Anthem

Medical Policy

Subject: Proprietary Algorithms for Liver Fibrosis
Document #: LAB.00019
Status: Revised

Publish Date: 12/28/2023
Last Review Date: 11/09/2023

Description/Scope

This document addresses proprietary algorithms utilizing serum markers to assist in the evaluation and monitoring of chronic liver disease, including, but not limited to hepatitis C, hepatitis B, and metabolic dysfunction-associated steatotic liver disease (MASLD). These markers are indirect and direct measures of liver fibrosis. This document does not address scoring systems that can be calculated bedside using common laboratory tests (for example, platelet count, or liver function tests).

Position Statement

Investigational and Not Medically Necessary:

Proprietary algorithms evaluating liver fibrosis are considered **investigational and not medically necessary** for all indications.

Rationale

Proprietary Serum Markers

Steatosis (also known as fatty liver disease) is a condition caused by an excessive buildup of fat in the liver. Steatotic liver disease is a term used to include the various etiologies of steatosis. One category of steatotic liver disease is MASLD. The excessive buildup of fat in the liver can cause liver fibrosis (thickening or scarring of the liver). Once fibrosis occurs, the stage of fibrosis is the most important single predictor of significant morbidity and mortality in individuals with chronic liver diseases, including hepatitis C, hepatitis B, and metabolic dysfunction-associated steatotic liver disease (MASLD) (formerly known as nonalcoholic fatty liver disease [NAFLD]). It is proposed that serum markers for liver fibrosis can be used as an alternative to liver biopsy in individuals with liver disease. Liver biopsy is required to definitively establish the histopathology of liver injury and fibrosis. Serum markers – which are surrogates for liver fibrosis, not biomarkers – have several limitations: they reflect the rate the liver turnover, which tends to be elevated in the setting of high inflammatory activity, and thus can be falsely low if there is minimal inflammation; are not liver-specific; and are affected by liver and biliary excretion rates. A number of proprietary algorithm-based serum markers for liver fibrosis are currently available in the United States, including, but not limited to the following:

- ASH FibroSURE® (Laboratory Corporation of America, Burlington, NC)
- FIBROSpect HCV® (Prometheus Biosciences, Inc., San Diego, CA)
- FIBROSpect NASH® (Prometheus Biosciences, Inc., San Diego, CA)
- HCV FibroSure® (Laboratory Corporation of America, Burlington, NC)
- NASH FibroSURE® (Laboratory Corporation of America, Burlington, NC)
- FibroMeter™ (ARUP Laboratories, Salt Lake City, UT)
- FibroTest-ActiTest™ (BioPredictive S.A.S., Paris, France)
- Enhanced Liver Fibrosis™ (ELF™, Siemens Healthcare Laboratory, LLC., Malvern, PA)
- LIVERFASt™ (Fibronostics, Orlando, FL)

Initial research into the FibroSure algorithm (known as FibroTest in Europe) involved testing an initial panel of 11 serum markers in 339 individuals with liver fibrosis who had undergone liver biopsy (Imbert-Bismut, 2001). From the original group of 11 markers, 5 were selected as the most informative, based on logistic regression and receiver operating curves. Markers included alpha-2 macroglobulin, haptoglobin, gamma globulin, apolipoprotein A1, gamma glutamyl transpeptidase (GGT) and total bilirubin. Using an algorithm-derived scoring system ranging from 0-1.0, the authors reported a score of less than 0.10 was associated with a negative predictive value of 100% (that is, absence of significant fibrosis, as judged by liver biopsy scores of METAVIR F0-F1). A score greater than 0.60 was associated with a 90% positive predictive value of fibrosis (that is, METAVIR F2-F4). The authors concluded liver biopsy might be deferred in those with a score less than 0.10.

Further evaluation of the FibroSure algorithm included a cross-section of individuals, including those with hepatitis C, participating in large clinical trials before and after the initiation of antiviral therapy. Poynard and colleagues (2003) evaluated individuals with hepatitis C participating in a randomized study of peginterferon and ribavirin. A total of 352 subjects were selected from the 1530 participants with stored serum samples and liver biopsies at study entry and at 24-week follow-up. The FibroSure score was calculated and then compared to the liver biopsy score. At a cutoff point of 0.30, the FibroSure score had 90% sensitivity and 88% positive predictive value for the diagnosis of F2-F4. The specificity was 36%, and the negative predictive value was 40%. There was a large overlap in scores for those in the F2-F4 categories, and thus the scoring system has been primarily used to subdivide individuals with and without fibrosis (that is, F0-F1 vs. F2-F4). When used as a monitoring test, individuals can serve as their own baseline. Those with a sustained virologic response to interferon also experienced reductions in the FibroTest or ActiTest scores.

Additional studies were done to formally validate the parameters used to calculate the FibroSure scores. Acceptable levels of “intra-laboratory and intra-patient variability” were reported (Halfon, 2002; Imbert-Bismut, 2004). Poynard and colleagues (2004) also evaluated discordant results in 537 individuals who underwent liver biopsy and the FibroTest and ActiTest on the same day; with the discordance attributed to either the limitations in the biopsy or serum markers. In this study, cut-off values were used for the individual METAVIR scores (that is, F0-F4) and for combinations of METAVIR scores (that is, F0-F1, F1-F2, etc.). The definition of a significant discordance between FibroTest, ActiTest and biopsy scores was at least two stages or grades in the METAVIR system. Discordance was observed in 29% of these individuals. Risk factors for biopsy failure included the biopsy size, number of fragments, and the number of portal tracts represented in the biopsy sample. Risk factors for failure of the FibroSure scoring system were presence of hemolysis, inflammation, possible Gilbert syndrome, acute hepatitis, drugs inducing cholestasis, or an increase in transaminases. Discordance was attributable to markers in 2.4%, to the biopsy in 18%, and could not be attributed in 8.2% of these individuals. The authors suggest that biopsy failure, frequently due to the small size of the biopsy sample, is a common problem. As noted in two

reviews, the bulk of the research regarding FibroSure was conducted by researchers with an interest in the commercialization of the algorithm (Afdhal, 2003; Lichtinghagen, 2004). Rossi and colleagues (2003) attempted to independently duplicate the results of FibroSure in 125 individuals with hepatitis C. Using the cut-off point of less than 0.1 to identify lack of bridging fibrosis (stages F0-F1) and greater than 0.6 to identify fibrosis (stages F2-F4), the negative predictive value for a score < 0.1 was 89%, compared to the 100% originally reported by Imbert-Bismut, and the positive predictive value of a score greater than 0.6 was 78% compared to 90%. The reasons for the inferior results in this study are unclear, but the authors concluded the FibroSure score did not accurately predict the presence or absence of fibrosis and could not reliably be used to reduce the need for liver biopsy.

Ratzui and colleagues (2006) conducted a study to determine the diagnostic validity of the FibroTest in non-alcoholic liver disease. For advanced fibrosis, FibroTest had a sensitivity of 77% and a specificity of 98%. Halfon and colleagues (2006) compared liver biopsy results with the FibroTest in individuals with chronic hepatitis C. In 18% of those tested, there were at least two stages of discordance between the serum test and liver biopsy. Poynard and colleagues (2007) studied the diagnostic value of FibroTest in chronic liver disease by performing meta-analyses of both published studies and individual data. Based upon study results, the authors concluded the FibroTest could be used as an alternative to biopsy in those with chronic hepatitis C and B, alcoholic liver disease, and non-alcoholic fatty liver disease. Shaheen and colleagues (2007) compared FibroTest and another technique (FibroScan) to biopsy in individuals with hepatitis C related fibrosis. For significant fibrosis, FibroTest had a sensitivity of 47% and a specificity of 90%. There was lesser accuracy for earlier stages of fibrosis. The authors noted these tests are not ready to replace liver biopsy and additional studies should be conducted.

