diagnosis in HCV patients. In a pragmatic approach, a stepwise optimized algorithm combining APRI and FT or HepaScore considerably increases diagnostic accuracy and avoided liver biopsies. One of the reported limitations of this study is the distribution of liver biopsies among the cohort, with 49% of patients with $\geq F2$, reflecting the fact that most centers were referral centers for liver disease. This may be a limitation of the study, as non-invasive markers of fibrosis may have different diagnostic accuracies depending on the prevalence of significant fibrosis in the studied population. The

authors noted that before HS can be used in routine practice, HepaScore should be validated on blood donor populations and on a larger population.

In a prospective study, Adams et al. (2005) used the HepaScore model to predict liver fibrosis in HCV patients (n=117). The model was validated in 104 patients from other institutions. The HepaScore produced AUROC of 0.85, 0.96, and 0.94 for significant fibrosis, advanced fibrosis, and cirrhosis, respectively. The Hepascore provided information for all patients: a score ≥ 0.5 was 89–92% specific for the presence of significant fibrosis (METAVIR F2); and a score ≤ 0.5 was 88–95% sensitive for the absence of advanced fibrosis (METAVIR F3). In the training set, a score ≥ 0.5 (range, 0.0–1.0) was 92% specific and 67% sensitive for significant fibrosis, a score < 0.5 was 81% specific and 95% sensitive for advanced fibrosis, and a score < 0.84 was 84% specific and 71% sensitive for cirrhosis. Among the validation set, the AUC for significant fibrosis, advanced fibrosis, and cirrhosis were 0.82, 0.90, and 0.89, respectively. A score ≥ 0.5 provided a specificity and sensitivity of 89% and 63% for significant fibrosis, whereas scores < 0.5 had 74% specificity and 88% sensitivity for advanced fibrosis. Thus, a HepaScore ≥ 0.5 provided high PPVs (87% and 88%) for the presence of significant fibrosis, a Hepascore < 0.5 provided NPVs of 95% and 98% for advanced fibrosis, and a HepaScore < 0.84 provided NPVs of 94% and 98% for cirrhosis. The authors noted that further validation is required in community-based patients versus tertiary referral centers. Also, longitudinal studies are needed to determine whether the model is responsive to fibrosis change in the same individual over time. This study had a small sample of patients with cirrhosis which limits conclusions regarding accuracy of the test in this population.

Comparative Study of Six Noninvasive Scores: In a prospective study, Leroy et al. (2007) compared the diagnostic performance of six scores (MP3, FT, Fibrometer, HepaScore, Forns' score and APRI). Liver fibrosis was staged according to the METAVIR scoring system (n=180). All patients were diagnosed with HCV. Overall diagnostic performance of scores determined by AUROCs ranged from 0.86 for Fibrometer to 0.78 for Forns' score (NS) for discriminating F0F1 versus F2F3F4. For discriminating F0F1F2 versus F3F4, AUROCs ranged from 0.91 for Fibrometer to 0.78 for Forns' score ($p < 0.02$). Significant or extensive fibrosis was predicted in 10–86% of patients with PPV ranging from 55–94%. Using logistic regression, statistical independence was indicated for MP3, FT and APRI. Diagnostic performance of paired-combination scores was then evaluated. The best combinations could select one-third of patients for whom either absence of significant fibrosis or presence of extensive fibrosis could be predicted with more than 90% of certainty. The authors reported that although the predictive values are promising, one in five patients would be misclassified if liver biopsy was not performed. Additionally, almost 50% of patients had intermediate values and could not be classified.

Multiple Serum Markers: In a cohort study, Martinez et al. (2011) compared the diagnostic performance of non-invasive tests for prediction of liver fibrosis severity and assessed changes in extracellular matrix markers after antiviral treatment. The performances of Forns' score, AST to platelet ratio index (APRI), FIB-4 index and Enhanced Liver Fibrosis (ELF) score were validated in 340 patients who underwent antiviral therapy. These scores were determined 24 weeks after treatment in 161 patients. Forns' score, APRI, FIB-4 and ELF score showed comparable diagnostic accuracies for significant fibrosis (AUROC 0.83, 0.83, 0.85 and 0.81, respectively). To identify cirrhosis, FIB-4 index showed a significantly better performance over APRI and ELF score (AUROC 0.89 versus 0.83 and 0.82, respectively). ELF score decreased significantly in patients with sustained virological response (SVR) ($p < 0.0001$) but remained unchanged in nonresponders. Non-1 hepatitis C virus (HCV) genotype, baseline lower HCV RNA, glucose, hyaluronic acid and higher cholesterol levels were independently associated with SVR. The authors reported several limitations. First, the lack of a follow-up liver biopsy, did not allow for the assessment of treatment on liver fibrosis. Second, the short period of time that elapsed between baseline and follow-up evaluations. As liver fibrosis decreases progressively after a SVR, the evaluation period of the study might have been too short to detect additional effects. Third, the proportion of patients with a biopsy size > 20 mm was suboptimal. Finally, although this is a cohort study, ECM assays were performed on stored serum samples, which were not available for all included patients.