There is minimal published data regarding FIBROSpect II. Patel and colleagues (2004) investigated the use of these serum markers in an initial training set of 294 individuals with hepatitis C and further validated the resulting algorithm in a validated set of 402 individuals. The algorithm was designed to distinguish between no or mild fibrosis (F0-F1) and moderate to severe fibrosis (F2-F4). With the prevalence of F2-F4 disease of 52% and a cut-off value of 0.36; the positive and negative predictive values were 74.3% and 75.8%, respectively. No studies were identified in the published literature in which results of the FIBROSpect II test were actively used in the management of the individual's medical care. Zaman and colleagues (2007) prospectively studied FIBROSpect II by obtaining serum from 108 consecutive individuals with hepatitis C seen at a single center hepatology clinic at the time of liver biopsy. The performance of FIBROSpect II was assessed by comparing the serum results with the liver biopsy. The sensitivity and specificity of FIBROSpect II were 71.8%, and 73.9%, respectively. Patel and colleagues (2008) prospectively compared the FIBROSpect II against pathology assessments and a quantitative measure of fibrosis. Liver biopsy specimens and serum were obtained from 252 individuals with chronic hepatitis C from three centers. Biopsy specimens were scored at each center and quantification of fibrosis was performed by digitized morphometry. Serum tests were blinded to clinical or histologic evaluation. The sensitivity and specificity of FIBROSpect II were determined to be 83.5% and 66.7%, respectively, with an accuracy of 80.2%. The authors noted: "Assessing the diagnostic utility of biomarkers is limited by variability in methods to quantify fibrosis and poor inter-observer agreement for histologic staging."

In a French study, Bourlier and colleagues (2008) attempted to validate the Hepascore in 472 participants with hepatitis C virus (HCV). Based on the results of their study, the authors concluded that before Hepascore can be used in routine practice it should be validated on blood donor populations and on a larger population.

Adams (2011) reported current limitations of serum markers for liver fibrosis to include "a significant indeterminate range and a predictive ability that is limited to only a few stages of fibrosis." The author also noted "what remains to be demonstrated is whether the use of biomarker models can influence patient outcomes." Serum markers included in this review were: FibroTest, Hepascore, and FIBROSpect II.

Sebastiani and colleagues (2011) reported on an international retrospective study investigating the effect of etiology and stages of hepatic fibrosis on the performance of liver fibrosis biomarkers. A total of 2411 individuals with compensated chronic liver disease were consecutively enrolled in 9 centers. AST to platelet ratio index (APRI), Forns' index, Lok index, aspartate aminotransferase-to-alanine aminotransferase (AST-to-ALT) ratio, Fibrosis-4 (FIB-4), platelets and FibroTest/FibroSure were tested against liver biopsy. Results included:

- Performance of APRI and FibroTest-FibroSure was noted to be higher than other biomarkers.
- Performance of FibroTest/FibroSure was good in all etiologies except for MASH.
- Performance of all biomarkers was reduced in hepatitis C cases with normal ALT.

The authors concluded that for the diagnosis of liver fibrosis, the performance of non-invasive biomarkers is not such to replace liver biopsy and recommended further prospective study. Study limitations include potential selection bias and suboptimal liver biopsy length.

In a 2013 systematic review, Chou and Wasson evaluated the accuracy of a wide variety of blood tests in determining fibrosis and/or cirrhosis. Both "simple" tests, such as platelet count, and more complex scoring systems, such as the FibroTest were included. A total of 172 studies were identified that compared the diagnostic accuracy of blood tests to liver biopsy. Blood tests associated with areas under the receiver-operating characteristic curve (AUROCs) of 0.70 or greater (range, 0.70 to 0.86) were considered fair to good for identifying fibrosis and AUROCs of 0.80 or greater (range, 0.80 to 0.91) were considered good to excellent for identifying cirrhosis. Tests for identifying clinically significant fibrosis with AUROCs of 0.70-0.86 included platelet count, age-platelet index, APRI, FibroIndex, FibroTest, and Forns index with median positive likelihood ratios of 5 to 10 at commonly used cutoffs. Tests for identifying cirrhosis with AUROCs of 0.80 to 0.91 included platelet count, age-platelet index, APRI, and Hepascore also with median positive likelihood ratios of 5 to 10. Most tests did not have high negative predictive values for fibrosis, and negative likelihood ratios were found in the moderately useful range (0.10 to 0.20) at commonly used cutoffs, only with FibroIndex and FibroTest. This suboptimal negative predictive value suggests that these tests perform better in identifying fibrosis than in ruling it out. Additionally, differences were small between the FibroTest or APRI and other blood tests, suggesting routinely available blood tests and simple calculations are not outperformed by additional blood tests and more complex algorithms in identifying fibrosis.

Salkic and colleagues (2014) conducted a heterogeneous meta-analysis of studies on the diagnostic performance of FibroTest/FibroSure (proprietary formula; Biopredictive, Paris, France) in chronic hepatitis B. The meta-analysis included 16 studies (n=2494) on liver fibrosis diagnosis and 13 studies (n=1754) on cirrhosis diagnosis. For significant liver fibrosis (F2-F4) diagnosis using all of the fibrosis studies, the area under the hierarchical summary receiver operating curve was 0.84 (95% confidence interval [CI], 0.78 to 0.88). At the recommended FibroTest/FibroSure threshold of 0.48 for a significant liver fibrosis diagnosis, the sensitivity was 60.9%, specificity was 79.9%, and the diagnostic odds ratio (DOR) was 6.2%. For liver cirrhosis (F4) diagnosis using all of the cirrhosis studies, the area under the hierarchical summary receiver operating curve was 0.87 (95% CI, 0.85 to 0.9). At the recommended FibroTest/FibroSure threshold of 0.74 for cirrhosis diagnosis, the sensitivity was 61.5%, specificity was 90.8%, and the DOR was 15.7. Although study results suggested that FibroTest/FibroSure may be useful for excluding cirrhosis in individuals with chronic hepatitis B, the authors concluded that the test had suboptimal performance in detection of significant fibrosis and cirrhosis and in exclusion of significant fibrosis.

Xu and colleagues (2014) performed a systematic review and meta-analysis of 30 studies to evaluate the effectiveness and accuracy of APRI, FIB-4 and FibroTest to detect fibrosis in individuals with hepatitis B. For significant fibrosis, the areas under the summary

receiver operating characteristic (SROC) curve for APRI, FIB-4, and FibroTest were 0.77, 0.75, and 0.84, respectively. For cirrhosis, the areas under the SROC curve for APRI, FIB-4 and FibroTest were 0.75, 0.87, and 0.90, respectively. The heterogeneity of FIB-4 and FibroTest were not statistically significant. The heterogeneity of APRI for detecting significant fibrosis was affected by median age, and for cirrhosis was affected by etiology. Limitations of the review reported by the authors included that "the analysis focused on only individuals with hepatitis B related fibrosis, without distinguishing between HBeAg negative and positive cases, or considering the virus replication rate due to the limited number of publications." The authors also reported that further studies are needed.

In a 2014 study, Leroy and colleagues compared FibroTest, FibroMeter, and Hepascore for diagnosing fibrosis in individuals with hepatitis C and hepatitis B. For 510 subjects, blood samples were collected the day of liver biopsy. To avoid spectrum bias, individuals with hepatitis C (n=255) and hepatitis B (n=255) were matched to stages of liver fibrosis. The authors found a significant correlation between the blood test results and the liver biopsy fibrosis stages, and hepatitis C and hepatitis B groups were similar: (FibroMeter: r=0.67 vs. 0.64, FibroTest r=0.58 vs. 0.62, and Hepascore r=0.57 vs. 0.60, p<0.001 for all tests). For significant fibrosis (F ≥ 2), FibroMeter (AUROC 0.84) was superior to FibroTest (0.79; p<0.001) and Hepascore (0.77; p<0.001). In addition, for extensive fibrosis (F ≥ 3), FibroMeter was superior (AUROC 0.88) to FibroTest (0.83; p<0.02) and Hepascore (0.84; p<0.05). For cirrhosis, there were no significant differences between the tests. The Youden method was used to define cut-offs for the hepatitis C and B groups. All of the blood tests underestimated extensive fibrosis (F ≥ 3) in hepatitis B and hepatitis C individuals: Fibrotest 47% vs. 26%, Fibrometer 24% vs. 6%, and Hepascore 41% vs. 24%, respectively (p<0.01). However, the blood tests were significantly lower for the chronic hepatitis B group, thus increasing the risk of underestimating severe fibrosis and cirrhosis in individuals with hepatitis B. The authors concluded:

> The overall diagnostic performance of blood tests of fibrosis is similar in CHB [chronic hepatitis B] and CHC [chronic hepatitis C]. However, applying to CHB the cut offs validated in CHC is clearly associated with a low but significant increased risk of under-diagnosing extensive fibrosis and cirrhosis. Stringent cut-offs should be used along with a fine analyse of the clinical condition and patient characteristics to avoid misdiagnosis of cirrhosis.

In a cross-sectional study, Boursier and colleagues (2016) compared 8 serum markers and elastography for the diagnosis of liver fibrosis against liver biopsy results in 452 individuals with MASLD. Within a week prior to liver biopsy, subjects gave fasting blood samples that were tested for MASLD-specific markers (BARD score, NFS, and FibroMeter MASLD) and non-specific markers (APRI, FIB4, FibroTest, Hepascore, and FibroMeter^{V2G}). Within 3 months of the biopsy, elastography (Fibroscan) was performed to evaluate liver stiffness measurement (LSM). For advanced fibrosis, FibroMeter^{V2G} had a significantly higher AUROC (0.817 ± 0.020) than the other blood tests (p≤0.041), and was similar to LSM (0.831 ± 0.019). For detecting fibrosis stages, LSM and FibroMeter^{V2G} had the best scores (Obuchowski index [ordROC] 0.834 ± 0.014, p≤0.001; 0.798 ± 0.016, p≤0.036, respectively). The authors note this is the first study that evaluates FibroMeter^{V2G}, Hepascore and LSM for MASLD. Limitations of the study included improvements in LSM technology since the study began. The authors state that the results "need validation in large cohorts of unselected MASLD patients with long-term follow-up allowing for the study of a sufficient number of events."

Houot and colleagues (2016) published an industry-supported systematic review and meta-analysis comparing the AUROCs between APRI, FIB4, FibroTest and transient elastography (TE). Using liver biopsy METAVIR scores as a reference, the authors compared the outcomes of hepatitis C and B subjects in 71 studies between 2002 and 2014. The FibroTest scored better than TE or APRI for identifying advanced fibrosis (credibility interval 0.06 [0.02-0.09] and 0.05 [0.03-0.07], respectively). For identifying cirrhosis, TE and FIB4 scored better than APRI, (0.07 [0.02-0.13] and 0.04 [0.02-0.05], respectively). Other comparisons were not statistically significant. The authors noted several limitations including the first-time use of the Bayesian method, the inability to assess pooled sensitivity and specificity data, lack of fibrosis staging information in some studies, and a relatively small number of studies for comparisons.

Munteanu and colleagues (2016) published the results of a study to compare the diagnostic performance of the FibroTest, SteatoTest, and ActiTest versus the steatosis, activity and fibrosis (SAF) histologic score in 600 subjects with MASLD. The mean (95% CI) Non Binary AUROC (NonBinAUROC) for all 3 serum tests was significant (p<0.0001): FibroTest (fibrosis staging) was 0.878 (0.864-0.892) for the prediction of all 5 SAF stages, 0.846 (0.830-0.862) for ActiTest (inflammation activity grading) predicting the 5 SAF activity grades, and 0.822 (0.804-0.840) for SteatoTest (steatosis staging) predicting the 4 SAF steatosis grades. In 574 subjects with blood samples the NonBinAUROC score was higher for FibroTest (0.877; 0.862-0.892) than body mass index, AST/ALT ratio, diabetes (BARD) (0.836; 0.820-0.852; p=0.0001), and FIB-4 (0.845; 0.829-0.864, p=0.007). FibroTest was not significantly higher than the MASLD score (0.866; 0.850-0.882, p=0.26). ActiTest had higher NonBinAUROC (0.846; 0.830-0.862) than BARD (0.810; 0.792-0.828; p=0.0003), FIB-4 (0.798; 0.780-0.816; p<0.0001), and MASLD (0.815; 0.805-0.825; p=0.005). Subjects that were included were known to have abnormal results and may not fully represent the MASLD population, further study in a wider variety of MASLD subjects is needed to determine if the FibroTest, ActiTest, and SteatoTest are able to stage fibrosis without the need for biopsy. The F2 and F3 stage for FibroTest was lower than the histologic evaluations, but it is not known if that is due to underestimation of the FibroTest or lack of standardization of F2 and F3 in the SAF scoring; additional study is warranted.

Tanwar and colleagues (2017) compared the performance of 10 serum biomarkers of liver fibrosis in subjects with hepatitis C and previous treatment failure. Serum samples were collected and stored after 80 subjects underwent liver biopsy. Within 6 months of collection, the samples were analyzed for direct markers (Hepascore, FibroMeter V2G, HA, enhanced liver fibrosis [ELF], and FIBROSpect II) and indirect markers (AST:ALT ratio, APRI, Forns, FIB4 and FibroMeter 3G) and compared to METAVIR scores. Good performance was defined as an AUROC > 0.8. All direct markers and FibroMeter V3G were able to detect moderate fibrosis, and FibroMeter V2G had the highest AUROC of 0.88 (95% CI, [0.80-0.95]; p<0.001). For the detection of advanced fibrosis, FibroMeter V2G had the highest AUROC of 0.84 (95% CI, [0.75-0.93]; p<0.001), but it was only found to be significantly higher than AST:ALT and APRI. All markers were able to detect advanced fibrosis except FIBROSpect II, AST:ALT and APRI. For the detection of cirrhosis, Forns had the highest AUROC of 0.92 (95% CI, [0.86-0.98]; p<0.001), and all markers had good performance except AST:ALT and APRI. For detecting fibrosis stages for subjects with hepatitis C, the FibroMeter V2G (Obuchowski measure [ordROC] 0.94) and FibroMeter V3G (ordROC 0.94) were only significantly higher (p<0.05) than AST:ALT and APRI. ELF and Hepascore, both ordROC 0.93, were best for detecting fibrosis for all liver disease etiologies. Because results differed for some biomarkers depending on the assay used, the researchers noted the importance of using the individual component assays that have been validated for each test. Limitations noted by the authors included a small sample size (predominately male).

In 2019, Sanyal and colleagues presented data on two trials which were being conducted to examine the use of simtuzumab for individuals with advanced fibrosis due to metabolic dysfunction-associated steatohepatitis (MASH). While these two trials were stopped due to lack of efficacy of simtuzumab, there was 2 years' worth of data analyzed which included serum marker tests including the ELF test, FibroSure/Fibro test, MASLD fibrosis score, FIB-4 index, and APRI index. The authors reported progression to cirrhosis was greater in those with higher baseline values of and greater increase in hepatic collagen content, level of alpha-smooth muscle actin, and ELF score. The authors acknowledge the generalizability of the results are uncertain due to the fact the population in the trials was not representative of the MASH population at large. They also note a follow-up of 2 years is a short time for a disease like MASH which is slowly progressive. The data obtained also included both groups from the discontinued trials (the placebo-treated group and the treatment group). While the trials were stopped due to lack of efficacy in the treatment group, it is impossible to confirm

with certainty there was no benefit.

Another study reported on data from trials which assessed the safety and efficacy of simtuzumab and selonsertib in individuals with MASH (Younossi, 2021). The population from the Sanyal study reported above is also included here. While neither of the drug studies met their primary clinical endpoints and were terminated for this reason, Younossi and colleagues assessed the association of non-invasive test scores with clinical outcomes and patient-reported outcome (PRO) scores. Using data from four phase 2 and phase 3 trials, 2154 participants were included. For those individuals with histologic or clinical evidence of disease progression, they were found to have had higher baseline non-invasive test scores for ELF, NFS, FIB-4, APRI, Fibrotest, and liver stiffness. While individuals were receiving treatment, it was noted those with a decrease in non-invasive test scores had improvement in their PRO scores and conversely for those who had an increase in their non-invasive test scores, their PRO scores worsened. The association seemed to be highest for ELF score, Fibrotest score, and NFS. This study has several limitations including PROs are self-reported which may lead to recall bias. All included participants with data analyzed were recruited for clinical trials with inclusion and exclusion criteria. This may limit the generalizability of the findings. The authors note “longer follow-up outside of the clinical trial setting is needed to validate our findings regarding the relationship between PRO trends and patients’ liver function indicators free of the clinical trial bias.”