In a retrospective study, Lieber et al. (2008) analyzed seven markers of liver fibrosis proposed as predictors of fibrosis in a subgroup of alcoholic patients (n=247). The seven serum markers included (TIMP1, tenascin, collagen VI, P3NP, MMP2, laminin, and HA). Additionally, the study included a diagnostic algorithm including three serum markers (TIMP1, P3NP, HA) and age. The patients were followed for 24 months and in whom liver biopsy was available at baseline and 24 months later. The authors reported that among the markers measured in this alcoholic subgroup all except collagen VI displayed significant correlation with degrees of fibrosis. Three markers, TIMP1, P3NP and HA adjusted for age, emerged as the most promising predictors of the degree of fibrosis in a population of alcoholics. However, there was little change over time as related to change in fibrosis.

In this subgroup the lower than expected accuracy of these markers, based on ROC, showed their limited use. The authors reported that in alcoholic patients, various markers have limited value in predicting and diagnosing the stages of fibrosis compared to liver biopsy.

In a retrospective study, Fontana et al. (2008) studied the utility of a panel of serum fibrosis markers along with routine laboratory tests in estimating the likelihood of histological cirrhosis in a cohort of prior nonresponders with chronic HCV. The relationship between serum markers and quantitative hepatic collagen content was also determined. Liver biopsy samples from 513 subjects enrolled in the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial were assigned Ishak fibrosis scores. The collagen content of 386 sirius-red stained, nonfragmented biopsy samples was quantified using computerized morphometry. Serum TIMP-1, P3NP, HA, and YKL-40 levels were determined using commercially available assays. Sixty-two percent of patients had noncirrhotic fibrosis (Ishak stage 2–4) whereas 38% had cirrhosis (Ishak stage 5, 6). Multivariate analysis identified a three-variable model (HA, TIMP-1, and platelet count) that had an AUROC of 0.81 for estimating the presence of cirrhosis. This model was significantly better than that derived from the cirrhosis discriminant score (AUROC 0.70), the AST-to-platelet ratio (AUROC 0.73), and a prior model developed in HALT-C patients (AUROC 0.79). Multivariate analysis indicated that the serum fibrosis markers correlated substantially better with Ishak fibrosis scores than with the log hepatic collagen content (AUROC 0.84 versus 0.72). The authors reported that a three-variable model consisting of serum HA, TIMP-1, and platelet count was better than other published models in identifying cirrhosis in HALT-C trial subjects. The stronger correlation of the serum markers with Ishak scores suggests that serum fibrosis markers reflect the pattern of fibrosis more closely than the quantity of hepatic collagen. The authors reported that limitations to this study are that models were not tested in an external validation cohort to confirm and refine them. Additionally, the authors were not able to differentiate among the individual Ishak fibrosis stages however; they felt that grouping fibrosis scores together would help reduce sampling error. The authors reported that it would have been desirable to compare their algorithm to that obtained using other models that include serum fibrosis markers such as the Fibrotest, and Hepascore. However, because serum samples were not prospectively assayed for haptoglobin, apolipoprotein A1 and alpha-2-macroglobulin, these analyses were not possible.

Meta-Analysis/Reviews: In a meta-analysis, Leroy et al. (2008) evaluated the diagnostic accuracy of liver fibrosis tests. Four independent centers provided four blood tests and Metavir staging from 825 patients with HCV. FibroMeter AUROC (0.840) for significant fibrosis was superior to those of Fibrotest (0.803, $p=0.049$), APRI (0.789, $p=0.001$) and Hepascore (0.781, $p<0.001$). The misclassification rate was lower for FibroMeter (23%) than for Fibrotest and Hepascore (both 28%, $p<0.001$). The variation in the diagnostic cut-offs of tests among centers, reflecting the overall reproducibility, was: FibroMeter: 4.2%, APRI: 24.0%, Fibrotest: 24.2%, Hepascore: 35.0%. Accordingly, the proportion of patients diagnosed with significant fibrosis changed: FibroMeter: 0.8%, Hepascore: 2.4% ($p=0.02$ versus FibroMeter), Fibrotest: 5.8% ($p<10^{-3}$), APRI: 18.2% ($p<10^{-3}$). The authors reported that this study on clinical applicability shows significant differences in diagnostic accuracy, inter-center reproducibility, and robustness of biomarkers to changes in population characteristics between blood tests.

Shaheen et al. (2008) conducted a systematic review and meta-analysis of the diagnostic accuracy of fibrosis marker panels in patients with HIV/HCV coinfection. Studies comparing serum marker panels with biopsy in HIV/HCV-coinfected patients were identified. Random effects meta-analyses and AUC examined test accuracy for detecting significant fibrosis (F2–4) and cirrhosis. Heterogeneity was explored using meta-regression. Five retrospective studies ($n=574$) including four fibrosis measures (APRI [$n=4$ studies], Forns' [$n=2$], FT [$n=1$], SHASTA [$n=1$]) met the inclusion criteria. The prevalence of significant fibrosis and cirrhosis were 51% and 16%, respectively. For the prediction of significant fibrosis, the summary AUC was 0.82 (95% CI 0.78–86) and diagnostic odds ratio was 7.8 (5.1–11.9). For cirrhosis, these figures were 0.83 (0.69–0.97) and 11.0 (4.6–26.2), respectively. Meta-regression including study factors (methodological quality and biopsy adequacy), patient characteristics (age, gender, CD4 count), and fibrosis measure failed to identify important predictors of accuracy. The authors summarized that available fibrosis marker panels have acceptable performance for identifying significant fibrosis and cirrhosis in HIV/HCV-coinfected patients but are not yet adequate to replace liver biopsy. Additional studies are necessary to identify the optimal measure.

Poynard et al. (2007a) conducted a meta-analysis to test two hypotheses, one, that the FT diagnostic value was similar in the three other frequent fibrotic diseases: HBV, ALD and NAFLD; and the other, that the FT diagnostic value was similar for intermediate and extreme fibrosis stages. The main end points were the FT AUROCs for the diagnosis of bridging fibrosis (F2F3F4 versus F0F1), standardized for the spectrum of fibrosis stages, and

the comparison of FT AUROCs between adjacent stages. Two meta-analyses were performed: one combining all the published studies (random model), and one of an integrated data base combining individual data. Sensitivity analysis integrated the independency of authors, length of biopsy, prospective design, respect of procedures, comorbidities, and duration between biopsy and serum sampling. A total of 30 studies were included which pooled 6378 subjects with both FT and biopsy (3501 HCV, 1457 HBV, 267 NAFLD, 429 ALD, and 724 mixed). Individual data were analyzed in 3282 patients. The mean standardized AUROC was 0.84 (95% CI, 0.83–0.86), without differences between causes of liver disease: HCV 0.85 (0.82–0.87), HBV 0.80 (0.77–0.84), NAFLD 0.84 (0.76–0.92), ALD 0.86 (0.80–0.92), mixed 0.85 (0.80–0.93). The AUROC for the diagnosis of the intermediate adjacent stages F2 versus F1 (0.66; 0.63–0.68, n=2055) did not differ from that of the extreme stages F3 versus F4 (0.69; 0.65–0.72, n=817) or F1 versus F0 (0.62; 0.59–0.65, n=1788). The authors report that one limitation of the study is that the number of studies and patients in non HCV related diseases is smaller than those in HCV. Another limitation was that there were few independent studies in other chronic liver diseases (one for HBV, one for NAFLD and none for ALD). However, two studies in HBV and two studies in ALD were mixed and three independent studies included HBV and ALD in their analyses with same results than in non-independent studies. The authors noted that neither biomarkers nor biopsy are sufficient alone to take definitive decision in a given patient and all the clinical and biological data should be taken into account.

Shaheen et al. (2007) systematically reviewed studies describing the accuracy of FT or FibroScan versus liver biopsy for the prediction of HCV-related fibrosis. Random effects meta-analyses and AUC were examined to characterize test accuracy for significant fibrosis (F2–4) and cirrhosis. Heterogeneity was explored using meta-regression. Twelve retrospective and prospective studies were identified, nine for FT (n=1679) and four for FibroScan (n=546). In heterogeneous analyses for significant fibrosis, the AUCs for FT and FibroScan were 0.81 (95% CI 0.78–84) and 0.83 (0.03–1.00), respectively. At a threshold of ~0.60, the sensitivity and specificity of the FT were 47% (35–59%) and 90% (87–92%). Methodological quality, the length of liver biopsy specimens, and inclusion of special populations did not explain the observed heterogeneity. However, the diagnostic accuracy of both measures was associated with the prevalence of significant fibrosis and cirrhosis in the study populations. For cirrhosis, the summary AUCs for FT was 0.95 (0.87–0.99). The authors summarized that FT and FibroScan have excellent utility for the identification of HCV-related cirrhosis, but lesser accuracy for earlier stages. Refinements are necessary before these tests can replace liver biopsy. Additionally, studies examining combinations of these tests, with an assessment of the impact of clinical outcomes are needed.

Parkes et al. (2006) conducted a systematic review to assess the performance of panels of serum markers of hepatic fibrosis in chronic HCV. Fourteen studies were included with ten different panels. The authors reported that serum markers can confirm or rule out fibrosis in up to 35% of patients but cannot differentiate stages of fibrosis. The authors state that continuing improvement of both the index and reference test is needed, including evaluation of clinical outcomes as a reference.

Crockett et al. (2006) reviewed the published literature on the available serum tests and panels of serum markers to assess liver damage, specifically focusing on their comparability to liver biopsy. The authors reported that additional studies are needed to evaluate the longitudinal and clinical validity of the serum tests. The authors also state that with more clinical experience, serum fibrosis testing will begin to replace many of the liver biopsies that are now used for prognostic and treatment planning. Similar conclusions were reported in a review by Mukherjee and Sorrell (2006) who state, "Much more needs to be done before markers of fibrosis are ready for prime time. Given the limitations of present methods for the detection of fibrosis, physicians need to decide from the outset how important it is to accurately stage fibrosis and whether this information will translate into improved outcomes."