In 2020, Harrison and colleagues published the results of a prospective derivation and global validation study of the proprietary blood-based biomarker panel (NIS4®, GENFIT, Cambridge, MA) for diagnosis of MASH. NIS4 panel is a molecular multi-analyte diagnostic test that includes miR-34a-5p, alpha-2-macroglobulin (A2M), YKL-40, and hemoglobin A1c (HbA1c), and is designed to rule in or rule out at-risk MASH by assigning a single score. The discovery cohort was made up of 239 individuals with biopsy-confirmed MASH that were negative for cirrhosis. External validation was completed by two independent cohorts, the first cohort included 475 individuals with suspected MASLD or MASH, and the second cohort included 227 individuals with suspected MASLD and risk factors for MASH or suspicion of fibrosis stage 2 or greater. The discovery cohort had higher concentrations of YLK-40, A2M, and miR-34a-5p in the individuals with at-risk MASH. The AUROC for NIS4 in the discovery cohort was 0.80 (95%CI, 0.73-0.85). The lower cutoff for NIS4 was established at less than 0.36, with 80.8% sensitivity, 65.2% specificity, and 81.5% negative predictive value. The upper cutoff was set to 0.63 or higher for a specificity of 90.4%, 45.2% sensitivity, and 78.3% positive predictive value. Indeterminate results occurred in 71/239 (30%) of individuals in the discovery cohort, and 168 (70%) had results that resulted in clinical action. The AUROC and test performances were similar across the validation cohorts. miR-34a-5p was previously found to be overexpressed in individuals with MASH, though the exact mechanism is not understood, A2M promotes liver fibrosis through inhibition of matrix protein catabolism in the inflamed or injured liver and is also included in other proprietary panels. YKL-40 is a biomarker for liver fibrosis but the exact mechanism is not well understood and HbA1c is included as it shows glycemic control. Additional research is needed to understand the effect of diabetic treatment intending to lower HbA1c, and whether it affects test performance. Limitations of the study include a lack of individuals with cirrhosis in the discovery cohort and only 25/702 in the validation cohort. Additional research is needed in the performance of NIS4 to identify individuals with cirrhosis, as NIS4 was designed to identify fibrosis with a MASH component. Further research is also needed to prospectively evaluate the performance of NIS4 and determine whether its use affects net health outcomes.

A 2021 randomized controlled trial by Are and colleagues reported on the prognostic significance of the ELF score in the prediction of short-term liver-related outcomes among those individuals with compensated MASH cirrhosis. The trial included 162 participants with biopsy-proven MASH with compensated cirrhosis and portal hypertension. At baseline, ELF, Fibrosis-4 index, aspartate aminotransferase-to-platelet ratio index, MASLD fibrosis score, Child-Turcotte-Pugh score, and MELD scores were obtained. Study duration was 52 weeks. With 161 participants available for analysis, the authors report 33 participants developed a liver-related event such as development or progression of varices, decompensations, Child-Turcotte-Pugh score greater than or equal to 2 or MELD score greater than 15. There were 14 participants who developed medium-to-large size varices or the presence of red signs. The authors reported those with an ELF score greater than or equal to 11.3 had higher frequency of liver-related events (hazard ratio, 4.81; 95% confidence interval [CI], 1.54–15.05; $p<0.01$). For those with an ELF score of 9.8 to 11.2, there was not a documented higher frequency of liver-related events. For those with an ELF score less than 9.8, the authors reported a correlation between ELF score and hepatic venous pressure gradient measurements. For ELF score less than 9.8, the sensitivity, specificity, PPV, and NPV for predicting liver-related outcomes at 52 weeks was 87.9%, 26.6%, 23.6%, and 89.5%, respectively. For ELF score greater than or equal to 11.3, the sensitivity, specificity, PPV, and NPV for predicting liver-related outcomes at 52 weeks was 51.5%, 72.7%, 32.7%, and 85.3%, respectively. The authors note their data is limited to a short period of follow-up with results only applicable to cirrhotic populations. Their results should be validated in large-scale studies with long-term follow-up.

A 2021 systematic review by Draijer and colleagues reported on the diagnostic accuracy of non-invasive methods of detecting and staging liver fibrosis in children with MASLD. They included 20 studies that addressed prediction scores, simple biomarkers, combined biomarkers, and imaging techniques. Of the 16 fibrosis tests in the studies, only 2 tests had accuracy data for the detection of mild fibrosis. Most of the studies lacked validation, and generalizability of the study results is difficult as the studies were performed in tertiary liver clinics. There is difficulty comparing accuracy due to the use of kits from different manufacturers. Comparison of accuracy of imaging techniques was also difficult due to different techniques and machines. Additional studies are needed to validate the most promising tests and study accuracy in a variety of settings.

In a 2021 systematic review by Sharma and colleagues, the authors reported on the accuracy of the ELF test for diagnosing advanced liver fibrosis and cirrhosis, with liver biopsy as the reference standard. There were 36 articles included; half of the articles did not specify how the liver biopsy was obtained. There was variation among the studies on how the fibrosis was staged, and variations among the studies about biopsy length requirements. There were 11 studies which reported on diagnosis of hepatitis C, 4 studies which reported on diagnosis of hepatitis B, 9 studies which reported on MASLD, 2 studies reported on alcoholic liver disease and 10 studies had mixed etiology. Some of the studies used different versions of the ELF algorithm to calculate a score, resulting in difficulty comparing data between the studies. Variations among the studies make generalization of results difficult. Bias may also be present, given that all included study participants had undergone liver biopsy. Finally, no data was presented regarding improvement in net health outcomes.

Other Scoring Systems

Other serum marker scoring systems have been developed that use non-proprietary formulas. These tests are not addressed by this document, but include the following:

The APRI scoring system (AST to platelet ratio) requires only the serum level of AST and the number of platelets and uses a simple formula that can be calculated at the bedside to produce a score for the prediction of fibrosis (Wai, 2003). Using an optimized cutoff value derived from a training set and validation set of subjects with hepatitis C, the negative predictive value for fibrosis was 86% and the positive predictive value was 88%. Rosenberg (2004) developed a scoring system based on an algorithm combining hyaluronic acid (HA), amino terminal propeptide of type III collagen, and tissue inhibitor metalloproteinase type-1 (TIMP-1). The algorithm was developed in a test set of 400 individuals with a wide variety of chronic liver diseases and then validated in another 521 subjects. The algorithm was designed to discriminate between no or mild fibrosis and moderate to severe fibrosis, and had a negative predictive value for fibrosis of 92%. Another system reported to help identify fibrosis (advanced) is the MASLD Fibrosis Score. The MASLD Fibrosis Score is based on age, body mass index, platelet count, albumin, AST/ALT ratio and is calculated using a published formula.

The FIB-4 index is a noninvasive estimate of liver fibrosis that combines common laboratory values (platelet count, ALT, and AST) and age. A simple published formula is used that can be calculated at the bedside. Publications including retrospective analyses and systematic reviews have evaluated the predictive accuracy of FIB-4 for liver fibrosis (Shah, 2009; Sterling, 2006; Vallet-Pichard, 2007). The BMI Z-score (standard deviation score) may be used to improve the performance of APRI, FIB-4 and B-AST in the pediatric population (Pokorska-Śpiewak, 2017). Wisteria floribunda agglutinin-positive Mac-2-binding protein (WFA+-M2BP) has been evaluated as a diagnostic biomarker for liver cirrhosis. Alterations of M2BP occur during the progression of liver disease and fibrosis as a result of changes in N-glycosylation. When comparing predictors of fibrosis, the AUSROC of WFA+-M2BP (0.79) was only greater than AST/ALT (0.74, p=0.048) for the prediction of significant fibrosis. WFA+-M2BP was similar to APRI, FIB-4, HA, and FibroScan® (Echosens™, Paris, France) in detecting advanced fibrosis but surpassed those measures in detecting cirrhosis (Feng, 2020).

There are a number of publications addressing multiple scoring systems including multicenter, retrospective cohort studies, systematic reviews and meta-analyses. The scoring systems were found to have low diagnostic accuracy therefore resulting in poor prediction of fibrosis (Bhat, 2017; Mansoor, 2015; Xiao, 2015; Xiao, 2017; Xu, 2019).

Other Considerations

In a clinical care pathway (Kanwal, 2017) on the screening and evaluation of hepatitis C, the American Gastroenterological Association (AGA) states:

> In the absence of clinically apparent cirrhosis, there is the need to assess degree of liver fibrosis. Such assessment can be done noninvasively via elastography (usually “vibration-controlled” or Fibroscan), serum biomarkers (FIB4 or aspartate aminotransferase to platelet ratio index), or various proprietary markers. The routine use of the invasive gold standard liver biopsy has become less popular, recognizing that even liver biopsy may miss the presence of cirrhosis. The results of non-invasive studies provide helpful information to patient and clinician regarding fibrosis stage, though all may suffer from occasional false readings and must be tempered by clinical judgment.

In 2017, the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) published a clinical practice guideline for the diagnosis and treatment of MASLD in children. The guideline states the following:

> Fibrosis in the setting of MASLD is currently determined by liver histology and staged using a semiquantitative scale of 0 to 4.
>
> The accuracy of currently marketed fibrosis biomarker tests in children, and markers such as AST to platelet ratio and hyaluronic acid (and their optimal cutoffs), remain to be determined.

The 2021 American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) recommendations for testing, managing, and treating hepatitis C include statements addressing both adult and pediatric care. The AASLD concludes the evidence shows benefit in adults but the pediatric population requires additional study for serum fibrosis markers. The guideline released the following statements and graded recommendations:

> Evaluation for advanced fibrosis using noninvasive tests (serum panels, elastography) 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). (Rating: Class I, Level A-Evidence and/or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective; data derived from multiple randomized clinical trials, meta-analyses, or equivalent).
>
> Disease severity assessment via routine laboratory testing and physical examination, as well as use of evolving noninvasive modalities (i.e., elastography, imaging, or serum fibrosis markers) is recommended for all children with chronic hepatitis C. (Rating: Class I, Level B-Evidence and/or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective; data derived from a single randomized trial, nonrandomized studies, or equivalent.)

The AASLD in conjunction with the AGA and the American College of Gastroenterology (ACG) published a practice guidance document (Chalasani, 2018) on the diagnosis and management of MASLD. The guideline does not recommend screening (including higher-risk individuals with diabetes or obesity) given significant gaps in knowledge regarding the diagnosis, natural history, and treatment of MASLD, as well as uncertainties around which diagnostic test to use (since liver enzyme levels may be normal in individuals with MASLD). The guideline also states the following:

- There should be a high index of suspicion for MASLD and MASH in patients with type 2 diabetes. Clinical decision aids such as NFS or fibrosis-4 index (FIB-4) or vibration controlled transient elastography (VCTE) can be used to identify those at low or high risk for advanced fibrosis (bridging fibrosis or cirrhosis).
- NFS or FIB-4 index are clinically useful tools for identifying MASLD patients with higher likelihood of having bridging fibrosis (stage 3) or cirrhosis (stage 4).
- Liver biopsy should be considered in patients with MASLD who are at increased risk of having SH [steatohepatitis] and/or advanced fibrosis.
- The presence of MetS, NFS or FIB-4, or liver stiffness measured by VCTE or MRE may be used for identifying patients who are at risk for SH and/or advanced fibrosis.

In a 2018 update on the prevention, diagnosis, and treatment of chronic hepatitis B (Terrault, 2018), the AASLD notes that:

- Liver biopsy offers the only means of assessing both fibrosis and inflammation. If the biopsy specimen shows moderate or severe inflammation (A2 or A3) or significant fibrosis (F2), treatment is recommended.
- 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.

A 2021 AGA clinical care pathway for the risk stratification and management of patients with nonalcoholic fatty liver disease recommends:

> all individuals in the target risk groups undergo a 2-tier process to assess for clinically significant liver fibrosis. The first tier involves using simple, nonproprietary fibrosis scores. […] The Pathway relies on the FIB-4 score because it has been shown to have the best diagnostic accuracy for advanced fibrosis compared with other noninvasive markers of fibrosis in patients with NAFLD.

Another publication by the AGA in 2022 (clinical practice update: diagnosis and management of nonalcoholic fatty liver disease in lean individuals) states: “ELF has not been tested in patients with lean NAFLD and further studies are needed. We concluded that ELF test

may be used as a confirmatory prognostic test in patients with lean NAFLD until further data are available."

A 2022 clinical practice guideline (for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings) released by the American Association of Clinical Endocrinology (AACE) and co-sponsored by the AASLD notes that the preferred noninvasive initial test is the FIB-4. Endocrinology and primary care clinicians must be aware of the limitations of blood panels, compared with a liver biopsy (ie, the "gold standard"). Overall, panels for the diagnosis of fibrosis have a good specificity and negative predictive value (NPV) that allow the clinician to rule out advanced fibrosis and use this as a rule-out test. However, they lack adequate sensitivity and positive predictive value (PPV) to establish the presence of advanced fibrosis. Furthermore, "Of note, their performance is dependent on the population being studied, with a better performance in hepatology clinics where more people have advanced disease than in primary care settings, where the FIB-4 and other tests have been less well characterized."

In 2023 the AASLD published their practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease, stating: "The Enhanced Liver Fibrosis (ELF) test is approved for prognostication when advanced fibrosis is suspected, although it can be ordered for secondary risk assessment…"

As an alternative to liver biopsy, using a blood sample, the OWLiver® test (CIMA Sciences, San Antonio, TX) is a non-invasive way to determine activity of the liver through the evaluation of 28 biomarkers. The test is designed to report those who may be at-risk or not at-risk for MASH. The test is not designed to report the probability of a diagnosis.

Conclusion

There is no compelling evidence indicating that changes in serum marker values, including those calculated proprietary algorithms, correlates with changes in liver fibrosis over time. Published studies have emphasized 'static' time points rather than changes over time. Additionally, no studies have been identified that use the results of any of the proprietary tests to reduce the number of biopsies, or to improve net health outcomes. Current evidence does not support the use of proprietary algorithms evaluating liver fibrosis in the evaluation and monitoring of chronic liver disease.

Background/Overview

Hepatic Fibrosis

Hepatic fibrosis results when excessive fibrous connective tissue (scar tissue) develops in the liver as a result of repeated injury, such as injury from inflammation. The inflammatory immune cells secrete messengers that cause hepatic stellate cell activation, leading to the overproduction of the extracellular matrix. The condition is progressive and can eventually lead to liver failure.

Hepatitis C

HCV causes liver inflammation and can lead to severe liver damage, cirrhosis, and hepatocellular carcinoma (HCC). It is estimated that 70% of all HCV-infected individuals will eventually develop chronic liver disease, and at least 20% will develop cirrhosis over 10 to 20 years. After 20 to 40 years, a smaller percentage of individuals with chronic liver disease develop HCC. The population identified as high-risk for developing HCC includes males, people with a history of substance abuse, those diagnosed with cirrhosis, individuals over age 40, and those infected for 20 to 40 years.

Antiviral therapy is the recommended treatment for individuals with a reactive enzyme immunoassay for antibody to HCV, the presence of HCV RNA, and compensated liver disease. Liver biopsy is typically recommended prior to the initiation of antiviral therapy, and repeat biopsies may be performed to monitor fibrosis progression. Liver biopsies are analyzed according to a histologic scoring system; the most commonly used is the METAVIR scoring system, which scores fibrosis from F0-F4. A METAVIR score of F2 to F4 indicates significant fibrosis, while a score of F3 and F4 signifies advanced fibrosis. Biopsies can also be evaluated according to the degree of inflammation present, referred to as the grade or activity level. For example, the METAVIR system includes scores for necroinflammatory activity ranging from A0 to A3 (A0 = no activity, A1 = minimal activity, A2 = moderate activity, A3 = severe activity). However, there are several limitations to liver biopsy, including its invasive nature and subjective grading system.

Hepatitis B

Like HCV, hepatitis B is a viral infection that can lead to chronic disease, resulting in liver inflammation, liver failure, or HCC. Chronic hepatitis B is much more prevalent in infants and children; 25-50% of children under 5 develop chronic infection compared to 5% of adults. Although the hepatitis B vaccination has greatly decreased the prevalence of the infection, there is currently an estimated 850,000 to 2.2 million people in the United States with chronic hepatitis B. The standard for identifying and monitoring fibrosis is liver biopsy and the METAVIR scoring system.