Afdhal and Nunes (2004) reviewed the clinical data related to the use of liver biopsy, radiology, and serological studies in the assessment of liver fibrosis. The authors reported that at the present time no definite algorithm can be given for the optimal serological test or tests, or for how to incorporate the tests into clinical practice. In the future, tests such as Forns index or FT could possibly be used to exclude patients with significant liver disease with a probability perhaps superior to liver biopsy. Additional prospective studies are needed to define the exact utility of serum markers and their ability to reflect the effect of antifibrotic treatments, and to monitor alterations in the course of disease.

Poynard et al. (2004b) evaluated the diagnostic value of a panel of biochemical markers FT-AT from the scientific literature for liver fibrosis (FT range: 0.00–1.00) and necroinflammatory histological activity (AT range:

0.00–1.00). A total of 16 publications were identified. An integrated database was constructed using 1570 individual pieces of data. The control group consisted of 300 prospectively studied blood donors. The results of the study showed that the FT negative predictive value for excluding significant fibrosis was only 91%. The AT negative predictive value for excluding significant necrosis was only 85%. In three studies, there was direct comparison in the same patients of FT versus other biochemical markers, including hyaluronic acid, the Forns index and the APRI. All of the comparisons favored FT ($p \leq 0.05$). However, the authors identified potential bias due to the fact that, in this study, the same group that developed the tests also performed most of the published studies. The researchers reported that future studies are needed before FT and AT may be recommended as an alternative to liver biopsy for the assessment of fibrosis.

Gebo et al. (2002) conducted a systematic review of the literature on the use of large panels of markers (i.e., matrix metalloprotein-2, hyaluronic acid, GGT) in predicting hepatic fibrosis. The researchers found that the five studies using large panels of serum markers, with sensitivities ranging from 50–80%, and specificities from 35–80%, had the greatest predictive values. A panel of matrix metalloprotein-2, 7S type IV collagen, and hyaluronic acid optimally predicted no/minimal fibrosis, with a sensitivity of 68% and specificity of 73%. The researchers reported that, despite the limitations of large panels of biochemical markers, they may have the greatest value in predicting the absence, or no more than minimal fibrosis on biopsy, and in predicting the presence of cirrhosis on biopsy. They could have a role in management of patients who have concerns about the risk of a liver biopsy or in clinical settings in which liver biopsy is not readily available.

Professional Societies/Organizations

The American Gastroenterological Association technical review on the management of hepatitis C states: “Neither clinical nor laboratory markers, individually or in combination, predict accurately the degree of necroinflammatory activity or the level of fibrosis in the liver. Therefore, despite sampling error, liver biopsy remains the gold standard for determining histologic grade and stage” (Dienstag and McHutchison, 2006a). There have been no updates to the technical review since 2006.

The National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (NIH) does not mention serum marker panels as a testing method for the grading and staging of liver disease for the management of chronic hepatitis C virus (HCV) (NIH, 2010).

The American Society for the Study of Liver Diseases issued a practice guideline on the diagnosis, management and treatment of hepatitis C. The guidelines state: “Although liver fibrosis markers are commercially available, they are currently insufficiently accurate to support their routine use. Until sensitive serum markers can be developed that will define all stages of fibrosis and mirror the information derived from liver biopsy, the procedure remains the only means of defining the severity of damage from HCV infection in many patients” (Strader, et al., 2004). There have been no updates to this practice guideline since 2004.

The National Institutes of Health (NIH) issued a consensus statement addressing the management of hepatitis C. The consensus statement declares that various noninvasive tests of hepatic fibrosis have been examined for the monitoring of patients with chronic liver infection. These include routinely available tests (e.g., platelet count, prothrombin time), as well as specific serum markers of fibrosis and inflammation that are not currently widely available or proven in the literature. The NIH concluded that no single noninvasive test or panel of serological markers can provide an accurate assessment of the intermediate stages of liver fibrosis. The panel also indicated that noninvasive tests could not replace the information provided by a liver biopsy (NIH, 2002). There have been no updates to this consensus statement since 2002.

Summary

Although numerous noninvasive biochemical markers have been studied in the published, peer-reviewed scientific literature as possible markers of fibrosis and/or inflammation, none has been proven to accurately differentiate and predict liver histology and fibrosis severity. Whether these markers, used in various combinations, can replace liver biopsy is not known at this time. Additional well-designed clinical trials are needed before the role of these markers in the diagnosis and management of liver disease can be established. The liver biopsy remains the standard method for the assessment and diagnosis of liver fibrosis and inflammation.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Experimental/Investigational/Unproven/Not Covered when used to report serum marker panels for the diagnosis or clinical management of liver disease:

CPT* Codes	Description
82172	Apolipoprotein, each
82247	Bilirubin; total
82465	Cholesterol, serum or whole blood, total
82947	Glucose; quantitative, blood (except reagent strip)
82977	Glutamyltransferase, gamma (GGT)
83010	Haptoglobin; quantitative
83520	Immunoassay, analyte, quantitative; not otherwise specified
83883	Nephelometry, each analyte not elsewhere specified
84450	Transferase; aspartate amino (AST) (SGOT)
84460	Transferase; alanine amino (ALT) (SGPT)
84478	Triglycerides
84999	Unlisted chemistry procedure

ICD-9-CM Diagnosis Codes	Description
070.0-070.9	Viral hepatitis
570	Acute and subacute necrosis of liver
571.0-571.9	Chronic liver disease and cirrhosis
572.0-572.8	Liver abscess and sequelae of chronic liver disease
573.0-573.9	Other disorders of liver
576.1	Cholangitis

*Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.

References

1. Adams LA, Angulo P. Role of liver biopsy and serum markers of liver fibrosis in non-alcoholic fatty liver. Clin Liver Dis. 2007 Feb;11(1):25-35, viii.
2. Adams LA, Bursara M, Rossi E, DeBoer B, Speers D, George J, et al. Hepascore an accurate validated predictor of liver fibrosis in chronic hepatitis C infection. Clin Chem. 2005 Oct;51(10):1867-73.
3. Afdhal NH, Nunes D. Evaluation of liver fibrosis: a concise review. Am J Gastroenterol. 2004 Jun;99(6):1160-74.
4. American Association for Clinical Chemistry. Lab tests online. Liver disease. Accessed February 3, 2011. Available at URL address: <http://www.labtestsonline.org/>
5. American Association for Clinical Chemistry. The perils of fatty liver disease. Can biomarkers replace biopsy? April 2010. Accessed February 7, 2011. Available at URL address: <http://www.aacc.org/publications/cln/2010/april/Pages/CoverStory1Apr2010.aspx>
6. Bataller R, Brenner DA. Liver fibrosis. J Clin Invest. 2005 Feb;115(2):209-18.
7. BioPredictive. Non-invasive solution. Accessed February 7, 2011. Available at URL address: <http://www.biopredictive.com/intl/non-invasive-solution>

8. BioPredictive. Practice of FibroTest for hepatitis C. Accessed February 7, 2011. Available at URL address: http://www.biopredictive.com/intl/physician/fibrotest-for-hcv/view?set_language=en
9. Bourliere M, Penaranda G, Ouzan D, Renou C, Botta-Fridlund D, Tran A, Rosenthal E, et al. Optimized stepwise combination algorithms of non-invasive liver fibrosis scores including Hepascore in hepatitis C virus patients. *Aliment Pharmacol Ther*. 2008 Aug 15;28(4):458-67. Epub 2008 May 22.
10. Bourliere M, Penaranda G, Renou C, Botta-Fridlund D, Tran A, Portal I, et al. Validation and comparison of indexes for fibrosis and cirrhosis prediction in chronic hepatitis C patients: proposal for a pragmatic approach classification without liver biopsies. *J Viral Hepat*. 2006 Oct;13(10):659-70.
11. Cales P, Oberti F, Michalak S, Hubert-Fouchard I, Rousselet MC, Konate A, et al. A novel panel of blood markers to assess the degree of liver fibrosis. *Hepatology*. 2005 Dec;42(6):1373-81.
12. Castera L, Pawlotsky JM. Noninvasive diagnosis of liver fibrosis in patients with chronic hepatitis C. *MedGenMed*. 2005 Nov 9;7(4):39.
13. Centers for Disease Control and Prevention (CDC). Recommendations for the prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. October 16, 1998. Last reviewed May 2, 2001. Accessed February 3, 2011. Available at URL address: <http://www.cdc.gov/mmwr/preview/mmwrhtml/00055154.htm>
14. Christensen C, Bruden D, Livingston S, Deubner H, Homan C, Smith K, et al. Diagnostic accuracy of a fibrosis serum panel (FIBROSpect II) compared with Knodell and Ishak liver biopsy scores in chronic hepatitis C patients. *J Viral Hepat*. 2006 Oct;13(10):652-8.
15. Crockett SD, Kaltenebach T, Keeffe EB. Do we still need a liver biopsy? Are the serum fibrosis tests ready for prime time? *Clin Liver Dis*. 2006 Aug;10(3):513-34, viii.
16. Dienstag JL, McHutchison JG. American Gastroenterological Association medical position statement on the management of hepatitis C. *Gastroenterology*. 2006a Jan;130(1):225-30.
17. Dienstag JL, McHutchison JG. American gastroenterological association technical review on the management of hepatitis C. *Gastroenterology*. 2006b Jan;130(1):231-64; quiz 214-7.
18. ECRI Institute. Hotline Response [database online]. Plymouth Meeting (PA): ECRI Institute; 2008 Nov 7. FIBROSpect II Serum Markers Panel for Evaluating Liver Fibrosis. Available at URL address: <http://www.ecri.org>
19. Fontana RJ, Goodman ZD, Dienstag JL, Bonkovsky HL, Naishadham D, Sterling RK, et al.; HALT-C Trial Group. Relationship of serum fibrosis markers with liver fibrosis stage and collagen content in patients with advanced chronic hepatitis C. *Hepatology*. 2008 Mar;47(3):789-98.
20. Gebo K, Jenckes M, Chander G, et al. Management of Chronic Hepatitis C. Evidence Report/Technology Assessment No. 60 (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No 290-97-0006). AHRQ Publication No. 02-E030. Rockville, MD: Agency for Healthcare Research and Quality. July 2002.
21. Gebo KA, Herlong HF, Torbenson MS, Jenckes MW, Chander G, Ghanem KG, et al. Role of liver biopsy in management of chronic hepatitis C: a systematic review. *Hepatology*. 2002 Nov;36(5 Suppl 1):S161-72. Grigorescu M. Noninvasive biochemical markers of liver fibrosis. *J Gastrointest Liver Dis*. 2006 Jun;15(2):149-59.
22. Guha IN, Parkes J, Roderick P, Chattopadhyay D, Cross R, Harris S, et al. Noninvasive markers of fibrosis in nonalcoholic fatty liver disease: Validating the European Liver Fibrosis Panel and exploring simple markers. *Hepatology*. 2008 Feb;47(2):455-60.