NAFLD/MASLD

According to the American Liver Foundation, MASLD currently affects 100 million individuals in the United States. The disease results from hepatic steatosis, the accumulation of excessive fat in liver cells. While alcohol consumption can increase fat in the liver and cause alcoholic liver disease, it is not the direct cause of MASLD. Instead, risk factors for MASLD include obesity, high triglycerides, diabetes, malnutrition, low physical activity, and rapid weight loss; however, some individuals have no risk factors and the cause is unknown. MASLD is subdivided into nonalcoholic fatty liver (NAFL), sometimes referred to as simple fatty liver, and MASH. In NAFL, hepatic steatosis is present without evidence of inflammation, whereas in MASH, hepatic steatosis is associated with hepatic inflammation that histologically is indistinguishable from alcoholic steatohepatitis. MASH can lead to fibrosis, cirrhosis, cancer, or liver failure.

Multiple therapies have been investigated for the treatment of NAFL and MASH. Weight loss is the only therapy with reasonable evidence suggesting it is beneficial and safe. Drug treatments are currently under investigation, including obeticholic acid and elabibranor (Chalasani, 2018).

Individuals with MASLD may have mild or moderate liver enzyme elevations, such as AST and ALT, although normal aminotransferase levels do not exclude MASLD, and the degree of aminotransferase elevation does not predict the degree of hepatic inflammation or fibrosis. Likewise, a normal ALT does not exclude clinically important histologic injury. A definitive diagnosis of MASLD requires demonstration of hepatic steatosis by imaging or biopsy, exclusion of significant alcohol consumption, exclusion of other causes of hepatic steatosis, and absence of coexisting chronic liver diseases. Liver biopsy is the standard method for identifying fibrosis and the presence of inflammation in individuals suspected to have MASH. Different scoring systems have been used to assess fibrosis in MASLD. For example, the MASLD Activity Score (MAS) is used to determine if MASH is likely based on the sum of individual scores: steatosis (0-3), hepatocellular ballooning (0-2), and lobular inflammation (0-3). Individuals with a MAS score ≥ 5 are thought to have MASH.

Noninvasive Serum Markers

A variety of laboratory tests have been proposed as an alternative to liver biopsy. These tests include ALT, AST, the ALT/AST ratio (also referred to as the AAR), MASLD fibrosis score, FIB-4 index, APRI, platelet count, plasma cytokeratin-18, and prothrombin index.

Proprietary serum markers for liver fibrosis commercially available in the United States are described below:

ASH FibroSURE (ASH test) assesses the liver status of individuals with alcoholic liver disease (ALD). Quantitative results of 10 biochemicals, including alpha-2-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 ASH. ASH FibroSURE is offered by LabCorp.

FibroTest-ActiTest uses a combination of 6 serum indirect biochemical markers of liver function plus age and gender in a patented algorithm to generate a measure of fibrosis and necroinflammatory activity in the liver corresponding to the METAVIR scoring system for stage (fibrosis) and grade (necroinflammatory activity). The biochemical markers include measurements of alpha-2 macroglobulin, haptoglobin, total bilirubin, GGT, apolipoprotein A1 and ALT is added for the ActiTest. FibroTest-ActiTest is offered by BioReference Laboratories, LabCorp, Mayo Clinic and Quest Diagnostics in the United States. The older version of the test, HCV FibroSure, is offered by LabCorp.

NASH FibroSURE (NASH Test) assesses the liver status of individuals with MASLD. Quantitative results of 10 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 MASH. Nash FibroSURE is offered by LabCorp.

FibroSpect HCV (formerly known as FibroSpect II) uses a combination of 3 markers that directly measure fibrogenesis of the liver, analyzed with the FIBROSpect HCV Index, a patented algorithm. The markers include HA, TIMP-1 and alpha-2 macroglobulin. FibroSpect HCV is offered by Prometheus Laboratories.

FibroMeter is a panel of tests for evaluating liver fibrosis in individuals with viral hepatitis, MASLD, and alcoholic liver disease (ALD). Fibrometer VIRUS, which assesses liver fibrosis in individuals with hepatitis C or B, is based on seven blood markers (platelet count, alpha-2-macroglobulin, ALT, urea, prothrombin index, GGT, and AST). FibroMeter MASLD utilizes a proprietary algorithm to calculate results using age weight, in addition to platelet count, AST, ALT, ferritin, and glucose. The results include a fibrosis score that signifies METAVIR stage F2 or higher, a cirrhosis score that signifies the probability of cirrhosis, and an activity grade that assesses necrotico-inflammatory activity. Fibrometer VCTE combines biomarkers with liver stiffness measurement by FibroScan for classification of individuals with chronic hepatitis B or C, or MASLD. The biomarkers measured include alpha-2 macroglobulin, AST, GGT, and prothrombin index. FibroMeter is offered by ARUP Laboratories.

Definitions

Algorithm: A process or set of rules by which a calculation or process can be carried out usually referring to calculations that will be done by a computer.

Biopsy: A procedure that involves obtaining a tissue specimen for microscopic analysis to establish a precise diagnosis.

Cirrhosis: Severe fibrosis, inflammation, and damage to the liver that can result in liver failure.

Fibrosis: The development of excess fibrous connective tissue in an organ.

Hepatic steatosis: The accumulation of excessive fat in the liver.

Metabolic dysfunction-associated liver disease (MASLD): A term for individuals who have hepatic steatosis and have at least one of five cardiometabolic risk factors.

Metabolic dysfunction-associated steatohepatitis (MASH): A type of MASLD, in which more than 5% of the liver is fat, and inflammation is present.

Nonalcoholic fatty liver disease (NAFLD): A term for liver diseases that result from the excessive accumulation of fat in the liver that is not a result of alcohol use.

Nonalcoholic fatty liver (NAFL): A type of NAFLD, in which more than 5 percent of the liver is fat, but inflammation is not present.

Nonalcoholic steatohepatitis (NASH): A type of NAFLD, in which more than 5 percent of the liver is fat, and inflammation is present.

Serum: The clear, straw-colored, liquid portion of blood plasma that does not contain fibrinogen or blood cells and remains fluid after clotting.

Steatohepatitis: Excessive fat in the liver that is present with inflammation.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When Services are Investigational and Not Medically Necessary:
When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
81599	Unlisted multianalyte assay with algorithmic analysis [when specified as serum markers for liver fibrosis, including FIBROSpect II, FibroMeter]
84999	Unlisted chemistry procedure [when specified as a proprietary algorithm using serum markers to evaluate liver fibrosis]

ICD-10 Diagnosis	
	All diagnoses, including but not limited to the following:
B16.0-B16.9	Acute hepatitis B

B17.10-B17.11	Acute hepatitis C
B18.0-B18.1	Chronic viral hepatitis B
B18.2	Chronic viral hepatitis C
B19.10-B19.11	Unspecified viral hepatitis B
B19.20-B19.21	Unspecified viral hepatitis C
K70.0-K77	Diseases of liver

When Services are also Investigational and Not Medically Necessary:

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 immunoassays, utilizing serum, prognostic algorithm reported as a risk score and risk of liver fibrosis and liver-related clinical events within 5 years
	Enhanced Liver Fibrosis™ (ELF™) Test, Siemens Healthcare Diagnostics Inc/Siemens Healthcare Laboratory LLC
81596	Infectious disease, chronic hepatitis C virus (HCV) infection, six biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, and haptoglobin) utilizing serum, prognostic algorithm reported as scores for fibrosis and necroinflammatory activity in liver
	HCV FibroSURE™, FibroTest™, BioPredictive S.A.S.
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)
	ASH FibroSURE™, 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)
	NASH FibroSURE™, 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
	LiverFASt™, Fibronostics
0344U	Hepatology (nonalcoholic fatty liver disease [NAFLD]), semiquantitative evaluation of 28 lipid markers by liquid chromatography with tandem mass spectrometry (LC-MS/MS), serum, reported as at-risk for nonalcoholic steatohepatitis (NASH) or not NASH
	OWLiver®, CIMA Sciences, LLC

ICD-10 Diagnosis	
	All diagnoses

References

Peer Reviewed Publications:

1. Adams LA. Biomarkers of liver fibrosis. J Gastroenterol Hepatol. 2011; 26(5):802-809.
2. Afdhal NH, Nunes D. Evaluation of liver fibrosis: a concise review. Am J Gastroenterol. 2004; 99(6):1160-1174.
3. Are VS, Vuppalanchi R, Vilar-Gomez E, Chalasani N. Enhanced liver fibrosis score can be used to predict liver-related events in patients with nonalcoholic steatohepatitis and compensated cirrhosis. Clin Gastroenterol Hepatol. 2021; 19(6):1292-1293.e3.
4. Bhat M, Tazari M, Sebastiani G. Performance of transient elastography and serum fibrosis biomarkers for non-invasive evaluation of recurrent fibrosis after liver transplantation: a meta-analysis. PLoS One. 2017; 12(9): e0185192.
5. Bourliere M, Penaranda G, Ouzan D, et al. Optimized stepwise combination algorithms of non-invasive liver fibrosis scores including Hepascore in hepatitis C virus patients. Aliment Pharmacol Ther. 2008; 28(4):458-467.
6. Boursier J, Vergniol J, Guillet A, et al. Diagnostic accuracy and prognostic significance of blood fibrosis tests and liver stiffness measurement by FibroScan in non-alcoholic fatty liver disease. J Hepatol. 2016; 65(3):570-578.
7. Callewaert N, Van Vleirberghe H, Van Heckle A, et al. Noninvasive diagnosis of liver cirrhosis using DNA sequence-based total serum protein glycomics. Nat Med. 2004; 10(4):429-434.
8. Chou R, Wasson N. Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection: a systematic review. Ann Intern Med. 2013; 158(11):807-820.
9. Colletta C, Smirne C, Fabris C, et al. Value of two noninvasive methods to detect progression of fibrosis among HCV carriers with normal aminotransferases. Hepatology. 2005; 42(4):838-845.
10. Crockett SD, Kaltenbach T, Keeffe EB. Do we still need a liver biopsy? Are the serum fibrosis tests ready for prime time? Clin Liver Dis. 2006; 10(3):513-534.
11. Draijer LG, van Oosterhout JPM, Vali Y, et al. Diagnostic accuracy of fibrosis tests in children with non-alcoholic fatty liver disease: a systematic review. Liver Int. 2021; 41(9):2087-2100.
12. Feng S, Wang Z, Zhao Y, Tao C. Wisteria floribunda agglutinin-positive Mac-2-binding protein as a diagnostic biomarker in liver cirrhosis: an updated meta-analysis. Sci Rep. 2020; 10(1):10582.
13. Halfon P, Bourliere M, Deydier R, 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; 101(3):547-555.
14. Halfon P, Imbert-Bismut F, Messous D, et al. A prospective assessment of the interlaboratory variability of biochemical markers of fibrosis (FibroTest) and activity test (ActiTest) in patients with chronic liver disease. Comp Hepatol. 2002; 1(1):3.
15. Harrison SA, Ratziu V, Boursier J, et al. A blood-based biomarker panel (NIS4) for non-invasive diagnosis of non-alcoholic steatohepatitis and liver fibrosis: a prospective derivation and global validation study. Lancet Gastroenterol Hepatol. 2020; 5(11):970-985.
16. Houot M, Ngo Y, Munteanu M, et al. Systematic review with meta-analysis: direct comparisons of biomarkers for the diagnosis of fibrosis in chronic hepatitis C and B. Aliment Pharmacol Ther. 2016; 43(1):16-29.

17. Imbert-Bismut F, Messous D, Thibaut V, 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; 42(3):323-333.
18. Imbert-Bismut F, Ratziu V, Pieroni L, et al. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. Lancet. 2001; 357(9262):1069-1075.
19. Kelleher TB, Afdhal N. Noninvasive assessment of liver fibrosis. Clin Liver Dis. 2005; 9(4):667-683.
20. Kelleher TB, Mehta SH, Bhaskar R, et al. Prediction of hepatic fibrosis in HIV/HCV co-infected patients using serum fibrosis markers: the SHASTA index. J Hepatol. 2005; 43(1):78-84.
21. Lackner C, Struber G, Liegl B, et al. Comparison and validation of simple noninvasive tests for prediction of fibrosis in chronic hepatitis C. Hepatology. 2005; 41(6):1376-1382.
22. Leroy, V, Sturm N, Faure P, et al. Prospective evaluation of FibroTest®, FibroMeter®, and HepaScore® for staging liver fibrosis in chronic hepatitis B: comparison with hepatitis C. J Hepatol. 2014; 61(1):28-34.
23. Lichtinghagen R, Bahr MJ. Noninvasive diagnosis of fibrosis in chronic liver disease. Expert Rev Mol Diagn. 2004; 4(5):715-726.
24. Mansoor S, Yerian L, Kohli R, et al. The evaluation of hepatic fibrosis scores in children with nonalcoholic fatty liver disease. Dig Dis Sci. 2015; 60(5):1440-1447.
25. Munteanu M, Tiniakos D, Anstee Q, et al. Diagnostic performance of FibroTest, SteatoTest, and ActiTest in patients with NAFLD using the SAF score as histological reference. Aliment Pharmacol Ther. 2016; 44(8): 877-889.
26. Patel K, Gordon SC, Jacobson I, 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; 41(6):935-942.
27. Patel K, Nelson DR, Rockey DC, et al. Correlation of FIBROSpect II with histologic and morphometric evaluation of liver fibrosis in chronic hepatitis C. Clin Gastroenterol Hepatol. 2008; 6(2):242-247.
28. Pokorska-Śpiewak M, Kowalik-Mikołajewska B, Aniszewska M, et al. Clinical usefulness of new noninvasive serum biomarkers for the assessment of liver fibrosis and steatosis in children with chronic hepatitis C. Clin Exp Hepatol. 2017; 3(4):198-202.
29. Poynard T, McHutchison J, Manns M, et al. Biochemical surrogate markers of liver fibrosis and activity in a randomized trial of peginterferon alfa-2b and ribavirin. Hepatology. 2003; 38(2):481-492.
30. Poynard T, Morra R, Halfon P, et al. Meta-analyses of FibroTest diagnostic value in chronic liver disease. BMC Gastroenterol. 2007; 7:40.
31. Poynard T, Munteanu M, Imbert-Bismut F, et al. Prospective analysis of discordant results between biochemical markers and biopsy in patients with chronic hepatitis C. Clin Chem. 2004; 50(8):1344-1355.
32. Ratziu V, Massard J, Charlotte F, et al. Diagnostic value of biochemical markers (FibroTest-FibroSURE) for the prediction of liver fibrosis in patients with non-alcoholic fatty liver disease. BMC Gastroenterol. 2006; 14(6):6.
33. Rockey DC, Bissell DM. Noninvasive measures of liver fibrosis. Hepatology. 2006; 43(2 Suppl 1):S113-S120.
34. Rosenberg WM, Voelker M, Thiel R, et al. Serum markers detect the presence of liver fibrosis: a cohort study. Gastroenterology. 2004; 127(6):1704-1713.
35. Rossi E, Adams L, Prins A, et al. Validation of the FibroTest biochemical markers score in assessing liver fibrosis in hepatitis C patients. Clin Chem 2003; 49(3):450-454.
36. Salkic NN, Jovanovic P, Hauser G, Brcic M. FibroTest/Fibrosure for significant liver fibrosis and cirrhosis in chronic hepatitis B: a meta-analysis. Am J Gastroenterol. 2014; 109(6):796-809.
37. Sanyal AJ, Harrison SA, Ratziu V, et al. The natural history of advanced fibrosis due to nonalcoholic steatohepatitis: data from the simtuzumab trials. Hepatology. 2019; 70(6):1913-1927.
38. Sebastiani G, Castera L, Halfon P, et al. The impact of liver disease aetiology and the stages of hepatic fibrosis on the performance of non-invasive fibrosis biomarkers: an international study of 2411 cases. Aliment Pharmacol Ther. 2011; 34(10):1202-1216.
39. Shah AG, Lydecker A, Murray K, et al. Nash Clinical Research Network. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2009; 7(10):1104-1112.
40. 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; 102(11):2589-2600.
41. Sharma C, Cococcia S, Ellis N, et al. Systematic review: accuracy of the enhanced liver fibrosis test for diagnosing advanced liver fibrosis and cirrhosis. J Gastroenterol Hepatol. 2021; 36(7):1788-1802.
42. Sterling RK, Lissen E, Clumeck N, et al. APRICOT Clinical Investigators. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006; 43(6):1317-1325.
43. Tanwar S, Trembling PM, Hogan BJ, et al. Biomarkers of hepatic fibrosis in chronic hepatitis C: a comparison of 10 biomarkers using 2 different assays for hyaluronic acid. J Clin Gastroenterol. 2017; 51(3):268-277.
44. Vallet-Pichard A, Mallet V, Nalpas B, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and FibroTest. Hepatology. 2007; 46(1):32-36.
45. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology. 2003; 38(2):518-526.
46. Xiao G, Yang J, Yan L. Comparison of diagnostic accuracy of aspartate aminotransferase to platelet ratio index and fibrosis-4 index for detecting liver fibrosis in adult patients with chronic hepatitis B virus infection: a systemic review and meta-analysis. Hepatology. 2015; 61(1):292-302.
47. Xiao G, Zhu S, Xiao X, et al. Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to detect fibrosis in patients with nonalcoholic fatty liver disease: a meta-analysis. Hepatology. 2017; 66(5): 1486-1501.
48. Xu XY, Kong H, Song RX, et al. The effectiveness of noninvasive biomarkers to predict hepatitis B-related significant fibrosis and cirrhosis: a systematic review and meta-analysis of diagnostic test accuracy. PLoS One. 2014; 9(6):e100182.
49. Xu X, Wang W, Zhang Q, et al. Performance of common imaging techniques vs serum biomarkers in assessing fibrosis in patients with chronic hepatitis B: a systematic review and meta-analysis. World J Clin Cases. 2019; 7(15):2022-2037.
50. Younossi ZM, Anstee QM, Wai-Sun Wong V, et al. The association of histologic and noninvasive tests with adverse clinical and patient-reported outcomes in patients with advanced fibrosis due to nonalcoholic steatohepatitis. Gastroenterology. 2021; 160(5):1608-1619.e13.
51. Zaman A, Rosen HR, Ingram K, et al. Assessment of FIBROSpect II to detect hepatic fibrosis in chronic hepatitis C patients. Am J Med. 2007; 120(3): 280.e9-e14.