23. Guha IN, Rosenberg WM. Noninvasive assessment of liver fibrosis: serum markers, imaging, and other modalities. *Clin Liver Dis*. 2008 Nov;12(4):883-900, x.
24. Halfon P, Imbert-Bismut F, Messous D, Antoniotti G, Benchetrit D, Cart-Lamy P, et al. A prospective assessment of the inter-laboratory variability of biochemical markers of fibrosis (FibroTest) and activity (ActiTest) in patients with chronic liver disease. *Comp Hepatol*. 2002 Dec 30;1(1):3.
25. Halfon P, Bourliere M, Deydier R, Botta-Fridlund D, Renou C, Tran A, Portal I, et al. Independent prospective multicenter validation of biochemical markers (fibrotest-actitest) for the prediction of liver fibrosis and activity in patients with chronic hepatitis C: the fibropaca study. *Am J Gastroenterol*. 2006 Mar;101(3):547-55.
26. Imbert-Bismut F, Messous D, Thibaut V, Myers RB, Piton A, Thabut D, et al. Intra-laboratory analytical variability of biochemical markers of fibrosis (Fibrotest) and activity (Actitest) and reference ranges in healthy blood donors. *Clin Chem Lab Med*. 2004 Mar;42(3):323-33.
27. Imbert-Bismut F, Ratziu V, Pieroni L, Charlotte F, Benhamou Y, Poynard T, et al. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. *Lancet*. 2001 Apr 7;357(9262):1069-75.
28. Lab21 Healthcare. FibroTest[®] & FibroMAX[™]. Product specification sheet. Accessed February 3, 2011. Available at URL address: <http://www.lab21.com/>
29. LabCorp. ASH Fibrosure[™]. A technical review. 2006a. Accessed February 4, 2011. Available at URL address: https://www.labcorp.com/pdf/08_ASH_FibroSure_Tech_Review_3711.pdf
30. LabCorp. NASH FibroSURE[™]. A technical review. 2006b. Accessed February 4, 2011. Available at URL address: https://www.labcorp.com/pdf/08_NASH_FibroSure_Tech_Review_3651.pdf
31. LabCorp DIANON Systems. Hepatitis C Virus (HCV) FibroSURE[™]. A technical review. 2006c. Accessed February 4, 2011. Available at URL address: https://www.labcorp.com/pdf/08_HCV_Fibrosure_TR_1080.pdf
32. Le Calvez S, Thabut D, Messous D, Munteanu M, Ratziu V, Imbert-Bismut F, et al. The predictive value of Fibrotest vs. APRI for the diagnosis of fibrosis in chronic hepatitis C. *Hepatology*. 2004 Mar;39(3):862-3; author reply 863.
33. Leroy V, Hilleret MN, Sturm N, Trocme C, Renversez JC, Faure P, et al. Prospective comparison of six non-invasive scores for the diagnosis of liver fibrosis in chronic hepatitis C. *J Hepatol*. 2007 May;46(5):775-82. Epub 2007 Jan 26.
34. Leroy V, Halfon P, Bacq Y, Boursier J, Rousselet MC, Bourliere M, et al. Diagnostic accuracy, reproducibility and robustness of fibrosis blood tests in chronic hepatitis C: a meta-analysis with individual data. *Clin Biochem*. 2008 Nov;41(16-17):1368-76. Epub 2008 Jul 11.
35. Lieber CS, Weiss DG, Paronetto F; Veterans Affairs Cooperative Study 391 Group. Value of fibrosis markers for staging liver fibrosis in patients with precirrhotic alcoholic liver disease. *Alcohol Clin Exp Res*. 2008 Jun;32(6):1031-9. Epub 2008 Apr 15.
36. Martinez SM, Fernández-Varo G, González P, Sampson E, Bruguera M, Navasa M, et al. Assessment of liver fibrosis before and after antiviral therapy by different serum marker panels in patients with chronic hepatitis C. *Aliment Pharmacol Ther*. 2011 Jan;33(1):138-48. doi: 10.1111/j.1365-2036.2010.04500.x. Epub 2010 Oct 26.
37. Morra R, Munteanu M, Imbert-Bismut F, Messous D, Ratziu V, Poynard T. FibroMAX: towards a new universal biomarker of liver disease? *Expert Rev Mol Diagn*. 2007 Sep;7(5):481-90.
38. Mukherjee S, Sorrell MF. Noninvasive tests for liver fibrosis. *Semin Liver Dis*. 2006 Nov;26(4):337-47.

39. Munteanu M, Ratziu V, Morra R, Messous D, Imbert-Bismut F, Poynard T. Noninvasive biomarkers for the screening of fibrosis, steatosis and steatohepatitis in patients with metabolic risk factors: FibroTest-FibroMax experience. *J Gastrointest Liver Dis.* 2008 Jun;17(2):187-91.
40. The National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (NIH). Chronic Hepatitis C: Current Disease Management. NIH Publication: 07-4230. January 2010. Accessed February 4, 2011. Available at URL address: <http://digestive.niddk.nih.gov/ddiseases/pubs/chronichepc/index.htm#c>
41. National Institutes of Health (NIH). National Institutes of Health Consensus Development Conference Statement: management of hepatitis C: 2002—June 10-12, 2002. *Hepatology.* 2002 Nov;36(5 Suppl 1):S3-20.
42. National Institute of Health (NIH). NIH Consensus Development Program Statements. Management of hepatitis C: 2002. Accessed February 4, 2011. Available at URL address: <http://consensus.nih.gov/PREVIOUSSTATEMENTS.htm>
43. Naveau S, Gaudé G, Asnacios A, Agostini H, Abella A, Barri-Ova N, Dauvois B, Prévot S, et al. Diagnostic and prognostic values of noninvasive biomarkers of fibrosis in patients with alcoholic liver disease. *Hepatology.* 2009 Jan;49(1):97-105.
44. Parkes J, Guha IN, Roderick PJ, Rosenberg WM. Performance of serum marker panels for liver fibrosis in chronic hepatitis C. *J Hepatol.* 2006 Mar;44(3):462-74.
45. Patel K, Benhamou Y, Yoshida EM, Kaita KD, Zeuzem S, Torbenson M, et al. An independent and prospective comparison of two commercial fibrosis marker panels (HCV FibroSURE and FIBROSpect II) during albinferon alfa-2b combination therapy for chronic hepatitis C. *J Viral Hepat.* 2009 Mar;16(3):178-86. Epub 2008 Oct 24.
46. Patel K, Nelson DR, Rockey DC, Afdhal NH, Smith KM, Oh E, et al. Correlation of FIBROSpect II with histologic and morphometric evaluation of liver fibrosis in chronic hepatitis C. *Clin Gastroenterol Hepatol.* 2008 Feb;6(2):242-7. Epub 2008 Jan 9.
47. Patel K, Gordon SC, Jacobson I, Hezode C, Oh E, Smith KM, et al. Evaluation of a panel of non-invasive serum markers to differentiate mild from moderate-to-advanced liver fibrosis in chronic hepatitis C patients. *J Hepatol.* 2004 Dec;41(6):935-42.
48. Poynard T, Morra R, Halfon P, Castera L, Ratziu V, Imbert-Bismut F, et al. Meta-analyses of FibroTest diagnostic value in chronic liver disease. *BMC Gastroenterol.* 2007a Oct 15;7:40.
49. Poynard T, Halfon P, Castera L, Charlotte F, Le Bail B, Munteanu M, et al. FibroPaca Group. Variability of the area under the receiver operating characteristic curves in the diagnostic evaluation of liver fibrosis markers: impact of biopsy length and fragmentation. *Aliment Pharmacol Ther.* 2007b Mar 15;25(6):733-9.
50. Poynard T, Ratziu V, Charlotte F, Messous D, Munteanu M, Imbert-Bismut F, et al.; LIDO Study Group; CYTOL study group. Diagnostic value of biochemical markers (NashTest) for the prediction of non alcoholic steato hepatitis in patients with non-alcoholic fatty liver disease. *BMC Gastroenterol.* 2006 Nov 10;6:34.
51. Poynard T, Munteanu M, Imbert-Bismut F, Charlotte F, Thabut D, Le Calvez S, et al. Prospective analysis of discordant results between biochemical markers and biopsy in patients with chronic hepatitis C. *Clin Chem.* 2004a Aug;50(8):1344-55. Epub 2004 Jun 10.
52. Poynard T, Imbert-Bismut F, Munteanu M, Messous D, Myers RP, Thabut D, et al. Overview of the diagnostic value of biochemical markers of liver fibrosis (FibroTest, HCV FibroSure) and necrosis (ActiTest) in patients with chronic hepatitis C. *Comp Hepatol.* 2004b Sep 23;3(1):8.