Government Agency, Medical Society, and Other Authoritative Publications:

1. American Association for the Study of Liver Diseases and Infectious Diseases Society of America. Recommendations for testing, managing, and treating hepatitis C. January 21, 2021. Available at: http://www.hcvguidelines.org/full-report-view. Accessed on October 17, 2023.
2. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018; 67(1):328-357.
3. Cusi K, Isaacs S, Barb D, et al. American Association of Clinical Endocrinology Clinical Practice Guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings: co-sponsored by the

American Association for the Study of Liver Diseases (AASLD). Endocr Pract. 2022; 28(5):528-562.
4. Kanwal, F, Bacon BR, Beste LA, et al. Hepatitis C virus infection care pathway—a report from the American Gastroenterological Association Institute HCV Care Pathway Work Group. Gastroenterology. 2017; 152(6):1588-1598.
5. Kanwal F, Shubrook JH, Adams LA, et al. American Gastroenterological Association: Clinical care pathway for the risk stratification and management of patients with nonalcoholic fatty liver disease. Gastroenterology. 2021; 161(5):1657-1669.
6. Long MT, Noureddin M, Lim JK. AGA Clinical practice update: diagnosis and management of nonalcoholic fatty liver disease in lean individuals: expert review. Gastroenterology. 2022; 163(3):764-774.
7. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023; 77(5):1797-1835.
8. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018; 67(4):1560-1599.
9. U.S. Food and Drug Administration 510(k) Premarket Notification Database. ADVIA Centaur Enhanced Liver Fibrosis (ELF) System Summary of Safety and Effectiveness. DEN No. DEN190056. Rockville, MD: FDA. August 21, 2021. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. Accessed on November 05, 2023.
10. Vos M, Abrams S, Barlow S, et al. NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children: recommendations from the expert committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). J Pediatr Gastroenterol Nutr. 2017; 64(2):319-334.
11. Wattacheril JJ, Abdelmalek MF, Lim JK, Sanyal AJ. AGA clinical practice update on the role of noninvasive biomarkers in the evaluation and management of nonalcoholic fatty liver disease: expert review. Gastroenterology. 2023; 165(4):1080-1088.

Websites for Additional Information

1. American Liver Foundation. https://liverfoundation.org. Accessed on October 17, 2023.

Index

ActiTest
ASH FibroSURE
ELF
FIB-4 Index
FibroMeter
FIBROSpect
FIBROSpect II
FibroSure
FibroTest
FSII
FT
HCV FibroSURE
LIVERFASt
NASH FibroSURE
OWLiver

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Revised	11/09/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Revised title to “Proprietary Algorithms for Liver Fibrosis.” Revised INV/NMN Position Statement. Updated Description/Scope, Rationale, Definitions and References sections. Updated Coding section with 01/01/2024 CPT changes, added 81517 replacing 0014M.
Reviewed	08/10/2023	MPTAC review. Updated Rationale and References sections.
Reviewed	08/11/2022	MPTAC review. Updated Rationale and References sections. Updated Coding section to correct descriptor for 0166U; added PLA code 0344U effective 10/1/2022.
	06/29/2022	Updated Coding section with 07/01/2022 CPT change to 0166U descriptor.
Revised	08/12/2021	MPTAC review. Title, Description/Scope, and Position Statement updated by editing Serum Markers to Proprietary Algorithms. Rationale, Websites for Additional Information, and References sections updated.
Reviewed	08/13/2020	MPTAC review. Rationale, Background, and References sections updated.
	04/01/2020	Updated Coding section with 04/01/2020 CPT changes; added 0014M, 0166U.
Reviewed	08/22/2019	MPTAC review. Rationale and References sections updated.
	12/27/2018	Updated Coding section with 01/01/2019 CPT changes; added 81596 and descriptor changes for 0002M and 0003M; 0001M deleted 12/31/2018.
Revised	09/13/2018	MPTAC review. Clarified INV/NMN statement. Rationale, Background, and References sections updated. Websites section added. Updated Coding section with 10/01/2018 CPT change to 0001M descriptor.
Reviewed	11/02/2017	MPTAC review. The document header wording updated from “Current Effective Date” to “Publish Date.” Rationale, Background, Index and References sections updated.
Reviewed	11/03/2016	MPTAC review. Rationale, Background and Reference sections updated.
Reviewed	11/05/2015	MPTAC review. Rationale, Background, Coding, Reference and Index sections updated. Removed ICD-9 codes from Coding section.
	07/01/2015	Updated Coding section with 07/01/2015 CPT change to descriptor for 0001M.
Reviewed	02/05/2015	MPTAC review. Rationale, Background and Reference sections updated.
Reviewed	02/13/2014	MPTAC review. Rationale, Background and Reference sections updated.
Reviewed	02/14/2013	MPTAC review. Rationale, Background, Coding, Index, and Reference sections updated.
	09/15/2012	Updated Coding section with CPT changes effective 09/15/2012.
Reviewed	02/16/2012	MPTAC review. Description, Rationale, Background, Reference and Index sections updated. Websites for additional information removed.
Reviewed	02/17/2011	MPTAC review. Description, Rationale, Definitions, Reference link, and Index updated.

Reviewed	02/25/2010	MPTAC review. Title of document, Description, Rationale, Background, and References updated.
Reviewed	02/26/2009	MPTAC review. Description, Rationale, References and Index updated. Wording of position statement clarified, but no change to stance.
Reviewed	02/21/2008	MPTAC review. Updated References. The phrase “investigational/not medically necessary” was clarified to read “investigational and not medically necessary” at the November 29, 2007 MPTAC meeting.
Reviewed	03/08/2007	MPTAC review. Rationale and References updated.
New	03/23/2006	MPTAC initial document development.

Applicable to Commercial HMO members in California: When a medical policy states a procedure or treatment is investigational, PMGs should not approve or deny the request. Instead, please fax the request to Anthem Blue Cross Grievance and Appeals at fax # 818-234-2767 or 818-234-3824. For questions, call G&A at 1-800-365-0609 and ask to speak with the Investigational Review Nurse.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member’s contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.