53. Poynard T, McHutchison J, Manns M, Myers RP, Albrecht J. Biochemical surrogate markers of liver fibrosis and activity in a randomized trial of peginterferon alfa-2b and ribavirin. *Hepatology*. 2003 Aug;38(2):481-92.
54. Prometheus[®] Laboratories. FIBROSpect[®] II. Accessed February 4, 2011. Available at URL address: http://www.prometheuslabs.com/products_diagnostics_fibrospect.asp
55. Quest Diagnostics. Liver fibrosis panel, HepaScore[™] test summary. Reviewed November 2009 Accessed February 4, 2011. Available at URL address: http://www.questdiagnostics.com/hcp/intguide/jsp/showintguidepage.jsp?fn=InfectDis/Hepatitis/TS_LiverFibrosisPnl_HepaScore.htm
56. Ratziu V, Massard J, Charlotte F, Messous D, Imbert-Bismut F, Bonyhay L, et al.; LIDO Study Group; CYTOL study group. Diagnostic value of biochemical markers (FibroTest-FibroSURE) for the prediction of liver fibrosis in patients with non-alcoholic fatty liver disease. *BMC Gastroenterol*. 2006 Feb 14;6:6.
57. Ray S, Thomas D. Hepatitis C. In: Mandell G, Bennett J, Dolin R, editors. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 7th ed. Churchill, Livingston, Elsevier. Philadelphia, PA. 2009. Ch. 154
58. Rosenthal-Allieri MA, Peritore ML, Tran A, Halfon P, Benzaken S, Bernard A. Analytical variability of the Fibrotest proteins. *Clin Biochem*. 2005 May;38(5):473-8.
59. Rossi E, Adams L, Prins A, Bulsara M, de Boer B, Garas G, et al. Validation of the FibroTest biochemical markers score in assessing liver fibrosis in hepatitis C patients. *Clin Chem*. 2003 Mar;49(3):450-4.
60. Rossi E, Adams LA, Bulsara M, Jeffrey GP. Assessing liver fibrosis with serum marker models. *Clin Biochem Rev*. 2007 Feb;28(1):3-10.
61. Sakugawa H, Nakayoshi T, Kobashigawa K, Yamashiro T, Maeshiro T, Miyagi S, et al. Clinical usefulness of biochemical markers of liver fibrosis in patients with nonalcoholic fatty liver disease. *World J Gastroenterol*. 2005 Jan 14;11(2):255-9.
62. Shaheen AA, Wan AF, Myers RP. FibroTest and FibroScan for the prediction of hepatitis C-related fibrosis: a systematic review of diagnostic test accuracy. *Am J Gastroenterol*. 2007 Nov;102(11):2589-600.
63. Shaheen AA, Myers RP. Systematic Review and Meta-Analysis of the Diagnostic Accuracy of Fibrosis Marker Panels in Patients with HIV/Hepatitis C Coinfection. *HIV Clin Trials*. 2008 Jan-Feb;9(1):43-51.
64. Snyder N, Nguyen A, Gajula L, Soloway R, Xiao SY, Lau DT, Petersen J. The APRI may be enhanced by the use of the FIBROSpect II in the estimation of fibrosis in chronic hepatitis C. *Clin Chim Acta*. 2007 Jun;381(2):119-23. Epub 2007 Mar 19.
65. Sporea I, Popescu A, Sirli R. Why, who and how should perform liver biopsy in chronic liver diseases. *World J Gastroenterol*. 2008 Jun 7;14(21):3396-402.
66. Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. *Hepatology* 2004 Apr;39(4):1147-71.
67. Zaman A, Rosen HR, Ingram K, Corless CL, Oh E, Smith K. Assessment of FIBROSpect II to detect hepatic fibrosis in chronic hepatitis C patients. *Am J Med*. 2007 Mar;120(3):280.e9-14.

Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	3/15/2008	0296	Serum Markers for Liver Disease

"CIGNA", "CIGNA HealthCare" and the "Tree of Life" logo are registered service marks of CIGNA Intellectual Property, Inc., licensed for use by CIGNA Corporation and its operating subsidiaries. All products and services are provided by such operating subsidiaries and not by CIGNA Corporation. Such operating subsidiaries include Connecticut General Life Insurance Company, CIGNA Health and Life Insurance Company, CIGNA Behavioral Health, Inc., CIGNA Health Management, Inc., and HMO or service company subsidiaries of CIGNA Health Corporation and CIGNA Dental Health, Inc. In Arizona, HMO plans are offered by CIGNA HealthCare of Arizona, Inc. In California, HMO plans are offered by CIGNA HealthCare of California, Inc. In Connecticut, HMO plans are offered by CIGNA HealthCare of Connecticut, Inc. In North Carolina, HMO plans are offered by CIGNA HealthCare of North Carolina, Inc. In Virginia, HMO plans are offered by CIGNA HealthCare Mid-Atlantic, Inc. All

other medical plans in these states are insured or administered by Connecticut General Life Insurance Company or CIGNA Health and Life Insurance Company.